Dr Jekyll and Mr Hyde?

Undue Pharmaceutical Industry Influence and the Institutional Corruption of the Medical Profession – A Qualitative Analysis of Industry-Medicine Relationships in Hungary and the Netherlands

Dr. Jekyll en Mr Hyde?

De ongewenste invloed van de farmaceutische industrie en de institutionele corruptie van het medische beroep - een kwalitatieve analyse van de relaties tussen industrie en geneeskunde in Hongarije en Nederland
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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Declaration

I declare that the research embodied in thesis is my own work and that the material contained herein has not been previously submitted at any other university.

I declare that I have not used commercial doctoral advisory services or any other sources of aid other than those listed in this thesis.

Contents

It was on the moral side, and in my own person, that I learned to recognise the thorough and primitive duality of man; I saw that, of the two natures that contended in the field of my consciousness, even if I could rightly be said to be either, it was only because I was radically both; and from an early date, even before the course of my scientific discoveries had begun to suggest the most naked possibility of such a miracle, I had learned to dwell with pleasure, as a beloved daydream, on the thought of the separation of these elements.

— Robert Louis Stevenson: The Strange Case of Dr Jekyll and Mr. Hyde

ABSTRACT

Pharmaceutical companies and the industry as a whole are gargantuan in size, multi-national in activity, successful in business, and vital to the global healthcare delivery structure, but these companies are as insidious as they are indispensable. The pharmaceutical industry possesses monopoly over a product of immense value – medication. Being small in size and big in demand make pharmaceuticals, and thus the pharmaceutical sector, ripe for deviance to emerge, and 'Big Pharma' as a criminogenic enterprise has become less conspiracy and more axiom. Much attention has been paid to crimes of pharmaceutical companies, but some authors claim that were it not for the contribution of doctors, these crimes could not be committed. Being the gatekeepers of human health, the profession of medicine is mandated by social contract, specialized knowledge, authority, and autonomy to promote patient interests in the face of industry financial gain, thereby acting as a countervailing power to industry interests which disregard patient needs. Not only has medicine failed to do so, but explanations are few and far between, tending to suggest that the abandonment of patient interests is an individual departure from codes of proper medical conduct – singling out a Dr Jekyll and proposing that he is converted to Mr Hyde. This thesis examines the proposition of physician culpability in industry criminality, but will challenge individual proclivities as the source of digression from the medical mandate, asking not only why or how doctors contribute to, but why the profession cannot curb industry malfeasance. By following the lifecycle of a pharmaceutical product and the process of delivery from laboratory to prescription, the relationships between industry and medicine are identified within the system of knowledge development of a pharmaceutical product: knowledge production (medical research and development), knowledge interpretation (evidence-based medicine), and knowledge application (informed clinical practice). It is in this system that industry-medicine relationships are formed, but also within which the interests of industry and medicine conflict. It will be argued that industry influence, and the inability of the medical profession to rein-in the interests of pharmaceutical companies, diverts and renders doctors incapable of achieving the institutional purpose of medicine. Employing qualitative research methodology, 83 interviews conducted in Hungary and the Netherlands between April 2015 and April 2017 construct the empirical backbone of the investigation of industry influence in medicine. Each account provided an interpretation and explanation of the realities of industry-medicine relationships, allowing for further exploration of literature, law, guidelines, and data used to support, verify, and illustrate the phenomena relayed by respondents. Favouring the view of embeddedness as an explanation of behaviour, this thesis presents a relational approach to the examination of undue industry influence and the institutional corruption of the medical profession.

SUMMARY

The profession of medicine and the pharmaceutical industry, although commonly seen as two separate actors within the pharmaceutical product delivery chain are in fact highly interdependent, to the point that understanding the role of industry in medicine as limited to drug production, manufacture, and distribution, while that of medicine steers scientific knowledge development, definition of illness and treatment, and clinical practice (Kitsis, 2011) is no longer valid. Increasing interdependency in all areas of the medicines lifecycle between the pharmaceutical industry and the profession of medicine brings with it the opportunity for conflicts of interest to emerge. These conflicts are between the profit incentives of the pharmaceutical industry, and the interests of autonomy and authority over the practice of medicine by the medical profession. More often than not, the interests of the pharmaceutical industry trump those of medicine (Stamatakis et al., 2013). In cases of pharmaceutical industry criminality (Braithwaite, 1948; Dukes et al., 2014), there are those who turn to the profession of medicine as having the duty and knowledge to curb industry deviance (Schafer, 2004; Bodenheimer, 2000; Gøtzsche, 2013) and act as a countervailing power to the interests of the pharmaceutical industry (Light, 2010). The inability of physicians to do so is explained as the result of the extraordinary amount of influence exerted by the pharmaceutical industry over medical professionals manifesting in industry-medicine relationships; pharmaceutical industry funding of medical research and development, industry funding of continuing medical educational events, and direct-to-physician industry advertising (Lexchin, 1993).

Industry-medicine relationships, as corrosive to medical professional autonomy and authority, have not enjoyed too much attention from scholars outside of medicine. While criminological inquiry pursues the crimes of the pharmaceutical industry, or crimes of the individual doctor, medical sociology shows a preoccupation with the relationship between the medical profession and the state, and physician-patient relationships (Busfield, 2006; Light, 2010). Apart from being largely restricted to the academic medical discourse, industry influence is taken to be understood as an external influential force which infiltrates medical practice and the minds of doctors. This is done by either controlling medical professional behaviour by holding hostage and conditionally releasing the finances needed for medical research, development, and education, or by way of using the seductions of financial gain to distort the independence and dutiful behaviour of physicians. These explanations prefer the over- and undersocialized view of man (Granovetter, 1985), limiting the understanding of deviance to that of professional dependency on industry funding, and individual greed. This research looks beyond such simplified explanations, which ultimately end up locating deviance within the mind of the individual, or as some sort of supra-individual corruptive force which cannot be resisted. Behaviour, however, is embedded within the social networks and relationships among actors in their efforts to achieve societal goals (Granovetter, 1985), the complexities of which require interactions between actors in possession of the different knowledge and capabilities needed to achieve goal attainment (Shapiro, 1990, 2005). It is in these relationships that conflict of interest manifests, and corruption emerges. Regarding industry influence in medicine, the inability of medicine to act as a countervailing power to

industry is seen to be a problem of institutional corruption, defined as manifest when an institution is rendered incapable of achieving, or is diverted from achieving its institutional purpose as a result of ethical, legal, systematic, and strategic influence (Lessing, 2013).

This thesis will examine the inability of the medical profession to achieve its institutional purpose by applying the theory of institutional corruption, asking the question: how have industry-medicine relationships induced the institutional corruption of the medical profession? Chapter 1 will introduce the subject of research of this thesis and discuss the research question, as well as specific sub-questions which form the conceptual, analytical, and structural framework of this thesis.

Chapter 2 will introduce research and academic literature which defines the healthcare system, healthcare system actors, and the phenomenon of corruption in the healthcare sector. This chapter provides an overview of literature on corporate crime in the pharmaceutical industry, medical professionalism and dominance from the medical sociological literature, as well as the academic medical discourse regarding industry influence in medicine.

Chapter 3 will conceptualize the purpose of the medical profession, which relies on medical sociological identification of medical authority and autonomy in practice. Building on prior research, conceptualization combines the arenas of medical autonomy and authority as related to the activities of medical knowledge production, medical knowledge interpretation, and medical knowledge application – macro, meso, and micro levels of medical autonomy, and autonomy as the conditional determinant of trust in the medical profession to pursue the interests of patients.

Chapter 4 discusses the methodology adopted in this research, and provides reasoning as to using methods as generative of data. The use of qualitative research, respondent-driven sampling, respondent triangulation, and co-constructionist interviewing techniques will be explained. Reasoning in prior chapters will provide the rationale behind conducting fieldwork in Hungary and the Netherlands.

Given that the structure of the analytical chapters in this thesis follows the technical process of the pharmaceutical product delivery chain, Chapter 5 provides the description of the role of the pharmaceutical industry in medicine, beginning with a description of the "marriage" (Timmermans & Oh, 2010, p. S100) between industry and medicine, an overview of the technical process of pharmaceutical drug research, development, and authorization, as well as introducing evidence-based medicine as the link between medical science and medical practice. Chapter 5 also provides an enumeration of the legal framework of the pharmaceutical product delivery chain, the harmonization of clinical trial regulation and authorization, legislation governing medicines authorization and distribution, as well as pharmaceutical industry self-regulation on ethical pharmaceutical advertising, and the codes of conduct of the medical profession.

Chapters 6, 7, 8, and 9 present the analysis of the data collected in Hungary and the Netherlands. Following the pharmaceutical product lifecycle, the chapters discuss what

types of relationships manifest between industry and medicine at each stage of the lifecycle, where and how autonomy in medical knowledge production (macro), medical knowledge interpretation (meso), and medical knowledge application (micro) is manifest, how industry influence is exerted, and how each level of medical autonomy is weakened. Presented in the form of interview analysis, a consideration of the legal framework, as well as illustrating industry influence via the use of case studies which evolved from the research, a description of the modus operandi of industry influence and how it diverts medicine from achieving its professional goal is elaborated.

Chapter 10 provides the conclusion of this thesis, but not before additional reasoning is provided as to how the profession of medicine is rendered incapable of achieving its institutional purpose. Analysis of the data presents the modus operandi of industry influence, and the processes by which the interests of medicine are subordinated to industry interests, but a final discussion will link the practical manifestations of industry-medicine relationships and industry influence to a conclusion which substantiates the institutional corruption of medicine.

ÖSSZEFOGLALÓ

Bár az orvosi szakmát és a gyógyszeripart gyakran a gyógyszerellátási lánc két, egymástól elkülönülő szereplőjének tekintik, e két fél valójában nagymértékben függ egymástól. E kölcsönös függés olyan mértéket ölt, hogy az értelmezés, amely szerint az ipar orvoslásban ellátott feladata a gyógyszerkészítésre, -gyártásra és -forgalmazásra korlátozódik, míg az orvoslás tevékenységeinek köre a tudományos ismeretek fejlesztésére, a betegségeknek és kezelésüknek a meghatározására, valamint a klinikai gyakorlatra terjed ki (Kitsis, 2011), immár nem helytálló. Az, a gyógyszer életciklusának minden szakaszában jelenlévő, fokozódó egymásrautaltság, amely a gyógyszeripar és az orvoslás között áll fenn, magában hordozza az összeférhetetlenség felbukkanásának lehetőségét. Leegyszerűsítve, az érdekek, amelyek egymással összeütközésbe kerülnek, a gyógyszeripari profitnövelés ösztönzése, valamint az orvosi szakma ahhoz fűződő érdeke, hogy megtartsa az orvosi gyakorlatban önállóságát (autonómiáját) és szaktekintélyét (autoritását). Ezek nem egymással tökéletesen egybevágó érdekek (Stamatakis et al., 2013), és igen gyakran az ipar érdekei meghatározóbbnak bizonyulnak az orvoslás szakmai szempontjainál. A gyógyszeripari bűnelkövetés eseteiben (Braithwaite, 1948; Dukes és tsai., 2014) vannak, akik azzal az előfeltevéssel fordulnak az orvosi szakma felé, hogy ő az, aki rendelkezik a megfelelő tudással és őrá hárul azon kötelesség, hogy visszaszorítsa az ipari kriminalitást (Schafer, 2004; Bodenheimer; 2000, Gøtzsche, 2013), és ellensúlyt képezzen a gyógyszeripar érdekeivel szemben. A magyarázat szerint, az orvosok arra való képtelensége, hogy ezt megtegyék, a gyógyszeripar egészségügyi szakemberekre gyakorolt, rendkívüli mértékű befolyásának eredménye. E befolyás ipari-orvosi összekapcsolódások formájában nyilvánul meg: ipar által finanszírozott orvostudományi kutatásokban és fejlesztésekben, ipar által fedezett orvosi oktatási eseményekben, továbbá közvetlenül orvosokat megcélzó ipari hirdetésekben (Lexchin, 1993).

Az eddigiekben az ipari-orvosi összekapcsolódásoknak, mint az orvosi szakma autonómiáját és autoritását kikezdő jelenségeknek, nem szenteltek igazán nagy figyelmet az orvostudomány területén kívüli kutatások. Míg a kriminológiai vizsgálódás a gyógyszeripar, esetleg egyes orvosok bűneinek leírására törekszik, addig az orvosi szociológiát az orvosi szakma és az állam közötti viszonyrendszer, valamint az orvos-beteg kapcsolatok foglalkoztatják (Busfield, 2006; Light, 2010). Azon túlmenően, hogy a megtárgyalása túlnyomórészt az orvostudományi diskurzusra korlátozódik, az ipar befolyására egy, az orvosi gyakorlatba és az orvosok elméjébe beszűrődő, külső hatásként tekintenek. E hatás vagy az egészségügyi szakember viselkedésének irányítása által lép működésbe – az orvostudományi kutatás-fejlesztéshez valamint az orvosi oktatáshoz szükséges pénzösszegek túszul ejtésével majd feltételekhez kötött átengedésével –, vagy az orvosok függetlenségének és kötelességtudó döntéshozatalának torzítása által érvényesül, csábító anyagi előnyök ígéretét felhasználva. E magyarázatok előszeretettel nyúlnak a túl- vagy alulszocializált emberképhez (Granovetter, 1985), a szakma ipari finanszírozástól való függésére és az egyének kapzsiságára szorítkozva a normáktól való eltérés értelmezésekor. Jelen kutatás célja, hogy meghaladja ezeket a leegyszerűsítő magyarázatokat, amelyek végső soron az egyén gondolkodásában találják meg a devianciát, vagy pedig valamiféle egyének

feletti szinten létező erőként tételezik azt fel, amelynek nem lehetséges ellenszegülni. A viselkedés, ugyanakkor, társadalmi hálózatokba beágyazva zajlik, és olyan cselekvők közötti kapcsolatokban, akik társadalomban megvalósuló célokat igyekeznek elérni (Granovetter, 1985). Összetettségüknél fogva, az említett célok elérése, egymástól eltérő tudások és képességek birtokában lévő cselekvők együttműködését feltételezi (Shapiro, 1990, 2005). Ezek a kapcsolatok azok, amelyekben megnyilvánul az összeférhetetlenség, és amelyekből kialakul a korrupció. Az ipar orvoslásra gyakorolt befolyásának vonatkozásában, e kutatás az orvoslás arra való képtelenségét, hogy ellensúlyozó erőként lépjen fel az iparral szemben, az intézményes korrupció problémájaként fogja fel; magát az intézményes korrupciót pedig úgy határozza meg, mint egy jelenséget, amely olyan esetekben mutatkozik meg, amikor egy intézmény – etikai, jogi, rendszerszintű és stratégiai hatások következtében – alkalmatlanná válik arra, vagy elterelődik attól, hogy intézményi szinten kitűzött célját el tudja érni (Lessing, 2013).

Jelen dolgozat az orvosi szakma intézményi szinten kitűzött céljának megvalósítására való képtelenségét vizsgálja meg azáltal, hogy felteszi a kérdést: milyen módon idézték elő az ipari-orvosi összekapcsolódások az orvosi szakmában jelenlevő intézményes korrupciót? Az első fejezet bevezeti a dolgozatban tárgyalt kutatás témáját, és megtárgyalja a kutatási kérdést, valamint a konkrét alkérdéseket is, amelyek megadják a dolgozat elméleti-fogalmi, elemzési és szerkezeti keretét.

A második fejezet bemutatja a kutatásokat és a szakirodalmat, amelyek definiálják az egészségügyi ellátórendszer fogalmát, és meghatározzák annak szereplőit, és a korrupció jelenségét az egészségügyi ágazatban. Ez az áttekintés egy kivonatos, felülnézeti képet ad a gyógyszeriparban előforduló vállalati bűnözésről szóló szakirodalomból, az orvosi szakma professzionalizálódásával és az orvosi dominanciával foglalkozó orvosi szociológiai szakirodalomból, valamint az ipar orvoslásban gyakorolt befolyását tárgyaló orvostudományi diskurzusról.

A harmadik fejezet az orvosi szakma céljának leírását célzó elméletalkotással foglalkozik – a gyakorlatban megvalósuló orvosi autoritás és autonómia orvosi szociológiai azonosítására támaszkodva. Az elméletalkotás, a korábbi kutatási eredményekre építkezve, egymás mellé illeszti az orvosi autonómia és autoritás területeit, amelyek az orvosi tudás produkciójának, az orvosi tudás interpretálásának, és az orvosi tudás alkalmazásának tevékenységeihez kötődnek: tehát az orvosi autonómia makro-, mezo- és mikroszintjeit, és az autonómiát, amely a meghatározó feltétel az orvosi szakmába vetett hit tekintetében, vagyis azzal a meggyőződéssel kapcsolatban, hogy az orvosi szakma a betegek érdekei szerint jár el.

A negyedik fejezet jelen kutatás során alkalmazott módszertant írja le, és indoklással szolgál az adatokat generáló módszerek használatához – a kvalitatív kutatás, a válaszadó-vezérelt mintavétel, a válaszadó háromszögelés és a strukturálatlan interjúkészítési eljárások használatának magyarázatát adja. A kutatáshoz szükséges terepmunka Magyarországon és Hollandiában folyt le, amely választást a megelőző fejezetekben felsorakoztatott érvek támasztják alá.

Lévén e dolgozat elemző fejezeteinek felépítése a gyógyszerellátási lánc technikai folyamatát követi le, az ötödik fejezet a gyógyszeripar orvoslásban betöltött szerepét járja körbe, kezdve az ipar és az orvoslás közötti „házasság" (Timmermans & Oh, 2010: S100) leírásával, a gyógyszerészeti kutatás, a gyógyszerfejlesztés és a gyógyszer-engedélyezés technikai folyamatának áttekintésével, valamint az orvostudomány és az orvosi gyakorlat között összeköttetést teremtő Bizonyítékalapú Orvoslás bemutatásával. Szintén az ötödik fejezet tartalmazza a gyógyszerellátási lánc jogszabályi kereteinek számbavételét, a klinikai vizsgálatok és az engedélyezési eljárások szabályozásának harmonizálását, továbbá a gyógyszeripar etikus reklámozással kapcsolatos önszabályozási elveit és végül az orvosi szakma magatartási kódexeit.

A hatodik, hetedik és nyolcadik fejezetek a Magyarországon és Hollandiában gyűjtött adatok elemzését mutatják be. A gyógyszeripari termékek életciklusát követve, e fejezetek az ipar és az orvoslás között létrejövő kapcsolatok típusaival foglalkoznak, végighaladva az életciklus mindegyik állomásán. Kifejtik, hogy hol és hogyan nyilvánul meg az autonómia az orvosi tudás produkciója (makro szint), az orvosi tudás interpretálása (mezo szint) és az orvosi tudás alkalmazása (mikro szint) során, hogy miként gyakorol az ipar befolyást az orvoslásra, és végül, hogy milyen módon gyengül meg az orvosi autonómia az egyes szinteken. A jogszabályi keretekkel kapcsolatos megfontolások; az ipar befolyásának szemléltetése a jelen kutatás anyagából kidolgozott esettanulmányok által; az ipari befolyás működésmódjának leírása és annak ismertetése, hogy az ipari befolyás miként tereli el az orvoslást szakmai céljainak elérésétől – mindezeket a témákat interjúelemzés formájában tárgyalják e fejezetek.

A tízedik fejezet tartalmazza a dolgozat következtetéseit. A következtetések levonását megelőzően azonban további, a korábbi fejezetekben található bizonyítékokat kiegészítő érvekre is hivatkozik azzal kapcsolatban, hogy az orvoslás miként vesztette el intézményi szinten kitűzött céljának elérésére való képességét. Az adatok elemzése feltárja az ipari befolyás működésmódját és azt, hogy az orvoslás mely érdekei rendelődnek alá az ipari érdekeknek. Ugyanakkor, a dolgozatot lezáró diszkusszió összefüggést vázol fel az ipari-orvosi összekapcsolódások gyakorlati megnyilvánulásai, valamint az ipar befolyása között – eljutva ezzel a végkövetkeztetésig, mely alátámasztja az orvoslásban az intézményes korrupció jelenlétét

SAMENVATTING

Hoewel de medische stand en de farmaceutische industrie in de aanbodketen van farmaceutische producten veelal worden beschouwd als twee verschillende spelers, is er in werkelijkheid sprake van een hoge mate van wederzijdse afhankelijkheid. Deze is zo groot, dat de opvatting dat de rol van de industrie in de geneeskunde beperkt zou zijn tot de productie en distributie van medicijnen, terwijl de geneeskunde zich zou bezighouden met het richting geven aan de ontwikkeling van wetenschappelijke kennis, de definitie van ziekte en behandeling, en aan klinische praktijken (Kitsis, 2011), niet langer standhoudt. De toenemende wederzijdse afhankelijkheid van de farmaceutische industrie en de medische stand in alle onderdelen van de levenscyclus van medicijnen bergt het risico van belangenverstrengeling in zich. Simpel gezegd heeft de farmaceutische industrie belang bij winstprikkels, en heeft de medische stand belang bij autonomie en autoriteit in de uitoefening van de geneeskunde. Deze belangen vallen niet naadloos samen (Stamatakis et al, 2013); maar al te vaak gaan de belangen van de industrie vóór de belangen van de geneeskunde. In het geval van criminele gedragingen van de farmaceutische industrie (Braithwaite, 1948, Dukes et al., 2014), richten sommigen hun pijlen op de medische stand, omdat deze de plicht en kennis zou hebben gehad tot het beteugelen van criminele gedragingen van de industrie (Schafer, 2004, Bodenheimer, 2000, Gøtzsche, 2013) en het vormen van een tegenwicht (Light, 2010) tegen de belangen van de farmaceutische industrie. De verklaring voor het onvermogen van de artsen om dit te doen, ligt in de buitengewone mate van invloed van de farmaceutische industrie op de medische professionals, die naar voren komt in de relaties tussen de industrie en de medische stand; de financiering door de farmaceutische industrie van het medisch onderzoek en de medische ontwikkeling, de financiering door de industrie van permanente medische educatie, en de rechtstreeks tot de arts gerichte reclame van de industrie (Lexchin, 1993).

Aan relaties tussen de industrie en de medische stand, waarvan een ondermijnende werking uitgaat op de autonomie en de autoriteit van medische professionals, is buiten de geneeskunde nog weinig aandacht besteed. Het criminologisch onderzoek richt zich op criminele gedragingen van de farmaceutische industrie of van de individuele arts, terwijl de medische sociologie zich focust op de verhouding tussen de medische stand en de overheid, en op de arts-patiënt relatie (Busfield, 2006, Light, 2010). Afgezien van het feit dat deze discussie zich vooral beperkt tot het academisch-medische discours, wordt de invloed van de industrie gezien als een invloedrijke, externe kracht die infiltreert in de medische praktijk en de hoofden van de artsen, hetzij door het gedrag van medische professionals te sturen door middel van de achterhouding en voorwaardelijke vrijgave van de gelden die benodigd zijn voor medisch onderzoek, medische ontwikkeling en medisch onderwijs, hetzij door artsen te verleiden door middel van financieel gewin, en zo hun onafhankelijkheid en plichtsgetrouw gedrag te ondermijnen. Deze opvattingen gaan uit van een over- en ondergesocialiseerde visie op de mens (Granovetter, 1985), waarbij de verklaring van het afwijkend gedrag zich beperkt tot professionele afhankelijkheid van financiering door de industrie en tot individuele hebzucht. Het onderhavige onderzoek kijkt verder dan dergelijke vereenvoudigde verklaringen, waarbij men de basis voor het afwijkend gedrag uiteindelijk

legt in de wil van het individu, of in een soort supranationale corrumperende kracht waaraan geen weerstand kan worden geboden. Gedrag is echter ingebed in de sociale netwerken en in de relaties tussen de actoren bij hun streven om maatschappelijke doelen te bereiken (Granovetter, 1985); de complexiteit ervan vereist interacties tussen de actoren, die beschikken over ongelijke kennis en capaciteiten tot het bereiken van het doel (Shapiro, 1990, 2005). Juist in de context van deze relaties wordt de belangenverstrengeling zichtbaar en treedt corruptie op. Wat betreft de invloed van de industrie op de geneeskunde wordt het onvermogen van de medische stand om een tegenwicht te vormen tegen de industrie gezien als een probleem van institutionele corruptie, die zich manifesteert wanneer een instelling ervan wordt afgehouden om haar institutionele doel te bereiken of hiervan wordt afgeleid ten gevolge van een ethische, juridische, systematische en strategische invloed (Lessing, 2013).

In dit proefschrift wordt onderzoek gedaan naar het onvermogen van de medische stand om haar institutionele doel te bereiken aan de hand van de theorie van de institutionele corruptie; de volgende vraag staat hierbij centraal: hoe hebben de relaties tussen de industrie en de medische stand de institutionele corruptie van de medische stand in de hand gewerkt? In hoofdstuk 1 wordt het onderwerp van dit proefschrift geïntroduceerd en wordt de onderzoeksvraag besproken, evenals specifieke deelvragen, die het conceptuele, analytische en structurele kader van dit proefschrift vormen.

In hoofdstuk 2 wordt onderzoeks- en wetenschappelijke literatuur geïntroduceerd, waarin het systeem van de gezondheidszorg, de actoren in de gezondheidszorg en het fenomeen van corruptie in de gezondheidszorg worden gedefinieerd. Dit hoofdstuk bevat een overzicht van literatuur over organisatiecriminaliteit in de farmaceutische industrie, medische professionaliteit en overwicht vanuit de medisch-sociologische literatuur, evenals wetenschappelijk medisch discours over de invloed van de industrie op de medische stand.

Hoofdstuk 3 bevat een conceptualisatie van het doel van de medische stand, die steunt op een medisch-sociologische identificatie van medische autoriteit en autonomie in de praktijk. De conceptualisatie bouwt voort op eerder onderzoek en legt een verband tussen enerzijds de arena's van medische autonomie en medische autoriteit in relatie tot de productie, de interpretatie en de toepassing van medische kennis, de macro-, meso- en microniveaus van de medische autonomie, en anderzijds autonomie als de bepalende voorwaarde voor het vertrouwen dat de medische stand de patiëntenbelangen behartigt.

In hoofdstuk 4 wordt de in dit onderzoek gehanteerde methodologie besproken, en wordt het gebruik van methodes zoals het genereren van data gemotiveerd. Dit hoofdstuk bevat een uitleg over het gebruik van kwalitatief onderzoek, respondentgestuurde steekproeftrekking, respondent triangulatie, en co-constructionistische interviewtechnieken. De argumentatie in de voorgaande hoofdstukken verschaft de basis voor het in Hongarije en Nederland verrichte veldwerk.

Gezien het feit dat de structuur van de analytische hoofdstukken van dit proefschrift parallel loopt met het technische proces van de aanbodketen van farmaceutische producten, volgt in

hoofdstuk 5 een beschrijving van de rol van de farmaceutische industrie in de geneeskunde, te beginnen met een beschrijving van het "huwelijk" (Timmermans & Oh, 2010: S100) tussen de industrie en de geneeskunde, een overzicht van het technische proces van research, development en autorisatie van farmaceutische medicijnen, evenals de introductie van evidence-based medicine als de schakel tussen de medische wetenschap en de medische praktijk. Hoofdstuk 5 geeft tevens een opsomming van het juridische kader van de aanbodketen van farmaceutische producten, de harmonisatie van de regulering en autorisatie van klinische proeven, wetgeving aangaande de autorisatie en distributie van medicijnen, evenals zelfregulatie van de farmaceutische industrie bij ethisch verantwoorde farmaceutische reclame, en de gedragscodes van de medische stand.

De hoofdstukken 6, 7, 8 en 9 betreffen de analyse van de in Hongarije en Nederland verzamelde gegevens. In deze hoofdstukken, die de levenscyclus van farmaceutische producten volgen, wordt besproken welk type relatie tussen de industrie en de geneeskunde zich in iedere fase van de levenscyclus manifesteert, waar en hoe autonomie bij de productie van medische kennis (macro), bij de interpretatie van medische kennis (meso) en bij de toepassing van medische kennis (micro) zich manifesteert, hoe de industrie invloed uitoefent en hoe elk niveau van medische autonomie wordt verzwakt. In de vorm van een interviewanalyse volgen een beschouwing van het juridische kader, een illustratie van de invloed van de industrie via het gebruik van casestudies die afkomstig zijn uit onderzoek, een beschrijving van de modus operandi van de invloed van de industrie en hoe dit de medische stand afleidt van het bereiken van haar professionele doelstelling.

Hoofdstuk 10 bevat de conclusie van dit proefschrift, echter pas na het aanvoeren van extra argumenten waaruit blijkt hoe de medische stand ervan wordt afgehouden om haar institutionele doelstelling te bereiken. De data-analyse toont de modus operandi van de invloed van de industrie, en de processen waardoor de belangen van de medische stand ondergeschikt worden gemaakt aan de belangen van de industrie, en tenslotte worden de praktische manifestaties van de relaties tussen de industrie en de medische stand en de invloed van de industrie gekoppeld aan een conclusie, die de institutionele corruptie van de medische stand staaft.

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CHAPTER 1: INTRODUCTION

In my first year as a criminology masters student in Budapest, the case of Thalidomide emerged in the classroom. Despite being advertised in the 1960s as so safe that it could be taken by expectant mothers to relieve morning sickness, Thalidomide proved to have adverse effects on the unborn child. These children were born without limbs, disfigured appendages instead of arms and legs, some had fused fingers, or malformed eyes and ears, deafness, cardiovascular complications, and defects of the kidneys and digestive tract. It is estimated that 24,000 babies were born with this condition world-wide, many dying as a result of their defects. In 2011, less than 3000 Thalidomide children were still alive (Dove, 2011). The company which placed Thalidomide (brand name Contergan) on the market, despite evidence of the drug causing Phocomelia in preclinical studies on mice, was never held criminally liable, nor did it ever admit to wrongdoing. When listening to our professor reiterate the case, a former classmate could not contain her outrage and almost shouted the question: "*How could this have been allowed to happen, and why was the company not held accountable?!*" The professor answered: "*Well, it's time you were told that the Easter Bunny does not exist*". I was among those that laughed at this reply, but over time I am embarrassed to have done so. All too frequently, cases of incredible injustice are diffused with comments regarding one's level of naivety as to understanding that this is just the way the world works.

The completion of a masters course in the Netherlands, my thesis comprised a criminological investigation into the case of Dr Nancy Olivieri, The Hospital for Sick Children, and the drug manufacturer Apotex Inc. In the late 1990s haematologist Dr Olivieri was involved in researching Deferiprone, a drug intended to increase the quality of life for patients suffering from Thalassemia. The drug company Apotex became the sponsor of the clinical trials needed for the drug's market authorization. High expectations of trial success were shattered when Dr Olivieri found evidence that Deferiprone may cause chronic liver disease in patients. Following her professional and ethical obligations, Olivieri immediately notified Apotex and the hospital research ethics committee, with the request to incorporate the new found risk into the patient consent form, and to be allowed to follow up on her findings of risk. Her requests were denied and her data was discredited by scientists hired by Apotex, her professional competencies were questioned, she was removed from heading the clinical trials, and subsequently fired from her position at the Hospital. Apotex shut down all clinical trials, and came to the determination that enough evidence was available for regulatory approval submission. The battle between Olivieri and Apotex had gained notoriety, especially after it was found that the President of the University of Toronto, Dr Olivieri's employer, lobbied the Canadian Prime Minister not to enact specific medicines patent legislation, which would have potentially affected Apotex's business operations. Apotex was planning to provide the University with a $30 million donation, which it claimed it could not do if the patent legislation were to be

implemented (Thompson, et al., 2001). Packing too much heat from the scandal, regulatory approval was sought in Europe instead of the US or Canada. Deferiprone was approved by the European Medicines Agency in 2000, but Dr Olivieri legally challenged the authorization in the European Court of Justice. The ECJ deemed her arguments "unconvincing" (T-326/99 2003:351, section 142) and as to any right that Dr Olivieri may have had in challenging a regulatory drug approval decision, the ECJ unmistakably negated her expert scientific evaluation.

"Unlike Apotex, the applicant for marketing authorisation (...) Dr Olivieri cannot claim entitlement to challenge, in an action for annulment, the scientific evaluation made by the CPMP and confirmed by the Commission. Admittedly, Dr Olivieri was particularly well qualified to supply the CPMP with important and relevant information because of her status as an acknowledged specialist in thalassemia major and her significant contribution to the research on which Apotex's application was based. Moreover, the Commission was required, in the interest of public health, to take into consideration and carefully evaluate the scientific data and the opinions which she had sent to it. However, in the context of the rules applicable to marketing authorisations, her role cannot be treated as equivalent to that of an applicant for marketing authorisation, who participates in the administrative procedure by virtue of a right which those rules have conferred on it."

Were it not for the fact that Apotex stopped Deferiprone trials abruptly, or that no opportunity was afforded to scientifically validate or disprove Dr Olivieri's findings of increased liver toxicity, this ECJ judgment is the effective depreciation of medical science to the role of data provider, and deprivation of any right to data evaluation for marketing authorization.

Baylis (2003) and Schafer (2004) touch upon a problem that runs deeper than whether the data by Dr Olivieri was substantively right or wrong, turning to ask whether limitations to academic freedom should run along the boundaries of private company interests or regulatory administrative processes. The Olivieri case is an assault on scientific freedom and integrity, the dislocation of scientific argumentation from the administrative proceedings of medicines authorization, and the inability of medical expertise to challenge a company even when a drug is feared harmful to patients by qualified physicians. The Olivieri case was for me, a terrifying thing to assess. Researching the literature for the masters thesis, I was exposed to numerous other cases where pharmaceutical companies had been implicated in unethical and criminal practices: conducting unsafe clinical trials, bribing medical professionals, misleading patients with fraudulent advertising, drug price-fixing, substandard manufacturing practices, concealing or manipulating research data, and state blackmail. From academic analysis to the investigative work of "crusading journalists" (Nelken, 2012, p. 624) and accounts from pharmaceutical industry insiders, the evils of "Big Pharma" (Law, 2006) have been documented at length, earning the industry the title of "Bad Pharma" (Goldacre, 2012). For all of these cases, however, this thesis is not about pharmaceutical industry criminality.

1.1. BAD PHARMA, GOOD DOCTOR?

In 2013 Peter Gøtzsche published a book which takes on another analysis of pharmaceutical industry criminality, but after listing numerous industry scandals that took place in the past 10 years under the subtitle "industry hall of shame", one sentence is poignant: "It is also important to note that many of the crimes would have been impossible to carry out, if doctors had not been willing to participate in them" (Gøtzsche, 2013, p. 37).

Physicians have not been immune to criticism in relation to crimes of the industry, the image of doctors receiving all-expenses-paid trips to conferences in exotic locations and being showered with money and gifts in return for drug prescription loyalty have made headlines, and filled research publications. The fact that pharmaceutical companies try to influence medical professionals to promote industry interests, however, is seen predominantly as additional proof of pharmaceutical industry evil, while the doctors they manipulate are labelled as rogue, morally bankrupt individuals, if doctors are blamed at all. Medical professionals partake in clinical trials, they monitor research data, publish findings in medical journals, subject knowledge about tested drugs to criticism and evaluation, educate their peers on advancements in medical science, deliberate over the use of medicines in treatment, and prescribe medicines to patients.

The Olivieri case depicts an image of absent professional autonomy and authority, and Schafer's (2004) assessment asks why medical scientists remained silent in the face of Apotex's restrictions on academic freedom and suppression of medical duties towards patients. Why had those involved, but also the general medical community, remained mute and limp in a situation that would have demanded dutiful resistance in the face of pharmaceutical industry interests? However, it is not an intrinsic individual inclination towards wrongdoing but also situational factors which may induce good people to do bad things (Braithwaite, 1948). Explanations of a good Dr Jekyll turned sinister Mr Hyde by pharmaceutical industry seductions that evoke a nestling evil in man is an easy explanation for those unwilling to entertain the idea that there is something very wrong with the way medicine has organized its professional activities, creating an improper dependency (Lessing, 2011, 2013) on the pharmaceutical industry in the execution of medical practice.

Having been exposed during research to multiple cases in which unsafe, harmful, and even deadly medications made it to market, I question the unavoidable risks associated with pharmacological experimentation as a conclusive and persistent explanation. I consider the profit incentives of the pharmaceutical industry as not only influencing the evolution of medical treatment, but incapacitating the autonomy and authority of the medical profession over the determination of its practice, as well as it's commitment to patients. In looking to the profession of medicine this thesis investigates the relationship between the medical profession and the pharmaceutical

industry, taking as its base the pharmaceutical product lifecycle – the stages of pharmaceutical drug production, evaluation, and distribution – a technical process defined by international regulation. In this lifecycle I will examine the activities of the pharmaceutical industry and those of the medical profession with regards to their roles in the knowledge produced about a pharmaceutical product (Busfield, 2006), and where the overarching goal (Oliveira, 2014) of promoting patient health requires relationships between industry and medicine to manifest along the pharmaceutical product lifecycle stages. I will argue that despite industry-medicine relationships manifesting as a functional prerequisite for drug development, evaluation, and distribution, the imperatives of the profession of medicine and industry do not coincide. Industry influence within the profession erodes medical autonomy and authority, incapacitating the pursuit of medicine's professional interests of promoting and protecting patient well-being.

1.2. RESEARCH QUESTION

Influence, or the ability to corrupt the moral and ethical standing of medical professionals, is commonly attributed to the role of the pharmaceutical industry as financial benefactor to medicine. Pharmaceutical companies provide the majority of funding for medical research aimed at developing new drugs, routinely engage in funding and organization of accredited medical conferences and continuing medical educational (CME) events, finance physicians' attendance at these events, and routinely bestow gifts and freebies to clinicians. Attributing these endowments with the power to corrupt a doctor, and persuade him/her to abandon the ethical duties of his/her profession would, however, be an erroneous oversimplification which stems from the use of traditional criminal-legal definition of crimes of corruption i.e. bribery, which predetermines a guilty mind. This approach fails to consider that there is an entire process of pharmaceutical product evidence production and interpretation, which precedes prescription practice influence, and it is within this process where industry-medicine relationships are established, and where undue industry influence manifests. This thesis will investigate not whether and by what means a doctor would be manipulated to engage in harmful prescribing practices, but seeks to investigate how the process of pharmaceutical product delivery fails to minimize the chances of such a drug making it to the market in the first place.

Assuming a research approach that sees behaviour as embedded in the networks of social interaction (Granovetter, 1985), I argue that it is industry-medicine relationships themselves that are corrupt, and it is these relationships that should be assessed. The theory of institutional corruption provides a fundamental basis for an analysis which sees influence and corruption as existing in the relational networks (Jancsics, 2014) between the pharmaceutical industry and the medical profession, and not solely as an interactional outcome. Institutional corruption is defined as the systematic and strategic, currently legal and ethical influence which is exerted in a fashion that debilitates an institution from achieving its purpose (Lessing, 2013).

This thesis will examine how industry-medicine relationships induce the institutional corruption of the medical profession, by analysing the following sub-questions.

- What are industry-medicine relationships, and where do they manifest along the pharmaceutical product lifecycle?
- What modes of influence manifest within industry-medicine relationships?
- How do industry-medicine relationships render the profession of medicine incapable of achieving its institutional purpose?

Regarding the profession of medicine, and in line with this theoretical underpinning, this thesis argues that the legal and often ethically viewed relationships between industry and medicine identified within activities of industry funding of clinical trials, the financing of medical educational events, and marketing to physicians, has systematically and strategically rendered the profession of medicine incapable of maintaining its professional integrity and autonomy, and as a result, is unable to fully accomplish its professional mandate of patient health promotion.

1.3. ACADEMIC RELEVANCE

1.3.1. A EUROPEAN CONTEXT

Industry influence in medicine, studied either under the guise of bribery of doctors, or the examination of corporate wrongdoing, is dominated by American scholarly inquiry, and many case studies involve analysis of companies based or operating in the United States. The Americanization of pharmaceutical crime I assume to be multifactorial: spawning from the image of Corporate America, Wall Street as the manifestation of greed, and the remnants of the American Dream which sanctifies the individual pursuit of material gain. Another factor may be that a combination of increased journalistic preoccupation with corporate criminality, as well as an "American injury culture" epitomized in US tort law and the active civil participation in claiming redress for consumer injury in civil, or class action lawsuits (Jain, 2006) making visible the crimes of companies and perhaps inducing the normalization of citizens actively challenging powerful conglomerates. However, pharmaceutical industry criminality is not solely an American problem.

Roughly half of the global top 20 pharmaceutical companies are American (Angell, 2004), the rest being European, Japanese, or Israeli. However, these companies can hardly be considered as belonging to one country, given that their economic activity spans across borders and continents. They are multinational conglomerates with headquarters in many countries, executing operations in various national and international markets, and are regulated by national and international law. The globalization of the pharmaceutical industry has been followed by the international standardization of medicines production, evaluation (ICH CGP, 1996) and distribution

(EFPIA, 2017); regulatory harmonization enabling international regulatory approval, market access, and use in medical care. Regulatory harmonization simultaneously conforms the relationships between industry and medicine along the pharmaceutical product delivery chain: preclinical and clinical testing, regulatory drug approval, and the adoption of evidence-based medicine as the cornerstone of Western medical practice. Adding to academic inquiry, this research is an analysis of industry influence, and the institutional corruption of the medical profession in the European context, more specifically in the European Union member states of Hungary and the Netherlands.

Analytical motivation for country selection is largely due to these EU member states being both geographically, but also socioeconomically, at the ends of the healthcare service delivery system spectrum. The Dutch healthcare system is ranked as being among the best in Europe, ranking 8th, while the Hungarian Healthcare system ranks 22nd of the EU 28 in overall health system performance (WHO, 2000). Salaries of healthcare providers in OECD countries are the lowest in Hungary, and the highest in the Netherlands (OECD, 2014, F11-071 EN 2011), while corruption in healthcare is perceived to be significantly low in the Netherlands, and high in Hungary (TI GCR, 2006). These healthcare system characteristics allow for assessments to be made as to variances in industry-medicine relationships and the institutional corruption of medicine, considering that low financial resources is often seen as a precursor to corruption susceptibility. From an analytical perspective, an element of comparison motivated inquiry. The data derived from Hungary and the Netherlands are treated as two case studies, and comparisons are made where relevant with regards to the evaluation of industry-medicine relationships along the pharmaceutical product delivery chain.

1.3.2. A QUALITATIVE APPROACH

To examine institutional corruption is to attempt to study whether an institution is achieving a purpose. In this instance the theory of institutional corruption applied to the profession of medicine would require the measurement of whether or not the medical profession achieves the purpose of promotion and protection of patient health, which is a particularly abstract concept. Institutional purpose achievement is visible in specific work (action) which has an identifiable goal, the achievement of which can be analysed as being in line with the institutional purpose. As such, the study of institutional purpose attainment must take a "ground up" approach which assesses work goal achievement and purpose compatibility. This research "is a process of synthesis, of combining the multiple specific goals to evaluate if the purpose that this combination implies is the same as the institutional purpose" (Oliveira, 2014, p. 14). Qualitative research methods presented a mode of inquiry whereby professionals described both the formal technical and regulatory structure of medicines development, evaluation, and distribution, but also provided "insider accounts" (Gray, 2013a) of the informal pressures, expectations, and tasks required in specific goal

attainment. Accounts were descriptions of goals, and analysis aimed to evaluate their institutional purpose compatibility. Using respondent-driven sampling and cold-call techniques, this thesis is based on 83 interviews with 84 respondents, 43 interviews from Hungary and 41 from the Netherlands. Using respondent triangulation as a method of respondent interview verification, the sample included respondents from the profession of medicine, the pharmaceutical industry, and respondents from government regulatory, medical and pharmaceutical self-regulatory bodies. Each interview was conducted with the employment of the Socratic-hermeneutic interpreview method and co-constructionist interview techniques (Dinkins, 2005) which allowed consolidation of information sourced from academic literature, formal regulatory documents, and other interviews. Substantiation of interview claims, cases, and examples were followed up on, which led to identification of smaller illustrative case studies within this research. Using qualitative methodology provided an effective means of access to respondents, but also a means of understanding the social networks between healthcare system actors captured in descriptions of the division of labour and knowledge along the pharmaceutical product lifecycle.

1.3.3. AN INTERDISCIPLINARY STUDY

The subject of this research has been inspired and informed by research from the fields of white collar, corporate, and organizational criminology, medical sociology, medical science, regulatory science, and ethics, given that the subject of this thesis necessitated a multidisciplinary approach.

White collar and corporate criminology, as well as organizational criminological inquiry, look to the analysis of crimes of powerful individuals and organizations which often go unpunished despite causing incredible damage and injury. Looking to a corporate culture, crimes of the powerful are explained by organizational situational factors, and not necessarily by individual propensity to crime. Corporate crime in the pharmaceutical industry has received criminological attention (Braithwaite, 1984; Dukes et al., 2014), but research concerning the medical profession has generated less intrigue, limited to the arena of white collar crime and medical malpractice (Jesilow et al., 1985; Hoffman, 2009; Miller, 2013). The role of the medical profession in pharmaceutical industry criminality has not yet been comprehensively investigated.

Medical sociology on the other hand analyses medical professionalism, examining the qualities of the profession within the relational context, as regards its professional obligations to society, and the balance between state regulation and medical autonomy. However, medical sociological research is preoccupied with the relationships between the medical profession and the state, or the doctor and the patient, negating the relationship that medicine has with private pharmaceutical companies (Busfield, 2006; Light, 2010).Interestingly enough, the majority of literature on the corrosive effect of industry-medicine relationships with regards to the autonomy of medicine has been written by medical professionals, for medical professionals, in medical journals. Revealing and incredibly vital as these articles were for this research, a purely medical

analysis is built on the perception that only doctors know enough about medicine to assess the danger posed by industry influence to its profession, which is "a myth of medical experience" (Freidson, 1983, p. 213).

Institutional corruption theory was originally developed to assess the corrosive effect of American Congress' financial dependency on private company financing (Thompson, 1995), and was adapted by Lessing (2013) into a theory which could be applied to other private and public entities. Although often challenged for definitional ambiguity and lack of applicability outside of its original context (Dawood, 2014; Newhouse, 2014), institutional corruption theory addresses the abscess on the criminological palate which it keeps tonguing: the bad apple or bad barrel argument. Not giving primacy to either the individual or the collective, institutional corruption recognizes that action is embedded in social relations, but more importantly the theory examines questions of ethicality, addressing the ethics of right and wrong beyond that which is captured by legal doctrine.

This thesis will address the gaps in research and theory about industry-medicine relationships and the institutional corruption of medicine. The organizational approach of white collar and corporate criminality motivate the embeddedness view of human behaviour in the social networks within which they operate, choosing to analyse the relationship between industry and medicine. To conceptualize the institutional purpose of medicine, I have relied on studies of medical professionalism, and authority and autonomy in medical practice. Medical scientific literature, insights from marketing studies, and formal regulatory documents shape analysis along the pharmaceutical product lifecycle. The identification of the subject of analysis, the conceptualization of the goals and purpose of the medical profession, and analysis of the context of a regulated pharmaceutical product delivery system are executed within the application of the theory of institutional corruption.

1.4. STRUCTURE

The structure of this thesis, in the chronology of its chapters and argumentation, follows the theoretical framework adopted in the research. Chapters 2, 3, 4 and 5, present the literature review, theoretical and conceptual framework, the description of methodology, as well as the contextual, regulatory, and technical framework of this research. The ensuing chapters 6, 7, 8 and 9 present the analysis of research data which follow the technical order of the pharmaceutical product lifecycle stages of medicines development, evaluation and authorization, and distribution as described in detail in chapter 5. Chapter 10 is subsequently the conclusion of this thesis.

Chapter 2: Literature Review
The chapter begins with an overview of research conducted by the World Health Organization, the European Commission and Transparency International, addressing the definitions of a healthcare system, its actors, and the general phenomenon of corruption in the healthcare sector identified in the medicines delivery chain, and the

interactions between various actors within a healthcare system. Subsequently, research on corporate crime in the pharmaceutical industry, undue industry influence in medical discourse, and the evaluation of medical professionalism will be introduced, concluding with an overview of an organizational criminological approach.

Chapter 3: Theoretical Elaboration and Conceptualization

Merging the various insights from research from the fields of criminology, sociology, and medicine, Chapter 3 presents the elaboration and conceptualization of the theoretical framework adopted in this research. The arguments for embeddedness are explained by descriptions of social relations in complex societies, which necessitate principal-agent relationships for goal attainment. The concept of trust and fiduciary obligations as enabling principal-agent relationships is addressed, explaining how trust simultaneously serves to hide agent deviance, thereby presenting white collar crime as an abuse of trust. Principal-agent relationships will be applied to descriptions of interactions between healthcare actors, and how abuse of trust arises within the conflict of interest inherent to principal-agent relationships. Conflict of interest as a structural characteristic of social interactions will then be discussed within the framework of institutional corruption theory. A conceptualization of institutional purpose as related to the profession of medicine will be addressed in an argument which examines the concepts of medical autonomy and authority, and argues medical autonomy to be a conditional determinant of institutional purpose achievement. Concluding this chapter is the identification of macro, meso, and micro levels of medical autonomy in the activities of medical knowledge production and interpretation, which manifests in medical work along the pharmaceutical product lifecycle and yields the relationships between industry and medicine.

Chapter 4: The Methodological Audit Trail

Detailed in this chapter are the theoretical and technical aspects of the research methodology. I will discuss the motivations behind choosing the countries studied, and the reasoning behind the use of qualitative research methods. The sampling procedure, respondent triangulation, access to respondents, and building of rapport will be discussed, as well as the use of method as data. The tactics of the Socratic-hermeneutic interpre-view techniques, and the importance of co-constructionism in the interview, scenario will be described. The mode of data collection, retention and analysis conclude this chapter.

Chapter 5: More Than a Manufacturer: The Role of Industry in Medicine

The question of the role of industry in medicine will be discussed in detail as pertaining to interactions between the medical profession's activities of medical knowledge production, interpretation, and application, and the pharmaceutical product lifecycle stages of pharmaceutical product development, regulatory approval, and distribution. A historical overview of the role of the pharmaceutical industry in medical practice is given, describing the development of medicines regulation and technical standardization of the pharmaceutical product development process. Similarly, it offers an overview of how standardization and regulation of the clinical trials process

provided the basis for adoption of evidence-based medical practice, and for the solidification of the role of industry in medical knowledge production interpretation, and application to clinical practice. A detailed enumeration of laws and regulations which govern the pharmaceutical product development process on the international and national level, as well as pharmaceutical industry self-regulation and codes of conduct regarding medicines advertising, present the legal framework within which industry-medicine relationships are governed, while medical codes of ethics present the textual base for medicines self-governance in practice. Additionally, the recent implementation of transparency codes requiring the disclosure of industry payments to healthcare providers and healthcare organizations is introduced. The technical and regulatory process behind medicines development, authorization, and distribution presents the structural basis for the analytical chapters which follow. Ensuing analysis follows the process of drug development, evaluation, authorization, and distribution, and assesses how the macro, meso, and micro levels of medical autonomy are executed within the drug development process in industry-medicine relationships.

Chapter 6: Industry Corruption of Medical Knowledge Production

This chapter is the first of 4 analytical chapters in this thesis. Chapter 6 will discuss the relationship between industry and medicine in basal and academic research bolstered by the pharmaceutical innovation crisis and international policy to promote public-private partnerships between industry and medical research institutions. The prominence of technology transfer in medical research, as well as the dominance of industry funding of clinical research and the reliance of medicine on pharmaceutical companies to fund research, presents a reformulation of the means by which medical research benefits society. Proliferation of industry funding of medical research increases risk of bias in clinical trials. The instrumentalist view of clinical testing is argued to negate physicians' attention to questions of ethicality in clinical trials. Following the pharmaceutical innovation crisis, industry strategies of limiting expenditure, and the trends of outsourcing clinical trials pursues the investigation of Clinical Research Organizations (CROs) in clinical trials execution. These CROs, working for industry, exert pressures for performance on medical professionals, lessening the control of researchers over the execution of a clinical trial.

Chapter 7: Between Knowledge Production and Knowledge Interpretation

This chapter explores a less researched arena altogether, which is the point where the stages of medical knowledge production and pharmaceutical drug development merge with medical knowledge interpretation and the stage of pharmaceutical drug evaluation. Beginning first with an analysis of post-authorization Phase IV clinical trials, this chapter discusses the function of Phase IV studies for increasing the external validity of preclinical trials conducted in a controlled setting. This vital function of post-approval research is said to be abused by pharmaceutical companies as a tool to increase prescription of an authorized drug (i.e. trials with marketing incentives), instead of collecting data about real-life medication use, and has earned these trials the pejorative label of 'seeding trials'. Physicians are unaware of, ill-equipped, or

unwilling to identify the marketing incentive behind seeding trials, given that the instrumentalist view of medical research, and the desire to contribute to medical research, substitute for a critical evaluation of marketing incentives, and two smaller case studies are provided to illustrate this claim. This analysis then evaluates whether marketing incentives manifest in pre-authorization clinical trials, and provides another case to describe how seeding trials also erode professional trust among physician colleagues. This assessment is then followed by data which discusses the role of national medicines regulatory agencies in providing doctors with evidence of drug safety and efficacy (the interpretation and evaluation of clinical trial data). Interview accounts show how current medicines approval processes contribute to the instrumentalist view of medical research, and the proliferation of seeding trials.

Chapter 8: Interpreting Science into Practice: Institutional Corruption of Medical Knowledge Interpretation

The activities of medical knowledge interpretation, the evaluation and interpretation of clinical trial data for its use in practice, is evinced in the standardization of evidence-based medical practice. Respondents were asked to evaluate EBM in practice and how this restricted or improved medical treatment decisions. Three vehicles of medical knowledge interpretation were identified in the practice of EBM; the use of medical guidelines, the importance of medical expert evaluation, and the obligation to participate in accredited continuing medical educational (CME) events. Each vehicle of knowledge interpretation was assessed in relation to the new-found role of the pharmaceutical industry in medical education. Medical guideline independence is examined from the perspective of availability and nature of the evidence which is implemented in the guideline, and pharmaceutical industry influence regarding medical guideline authorship. By way of respondent triangulation, a Dutch case study was undertaken, which reveals the financial and professional relationships between medical guideline authors and pharmaceutical companies. The second vehicle of medical knowledge interpretation manifests in a professional trust in the opinions of medical experts – also known as medical Key Opinion Leaders. Analysis argues that the KOL status is not a status devised by the profession alone, but is consolidated by KOL financial agreements with pharmaceutical companies. The pharmaceutical industry is then capable of exerting influence by proxy, by concealing marketing under the trust afforded by KOL expert status. Finally, industry funding of medical educational events will present arguments for industry influence over the content of CMEs, by way of financial dependency on the pharmaceutical industry. Presented in secondary data analysis from the Netherlands, and data not yet presented or analysed in this manner from Hungary will be offered as regards Medical Associations' financial dependency on industry funding of CMEs. A final link is made regarding financial links between medical associations and pharmaceutical companies in an argument of conflict of interest, in that medical guidelines are issued, evaluated, and adopted by the financially dependent Medical Associations.

Chapter 9: Institutional Corruption of Medical Knowledge Application

The final stage of pharmaceutical product distribution will be examined with regard to its institutional corruption of medical knowledge application. Gleaned from fieldwork, this chapter introduces coping strategies of medical professional regarding the immense amount of scientific medical information that must be evaluated by individual physicians. I will argue that too much information creates a propensity to devise modes of access to information which place emphasis on quantity over quality of information. Two important information sources were identified by respondents; continuing medical educational events, and information supplied by pharmaceutical sales representatives. While CMEs are mandatory for doctors to attend, participation is a costly endeavour, and financial contributions to individual doctors is seen as the only viable means of accessing CMEs, paid to doctors in the form of hospitality costs. An examination of pharmaceutical industry codes of ethics reveals that formal doctrine establishes some form of definition as to what would constitute a rational amount for hospitality contributions, as well as formally designating a preference for funding to go towards physicians' participation in events of a scientific quality and an independent nature. Research data, however, shows that such formal textual designation of CMEs has little validity in the real-life interpretation of doctors regarding the quality or objectivity of events, the accreditation system substituting professional evaluation of quality and independence of an event for an emphasis on quantity - the attainment of credits required for medical licensure. Pharmaceutical sales representatives present a visible form of industry-medicine relationships, and although touching upon their use of seductive marketing tactics in direct-to-physician advertising, this chapter evaluates the sales representative as an informational coping strategy for professionals, and an important gateway to the industry coverage of CME attendance previously described. The sales representative is also the most criticized form of industry influence, and this chapter will conclude that scrutiny of doctors for fostering relationships with detailers, and for receiving financial support for CME sponsorship, prompts doctors to devise methods of concealing and confounding the financial trail of industry hospitality payments by abusing the loopholes of the very regulation that was implemented to promote payment transparency.

Chapter 10: Conclusion

Chapter 10 presents the conclusion of this thesis, readdressing the research question which sought to examine how industry-medicine relationships induce the institutional corruption of the medical profession. In the evaluation of all the data presented in the analysis, I present a challenge to myself and the validity of the claim of institutional corruption, posing an argumentative question; patients still trust the profession of medicine, and medical professionals still succeed in maintaining patient well-being. How then can one conclude that medicine is not achieving its institutional purpose, and that industry-medicine relationships have institutionally corrupted the medical profession? In a final evaluation of the entirety of the analysed data in its procedural context, I present the arguments for institutional corruption by institutional design, and inadequate means-ends pairing in the work breakdown structure, the goal motivation,

and formalization and communication features of industry-medicine relationships. Revisiting the primary theoretical claim, that institutional corruption is manifest in the relationships between industry and medicine, and not within the outcome of the relationship itself, inadequate means-ends pairing sanctifies any means in pursuance of a working goal. While the purpose of the institution is served, the constriction of means by which to achieve a goal may increase the risk of the distortion of means ethicality, thereby sanctifying institutional purpose achievement by the use of harmful means, which inevitably spills over into institutional purpose distortion. The analysis is re-examined in this light, concluding with the argument that industry-medicine relationships result in the institutional corruption of the medical profession.

CHAPTER: 2 LITERATURE REVIEW

2.1. CORRUPTION IN THE HEALTHCARE SECTOR

The World Health Organization (WHO) provides very general concepts of health systems, health services, health service delivery systems, and health workers. Healthcare definitions for the WHO begin with the definition of health itself: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (Preamble to the Constitution of the World Health Organization, 1948). A globally applicable definition concedes a broad interpretation of a health system – but as allocated by the WHO, requires "a robust financing mechanism; a well-trained and adequately paid workforce; reliable information on which to base decisions and policies, well maintained facilities and logistics to deliver quality medicines and technologies" (WHO website). A system of healthcare thus differs from country to country, similarly in Europe and the European Union (within which this research is conducted) where systems of healthcare delivery are left to national governments to devise. The system of healthcare delivery, and the healthcare sector are different terms, while the systems (modes of finance, workforce, salaries, policies, facilities, and logistics) may differ, healthcare as a sector is defined as "an economic and social sector concerned with the provision, distribution, and consumption of healthcare services and related products" (EC Study, 2013, p. 15). Good healthcare delivery systems and efficiency of the healthcare sector (local and global) is continuously assessed by international organizations both regarding progress in healthcare delivery as well as its shortcomings – such as a concern with economic interests, both public and private, having undesirable effects on the actual delivery of care to patients such as access to medicines, high prices of vital medication, healthcare insurance coverage, and national healthcare expenditure.

In 2010 under the WHO "Good Governance for Medicines Programme", Baghdadi-Sebeti and Serhan (2010) addressed the issue of "corruption in the pharmaceutical sector" in a public report, assessing the entire pharmaceutical product delivery chain and the identification of "unethical and corrupt practices" which impair medicines access and drive up healthcare expenditure. The delineation of the term "corruption" in the WHO GGM programme adopts that of the 2006 Transparency International Global Corruption Report (TI GCR), which focused specifically on healthcare corruption, and used the following definition:

"Transparency International defines corruption as 'the abuse of entrusted power for private gain'. In the health sphere corruption encompasses bribery of regulators and medical professionals, manipulation of information on drug trials, the diversion of medicines and supplies, corruption in procurement, and overbilling of insurance companies. It is not limited to abuse by public officials, because society frequently entrusts private actors in health care with important public roles. When hospital administrators, insurers, physicians or pharmaceutical company executives

dishonestly enrich themselves, they are not formally abusing a public office, but they are abusing entrusted power and stealing precious resources needed to improve health" (TI GCR, 2006, xviii).

Taking on this comprehensive definition of corruption in healthcare, the WHO has identified unethical practices and corruption to manifest within and along the entire medicines delivery chain. The image below illustrates the stages in the medicines chain and the practices which impede proper medicines delivery processes (Baghdadi-Sebeti & Serhan 2010, p. 2).

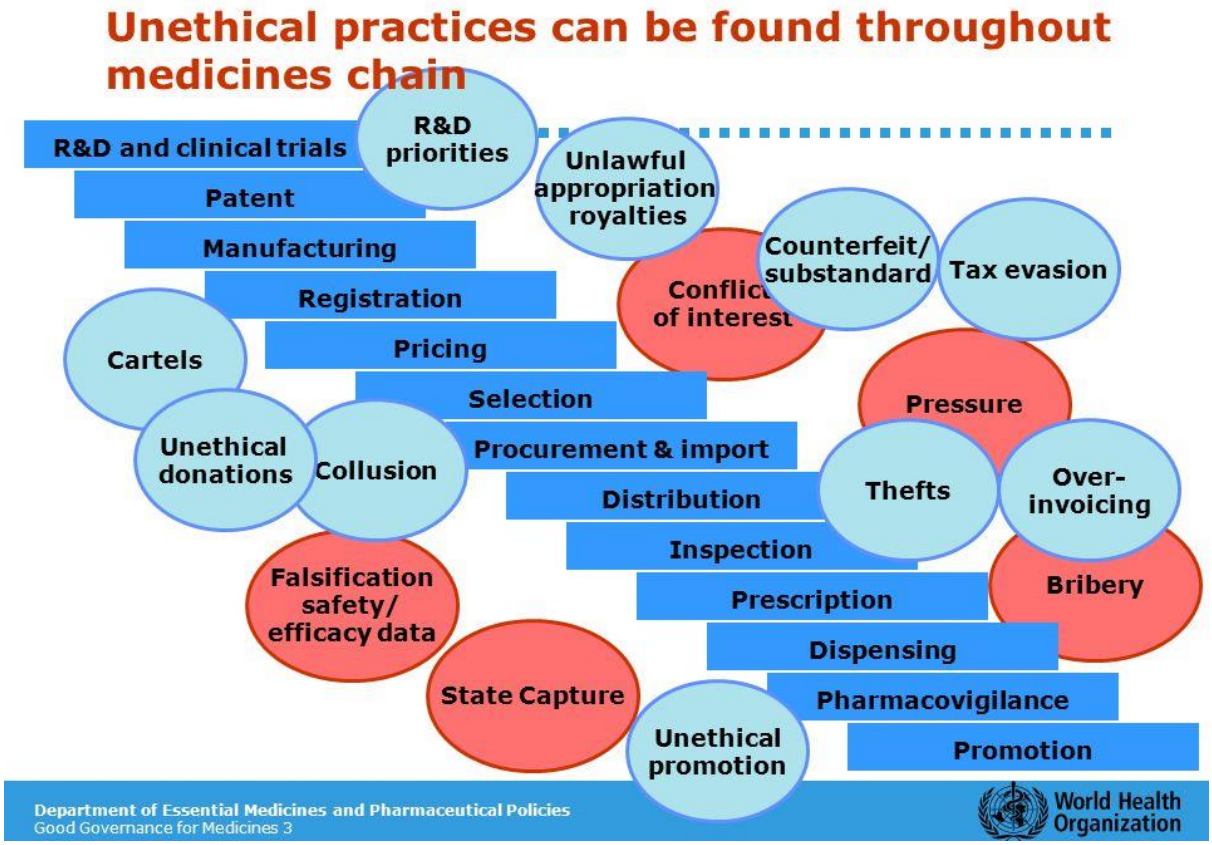


Image source: Baghdadi-Sebeti & Serhan (2010) *WHO Good Governance for Medicines Programme: an innovative approach to prevent corruption in the pharmaceutical sector.* World Health Report Background paper 25.

That corruption is more than just abuse of public power for private gain in healthcare will be discussed in the theoretical chapter because the issue of the concept's definition and applicability in organizational crime research is still debated. However, for the time being, the image above shows that there is a very complex process behind drug delivery, and corruption manifests along the entire chain – pharmaceutical advertising and drug promotion, considered to be the dominant arena of industry influence, is but only the tip of the influence iceberg. The role of the pharmaceutical industry in the healthcare system is significant, given that access to medicines, availability of medication for rare diseases, medicines pricing and consequently national healthcare expenditure, are linked to pharmaceutical companies. Having a monopoly over the

medicines market, being one of the most profitable industries in the world, and occupying a cornerstone position in medicines development, manufacture, and distribution, makes the industry a vital healthcare actor, but one which possesses an incredible amount of influence within healthcare service delivery, influence which some argue is more than desirable. Undue influence or the ability of pharmaceutical companies to sway healthcare decisions and outcomes which benefit their economic interests has to do with the monopoly over medicines (Silverstein & Taylor, 2004), which means private control over a product that fulfils a public interest.

In 2013, the European Commission (EC) published its report on "Corruption in the Healthcare Sector" and took an approach that sourced corruption types based on healthcare actor relationships. Thus instead of allocating specific stages (activities) in the medicines delivery chain, healthcare actor identification and actor relationships were used as the corruption typology baseline, identifying the risk of corruption manifesting itself within the diverging interests of each actor. Note that this study defines the "industry" to include pharmaceutical companies as well as medical device companies and intermediary companies. The traditional corruption definition – abuse of public power for private gain – is once again stretched to "encompass 'aspects that go beyond the criminal law aspects, thus including situations such as conflict of interest, favouritism, etc.' Most definitions of corruption stress the involvement of two willing actors – the corrupter and the corrupted. This differentiates corruption from fraud, which can be committed by one single actor" (EC Study 2013, p. 17).

Main actors	Typology	
Provider – Patients	Bribery in medical service delivery	Typology 1
Industry – Providers	Procurement corruption	Typology 2
Industry – Providers	Improper marketing relations	Typology 3
Industry – Regulators	Improper marketing relations	
All actors (except patients)	Misuse of (high) level positions	Typology 4
Providers – Payers	Undue reimbursement claims	Typology 5
Providers	Fraud and embezzlement of medicines and medical devices	Typology 6

Source: EC study (2013) *Corruption in the Healthcare Sector*, p.51

What is particularly interesting is that the EC study did not intend to include so-called "improper marketing relations" between industry actors and healthcare providers within its study, despite undue pharmaceutical influence being most obviously manifest in direct-to-physician advertising (Norris et al, 2005; Mintzes, 2005, 2012;

Spurling, et al., 2010; WHO/HAI Collaborative Project, 2010). It was only during interviews conducted for the study in 28 EU member states that researchers acknowledged improper marketing relations described by respondents as too prevalent to be disregarded. This is slightly ironic since improper marketing relations, or industry influence via promotion to doctors as problematic for medical practice, was already addressed by a study conducted by the World Health Organization (WHO), and the NGO Health Action International (HAI) 9 years earlier. The WHO-HAI publication (Norris et al., 2005) presented its findings on drug promotion, a study born of an attempt to build and publicly make accessible a database containing "books, journal articles, magazine and newspaper stories, articles from drug bulletins/newsletters, video, radio and television transcripts, and guidelines from organizational and professional bodies" (Norris et al., 2005, p. 3) in an endeavour to create the first database to make accessible all that is known about drug promotion and its influence over clinician decisions.

The publicly accessible database which was up and running in mid-2002 is no longer available, however the study itself offers an extraordinary literature review answering the questions of 1) what attitudes lay and medical professionals have towards drug promotion, 2) how promotion affects attitudes and knowledge, 3) what impact promotion has on behaviour, and 4) what promotion-counteracting interventions have been attempted. In brief, the study itself is revealing as to what research (the database containing articles from 1970 till roughly the year of publication) has been executed. The WHO-HAI meta-analysis is inconclusive, calling for much-needed further studies. Although no determinate conclusions could be drawn, the issue of influence via promotion was indeed introduced as an opportunity by which industry could not only exert influence, but also manipulate doctors by providing false or misleading advertising, increase healthcare costs by increasing prescriptions, and induce irrational prescribing behaviour which could have negative consequences for patients (Norris et al., 2005).

Presumably the initial intention to disregard improper marketing by the 2013 EC Study was because advertising itself is completely legal. This type of corruption could be classified neither as procurement corruption, nor as bribery in medical service delivery, but respondents in the study claimed that the influence of industry actors over prescription policies and practices of healthcare providers is the most problematic element in the industry-provider, and industry-regulator relationships. Further assessment led to the study identifying subtypes of improper marketing relations, as well as its features – the direct influence of prescribing behaviour through either quid-pro-quo deals or indirect influence through creation of loyalty to a company product, exerting undue influence over positive list promotion, and influence within the medicines or medical device authorization processes. The modes of influence can be present in the exchange of money and/or gifts, paying physician hospitality costs (conference attendance), sponsorship (research or equipment) and consultancy

contracts. These are not categorically corrupt behaviours, but hold potential for undue influence and thus improper marketing relations (EC Study, 2013, p. 74)

The EC study is a good starting point for further research but it is the only European Union study of its kind. Being part of the EU Anti-Corruption Package adopted in 2011, it highlighted corruption in the healthcare sector as an area that should be monitored within EU Member States and complemented the EU Commission Anti-Corruption Report published in 2014. However, the Anti-Corruption Report, which was scheduled to be published every 2 years, was dropped by the EU Commission (Nielsen, 2017). In a letter to the chair of the EU Parliament's civil liberty committee, and the Presidency of the Council of the European Union, Frans Timmermans questioned the necessity of further such reports, being that the first study was deemed immensely successful in initiating a process of change. "While the first report was useful in providing an analytical overview and creating a basis for further work, this does not necessarily mean that a continued succession of similar reports in the future would be the best way to proceed"[1] (25 January 2017). Transparency International (TI) was not as convinced of the decision (Nielsen, 2017) and has not let the matter rest. In June 2016 TI published its own research on "Corruption in the Pharmaceutical Sector" under the TI Pharmaceuticals & Healthcare Program. Similarly to the WHO-HAI study (Norris et al., 2005), TI examined corruption along the medicines chain (TI Study 2016a), interviewing 37 key informants and supplemented the analysis with case studies. The TI study is slightly more descriptive regarding industry influence in the medical profession, broadening the concept of marketing influence to include manifestations in medical research (post-marketing studies) and industry sponsorship of CMEs, in addition to traditional advertising practices (sales representatives). Thus marketing takes on a malleable understanding, extending to influence outside of defined advertising practices.

TI published another, more categorical study "Diagnosing Corruption in Healthcare" (TI Study, 2016b), building on its prior publication and which included media report analysis, a literature review, an online anonymous survey, and interviews with industry compliance officers, healthcare fraud and corruption investigators, and specialist physicians. It identified 37 types of corruption in the healthcare sector "clustered into 8 categories": health system governance, health system regulation, research and development, marketing, procurement, product distribution and storage, financial and workforce management, and delivery of health services. A focus on pharmaceutical industry criminality spurs further anti-corruption initiatives and studies, especially healthcare actor and medical service delivery chain orientated inquiry, and these are profoundly important in that such studies place pharmaceutical industry criminality in the larger context of the healthcare system. These studies and reports address industry criminality not purely as a corporate attribute, but one which sees corruption as an opportunity that arises within a complex system: corruption as opportunity and not an inherent corporate evil. Additionally, the role of healthcare professionals in healthcare

[1] http://transparency.eu/wp-content/uploads/2017/02/20170130-Letter-FVP-LIBE-Chair.pdf

corruption, and in particular physician conduct, is receiving critical attention. The TI studies (2016a, 2016b) see medical research and development, consultancy contracts between industry and physicians, sponsorship of medical educational events and physician attendance, and advertising to physicians, as instances where undue influence, conflict of interest, and corruption may occur.

Establishing that corruption is rife in the healthcare sector, the problem identification comes with an initiative to conjure a solution, or reduce opportunity for corruption. More often than not, and especially in cases where research and analysis is taken up by international bodies such as the WHO, HAI, the EC, and TI, solutions seek to expand upon already existing definitions (i.e. corruption), or development of additional regulation, guidelines, or policies that sanction, control, or minimize corruption. Although revealing as these studies are, a regulated systems perspective runs the risk of viewing healthcare delivery systems as a mechanical functional process. The actors identified within the healthcare system are much more complex entities fulfilling also ethical roles, and each institutional actor is endowed with goals or interests which produce the basis of an institutional goal towards which institutional members work. Informed by the aforementioned studies, this thesis moves to focus in-depth on the relationships between the pharmaceutical industry and the medical profession.

2.2. CORPORATE CRIME IN THE PHARMACEUTICAL INDUSTRY

Pharmaceutical companies and the pharmaceutical industry as a collective is defined as those companies "involved in production, distribution and consumption" (EC Study, 2013, p. 15) of "any chemical substance intended for medical diagnosis, cure, treatment or prevention of disease" Directive 2004/27/EC In: EC Study 2013, p. 40). The criminogenicity of the industry is well documented; Braithwaite's (1984) study on corporate crime in the pharmaceutical industry is the first and most comprehensive empirical criminological analysis of industry evils and concludes that "the pharmaceutical industry has a worse record of international bribery and corruption than any other industry (…), a history of fraud in the safety testing of drugs (…), and a disturbing record of criminal negligence in the unsafe manufacture of drugs (…) (Braithwaite, 1984, p. 5). The pharmaceutical industry has become a classroom poster child for corporate and white collar crime students, given that its actions epitomize crimes such as fraud, antitrust, collusion, corruption, bribery, and illegal marketing. The victims and harms generated by these crimes are identifiable – patients suffering health deterioration and sometimes even death. For pharmaceutical companies the responsibility for aligning business decisions with societal interests comes with the "particular monopoly" they possess over medicinal products. Monopolies over "(utilities in particular), have historically been recognized as different and are subject to more stringent requirements" (Silverstein & Taylor, 2004, p. 260).

The subject of pharmaceutical industry deviance has not been limited to the outsider criminological or academic study; insiders have published their own accounts of just

how bad the industry really is. Marcia Angell, former editor in chief of the New England Journal of Medicine (one of the most prestigious scientific medical journals to this day) published a damning exposé of drug industry business practices: inflating drug research and development costs in order to hike drug prices, feigning innovation and product improvement, abusing patent regulation to extend market monopoly, concealing bribery as philanthropy, and feeding advertising through educational and scientific funnels (Angell, 2004). Drawing on 21 years of experience at the NEJM and being a qualified medical doctor, Angell's book shatters the image of a socially responsible industry. Ben Goldacre, epidemiologist and advocate for clinical trial data transparency and condemner of "Bad Science" (2008) and quackery, assessed in a similar vein the deceptions of "Bad Pharma" (2012) with emphasis on the industry's manipulation of medical research and clinical trial technical design. Goldacre advances criticism with suggestions as to what can be done by doctors and patients alike, and goes further than pure industry condemnation, implicating a failed commitment to accessibility, transparency and independence of scientific data by academic medicine, professional medical organizations, medical ethics committees, medical journals, and regulators (Goldacre, 2012).

Pharmaceutical industry misconduct has been documented in case study analyses which focus on single pharmaceutical scandals such as the likes of Thalidomide (Knightley et al., 1979) or Vioxx (Nesi, 2008), exposing multiple crimes in a collection of industry cases (Law, 2006; Gøtzsche, 2013) or executing research into a specific medical profession – psychiatry being one of the common targets (Healy, 1997, 2004; Whitaker 2001, 2010; Whitaker & Cosgrove, 2015) – or exposed by whistle-blowers documenting personal experience of criminality at specific pharmaceutical companies, such as Pfizer (Rost, 2006) or Hoffman La Roche (Adams, 1984). Dukes et al. (2014) revisit all the crimes of pharmaceutical companies, from fraudulent and biased research, unsafe drug manufacturing, unethical and illegal marketing practices, manipulation, corruption, counterfeiting, fraud, antitrust, racketeering, price fixing and cartelization, and conclude with 10 lessons to learn. Pharmaceutical (corporate) crime "kills and defrauds" and these practices are "getting worse". While there are employees who remain committed to ethical conduct, lack of protection for whistle-blowers dissuades them from "speak(ing) out". Companies will often turn to "scapegoating" when accused of criminality and the "complexity of transnational pharmaceutical production" allows evading accountability and obstructs general understanding and awareness. Regulators must adopt a multi-stakeholder approach in the issuance of regulatory controls, because legal loopholes provide opportunities to "game the law". Corporate Social Responsibility of pharmaceutical companies should be an obligatory requirement. The reduction in truly innovative drugs coming to market will affect not only industry profitability, but provides opportunity to challenge the industry's basal argument of maintaining high drug prices to ensure R&D investment returns. (Dukes et al., 2014, pp. 275-278).

The picture painted is not just of industry criminality, but of a worsening phenomenon suggesting that the boundaries of industry evil are elastic. As to a solution, increasing

regulation and tightening standards seems to be the only answer, albeit creative forms such as substituting sanctions for incentives to adhere to the law and the interests of patients, public shaming of companies, and increasing public and regulatory awareness as to industry deviance are argued for (Dukes et al., 2014). One of the most drastic measures is a call for the reformation of the drug patent system, eliminating much of the deviance which comes from patent exclusivity competition, or "sequestration" (Schafer, 2004) which advocates that financial relationships between industry and medicine should be severed completely. The arguments for sequestration are spurred by the indignation with the industry playing a much more prominent role in medicine than some see as proper. Silverstein and Taylor (2004, p. 255) call it an "influence industry" which manipulates with money. The financial power of industry is often seen as the source of all evil deeds; the industry's thirst for riches motivates transgressions of the law, and the possession of money softens the blow of retaliation.

Peter Gøtzsche, epidemiologist, head of the Nordic Cochrane Centre and an ex-industry insider, sees industry criticism as only one side of the story, claiming that while continued industry malfeasance has scathed healthcare, these devastating crimes of industry are rarely possible without active contribution by physicians (Gøtzsche, 2013). His book, which alleges an already "corrupted healthcare" in the subtitle, is an unapologetic criticism describing how pharmaceutical companies disregard patient interests and buy-off individuals, professionals, institutions, organizations, and regulators who should constrict the abandonment of patient interests for the industry's pursuit of profit. Upon providing clear, and concisely argued descriptions of the crimes of industry, the "system failure" of healthcare actors is described as a phenomenon where "The control of medical practice by market economics does not serve the needs of patients very well, and is not compatible with an ethnically based profession" (Gøtzsche, 2013, p. 264). Reform, in Gøtzsche's view, is possible only by ensuring the independence of academic medicine and clinical trials from pharmaceutical industry funding, revaluation of clinical trial design, public funding of drug regulatory agencies, increased evidentiary requirements in drug approval decisions, transparency of clinical trial data, introduction of financial conflict of interest transparency and enforcement of incompatibility clauses, and the eradication of industry control which is exerted predominantly through monetary influence. These studies, memoirs, journalistic investigations, case studies, and professional accounts challenge company slogans of pursuing patient well-being above all else. That corporations care only about the bottom line, is not a revelation since media, and popular culture has made sure that the 'wall street wolves' and corporate criminals are exposed. Less easily accepted is that medical professionals are unable to ensure that our medicines are really helpful, and that their inability is rendered by industry influence which permeates medical practice. Industry influence as having infiltrated medicine to the point of coercion is a discussion which is condensed within academic medical literature, largely comprising doctors, writing about doctors, for doctors.

2.3. UNDUE INDUSTRY INFLUENCE IN THE MEDICAL DISCOURSE

Although criminogenic itself and prone to exploiting its monopoly over medicines, industry criminogenicity is also described in terms of its ability to unduly influence other actors in the healthcare sector – exercising influence predominantly with financial seduction. Undue influence over the activities of the medical profession has generated a large body of literature, which describes this phenomenon, most of which can be found in medical journals, medical ethics journals, and business management publications. Often focusing on the fiscal power of industry, medical professionals recognize that "This excessive financial capacity and the associated political and lobbying power allow the industry to dictate the rules of the healthcare game to serve its interests at several levels. The industry's interests are often at stark contrast to those of the patients and the society" (Stamatakis et al., 2013, pp. 1-2). Industry funding of medical activities is prolific, and Lexchin's (1993) assessment of the medical literature locates industry influence to be manifest in the activities of 1) company funding of clinical trials, 2) company funding of continuing medical education (CME), and 3) information received by doctors from pharmaceutical sales representatives.

Pharmaceutical companies fund the majority of clinical trials across the globe (Atal et al., 2015), and they are estimated to finance 70-75% of clinical trials in the United States (Bodenheimer, 2000; Chopra, 2003; Sismondo, 2007, 2008). In the EEA and the European Union, about 61-79% of clinical trials are sponsored by pharmaceutical companies (EurdraCT official statistics, EMA website). That industry funds the majority of clinical trials also results in industry skewing medical research to focus on answering questions which benefit sponsors rather than addressing societal needs (Angell, 2000, 2004; Lewis et al., 2001; Gøtzsche, 2013) funnelling money into research which has a higher probability of producing a marketable drug than developing new knowledge. Apart from controlling the subject of research, industry-funded clinical trials have a higher probability of producing results that are favourable to the sponsor than trials that are financed by other non-industry sources (Davidson, 1986; Ridker & Torres, 2006; Lexchin et al., 2003, 2012; Sismondo, 2007, 2008; Stamatakis et al., 2013; Lundh et al., 2012; Lundh et al., 2017). Clinical trial design may predetermine the production of positive data (Dukes et al., 2014; Lexchin, 2012; Goldacre, 2012; Brown, 2013). Seife (2015) assessed clinical trials that had received a classification of Official Action Indicated (OAI) by the US Food and Drug Administration – an AOI is the most severe classification given if inspection of a clinical trial is found to have "objectionable conditions or practices significant enough to warrant regulatory actions" (Seife, 2015, p. E2). Trials that were found to have cases of falsification of information and adverse drug reaction reporting, clinical trial protocol violations, bad record keeping, and problems with maintaining patient safety and informed consent, were given OAI classification. The study outcome was not purely violation identification in trials, but under-reporting of these violations in the peer-review study publications. Although industry funds the majority of clinical trials, this study did not assess any correlation with clinical trial sponsors, and there is no

evidence to suggest that the quality of industry-funded clinical trials is better or worse than independent studies (Lexchin, 2012). Errors in a clinical trial may manifest in both industry and non-industry sponsored studies, however Davidson's (1986) analysis did reveal that promoting positive results of clinical trials was a common tendency in industry-funded research. His suggestions see physicians' unwillingness to raise issue with funding preference, or the design of trials so as to generate favourable outcomes, as something induced by a fear of investment termination if results fail to impress the sponsor. The literature on industry influence in psychiatry is particularly condemning, claiming that data establishing the ironic link between the use of anti-depressants and increased suicidal tendencies has been purposefully covered up by pharmaceutical companies (Healy, 1997, 2004; Whitaker 2001, 2010; Whitaker & Cosgrove, 2015). Uncertain or problematic data from clinical trials has also been identified in other areas of medicine; cardiology (Simvastatin: Greenland & Lloyd-Jones, 2008a, 2008b), reproductive medicine (Hormone Replacement Therapy: Fishman, 2004), endocrinology (Diabetes, Rosiglitazone: Cohen, 2010; Drazen at al., 2007), and analgesic medication (Vioxx: Hill et al., 2008)

There are also other means of trial result distortion which does not require deliberate data manipulation. Melander et al. (2003) correlate industry funding of clinical trials to publication bias in medical literature by methods of selective publication, selective reporting, and pooling clinical trial results i.e. hiding a negative result under many positive results, or publishing single articles on an unsuccessful trial while publishing multiple articles on a successful trial. Bias in peer-review literature has raised the issue of conflict of interest between pharmaceutical companies and study authors. Ross et al., (2008) document how drug company Merck paid prominent doctors to write favourably about the company's drug Vioxx for example, or companies may simply pay doctors for their names – listing them among the publication's authors, despite not actually contribution to the research. The latter is known as ghost-writing, wherein pharmaceutical company employees write an article, and doctors are paid to add their names as authors, providing the article with an academic validity. Ghost-writing, however, is very difficult to prove, and is often limited to case studies such as Vioxx (Ross et al., 2008), Prempo (Fugh-Berman, 2010), Zoloft, Paxil, Seroxat, and Neurontin (McHenry, 2010), although the phenomenon is considered a general problem (The PLoS Medicine Editors, 2009; Gøtzsche et al, 2007).

Ghost-writing is linked to the well-documented phenomenon of conflict of interest in financial relationships in the form of consultancy agreements between reputable names in the medical profession and pharmaceutical companies, studied under the aegis of the Key Opinion Leader (KOL) phenomenon (Moynihan, 2008; Moynihan et al., 2002; Dukes et al., 2014; Sah & Fugh-Berman, 2013; Sismondo, 2013). This particularly deceptive form of influence relies on the status and professional recognition of experts in the field, who are sought-out and paid by companies to promote their products in medical journals, conferences, and medical educational events (Liberati & Magrini, 2003). Not only are KOLs described as industry spokespersons but also as industry

pens, since these KOLs are also called upon to author medical guidelines (Choudhry et al., 2002; Moynihan et al., 2002), and Medical Associations which issue both codes of ethical medical conduct and clinical treatment guidelines are also heavily financed by pharmaceutical companies for the organization and realization of Continuing Medical Education (CME) which doctors are mandated to attend (Rothman et al., 2009; Stamatakis et al., 2013; Rodwin, 2012, 2013; Field & Lo, 2009; Brennan et al., 2006; Moynihan, 2003).

Industry influence is most heavily described in the advertising and seduction tactics employed by pharmaceutical sales representatives (also known as detailers) to coax doctors into prescribing a particular drug. Doctors are many times the beneficiaries of free merchandize and other perks offered by companies, the most visible being the small gifts and company brand-name embellished paraphernalia; pens, notepads, stress balls, calendars etc. which adorn the offices of physicians, usually left there as a token after a visit by a pharmaceutical sales representative. Numerous researchers have drawn correlations between the number of sales representative visits and changes in prescribing habits (Wazana, 2000; Oldani, 2004; Chimonas et al., 2007; Watkins et al., 2003; Fischer et al., 2009; Norris et al., 2005). Advertising works, and although doctors are confident about the insignificance of a pen, social psychology suggests that even gifts of small value can produce feelings of sympathy, reciprocity, and loyalty towards a company (McFadden et al., 2007; Sah & Fugh-Berman, 2013). The giving of gifts has been subject to stringent regulation in the US and more recently in Europe, however sales representatives are able to talk doctors into accepting gifts, or persuade them without gifts by employing conversational tactics such as reminding doctors of their personal sacrifices – lengthy education or serving the public (Sah & Loewenstein, 2010) and thus dignify feelings of deserving of perks offered. Detailers are also trained in various conversational methods, the likes of which Edwards (2011, p. 31) calls “anecdote circles” which involves drawing out “stories” to initiate friendly conversations while evading subjects that may cause confrontation, building trust and sympathy from the doctor.

These studies are as important as they are astounding, and the reader may start to sense that industry influence in medicine is prolific, extending further than just the practice of medicine in the clinic, and comprises far more than the sales representative and influential advertising. Influence extends to the manipulation of medical science and research, as well as medical guidelines, medical literature, and CMEs. Industry influence is generally described as an external pressure from the outside, its ability to influence medicine is due to its financial dominance, whereby it exerts influence by holding hostage the money that is needed to conduct medical activities (executing research, publishing papers, and organizing medical conferences and educational events) or by using money as a tool, relying on the cardinal sins of human avarice and vainglory to inveigle doctors into sacrificing or disregarding their duty to patients and society. Although riches, power, and status are tempting to acquire, an approach that describes undue influence as an individual fall from grace supports a simplistic

explanation of people being an amalgam of good and bad, and behaviour as being the product of effective titillation awakening an inherent dual disposition. Additionally, influence as explained by individual susceptibility to the economic power of the pharmaceutical industry strips physicians of their agency, seeing medical professionals as puppets who are unaware and helpless in the face of influence. Inquiring into the validity of medical professional weakness brings to the fore a discussion on medical control over its profession, as well as its demise, which is studied in most detail within the medical sociological literature.

2.4. REFLECTIONS ON THE MEDICAL SOCIOLOGICAL LITERATURE ON THE "CHANGING NATURE OF PROFESSIONAL CONTROL"

Scholarly literature has brought the legitimacy of medical autonomy and dominance under question, discussed as the phenomena of (de)professionalization, proletarianization, bureaucratization, industrialization, and corporatization of medical practice (Cheraghi-Sohi & Calnan, 2013; Calnan & Spyridonidis, 2011; Calnan, 2015; Sullivan, 2000; Lee & Tham, 2014; Rastegar, 2004; Rees, 2008; Sah & Fugh-Berman, 2013). Criticism towards the legitimacy of medical autonomy proposes that "the organization of clinical care is more a matter of politics than medical expertise" (Rees 2008, p. 390), and that the growing complexity of bureaucracy and healthcare management has changed the role of the physician. As such, the physician has become a "stranger" who provides service on behalf of a corporate manager (Lee & Tham, 2000); industrialization, standardization and corporatization have reduced the medical profession to an externally-controlled executive entity acting upon cost-benefit and efficiency incentives rather than traditional Hippocratic ideals (Sullivan 2000; Rastegar, 2004). Integrity requires that "one's actions should be consistent with one's beliefs, values and commitments" (Marks, 2013, p. 10), and restrictions in autonomous practice may disrupt medical integrity. Relman (1980) analysed the rise of healthcare as a for-profit service, and named this as the emergence of a "new industry-medicine complex" which he defined as the "large and growing network of private corporations engaged in the business of supplying healthcare services to patients for profit" (1980, p. 963). The medicine-industry complex or the industrialization of medicine, argues that a decline of medical professionalism, autonomy, authority, and professional dominance has occured. The loss of autonomy and the rise of business in medicine are reflected in the evolution of medicine as a self-controlling profession, and "Bureaucratic organization is assumed to be antithetical to the freedom of activity traditionally imputed to the professional" (Freidson, 1984, p. 10).

Modern medicine as we know it today, its organization, as well as its professional dominance, traces its history to the development of Western Medicine in the late 1800s. Until the end of the 19th century it was solely doctors that concerned themselves with the organisation of clinical practices, of treating patients, and making advancements in medical technology, but the practice of medicine was still

characterised by enormous uncertainty, different treatments succeeding more on a whim than on proven efficacy, and largely not successful enough to warrant monopoly over the ability to cure (Cockerham, 2016). It was during the 19th and 20th centuries when the profession of medicine sought to institutionalize its societal, economic, and political power, ultimately envisaged in the right to dominate the content of, as well as the right to self-regulate, medical practice (Freidson, 1970). The medical profession aimed to achieve dominance over work by exercising control over the number of physicians through reformation of medical education and licencing requirements, and by gaining economic protection by the state from other healthcare practitioners. This control over professional work eventually led to doctors establishing private practices (fee-for-service), determine qualification standards for physicians, and curb any external parties from dictating the circumstances of the doctor-patient relationship. Until this point, the professional nature of medicine, although based to some extent upon generally accepted medical knowledge, was still fighting for legitimacy over monopoly of practice. The eventual consolidation of professional power came after World War II (Timmermans & Oh, 2010), an era known as the "golden age of doctoring" (McKinlay & Marceau, 2002; Calnan, 2015), and was largely indebted to advances made in the science of bacteriology and germ theory (Louis Pasteur and Robert Koch) which lead to the identification of the origins of many diseases such as typhoid, tetanus and diphtheria. It was this scientific revolution and the discovery of penicillin by Alexander Fleming in 1928, which provided the scientific-technological basis for the solidification of professional dominance. Doctors achieved complete autonomy over their practice by both institutionalization of the profession under the aegis of Hippocratic norms, as well as grounding itself on a body of scientifically-founded knowledge.

The golden age of doctoring, the achievement of professional dominance, power, and control over the field, and the practice of medicine, ironically lead to its demise. Light (2001) describes the conflict occurring between the medical profession and the state as the conflict that resulted from the medical profession being allowed to create demand, through its ability to control the subject of its practices. "Medicine advanced rapidly and a growing number of social problems, such as unruly children, alcoholics, political dissidents, and others, became medicalized and treated with drugs, surgery, or other techniques." (Light, 2001, p. 1157) While hailed for its contributions to societal health, the medical profession was seen as creating its own demand, and thus contributing to the rise of healthcare costs; the monopoly over healthcare provision allowed physicians to abuse their position for profit (Timmermans & Oh, 2010; Light, 2001). Autonomy sought by the medical profession ended up becoming its enemy, with fee-for-service driving up healthcare costs while individual physician autonomy allowed for the profit motive to simultaneously maintain the inconsistencies of healthcare delivery (Light, 2001, 2010), ultimately eroding the trust in the altruistic qualities of the medical profession. To cut back on healthcare spending, and remedy the inequalities of healthcare delivery, as well as hold physicians accountable for their practices, government regulators introduced managed care, as well as different

systems for replacing the fee-for-service model by cracking open the protected professional market through private insurance schemes. (Timmermans & Oh, 2010; Light, 2001). This process, beginning in the 1970s, led to what medical sociologists call the end of the "golden age of doctoring", and this is also the period when sociological inquiry took to the analysis of the medical profession and its ability to retain its autonomous nature. The advancement of medical knowledge, however, is also characterized by ambiguity and uncertainty (Karreman et al., 2002; Abraham, 1997); treatment and care are infused with many risks to patients that, despite best intentions, may be unforeseen by the medical professional. Bureaucratization in this sense can be considered an answer; an operative intention to stabilize uncertainties and reduce risk to both patients and physicians. Standardization in quality assurance, and the introduction of clinical guidelines in this sense alleviates the possible negative implications of full autonomy, namely the great variations in medical care provided by physicians of the same specialization (Rees, 2008; Rastegar, 2004). An example of this debate is the study by Cheraghi-Sohi and Calnan (2013) examining whether the implementation of a Quality and Outcomes Framework (QOF) in the practice of General Practitioners (GPs) in the UK affects individual physician discretion in daily practice. GPs were generally convinced as to the benefits of a standardization system and saw it as a necessity for equality in treatment. However, other GPs were concerned that "[QOF] changes the concept of consultation", patients then complaining of the impersonal nature of GP visits, while healthcare management creates pressure that ultimately directs focus away from the patient to constantly thinking about the bureaucratic 'to do' list (Cheraghi-Sohi & Calnan 2013, p. 55). The debate regarding the degree of management and quality control in medical practice is still on-going; however bureaucratic management is not the only challenge to medical autonomy. The erosion of the professional autonomy of medicine is also expressed in the arguments about deprofessionalization and proletarianization. These two concepts describe the relationship of the medical profession in relation to the public (deprofessionalization), and in relation to the institutionalization of medicine and state controls over the provision of healthcare (proletarianization)

The deprofessionalization thesis, developed by American sociologist Marie Haug (In: Calnan, 2015; Light & Levine, 1988; Freidson, 1984) asserts that the trust in, and prestige of, physicians is eroded as a consequence of losing the monopoly of medical knowledge. Due to modern forms of storing and accessing information (such as via a computer), as well as the overall increase in the education of the general population, patients now question the decisions their doctors make and do not comply with doctors' orders simply due to the fact that they don a white coat. Deprofessionalization is also documented in the study of the "expert patient" or the "informed patient" (Abraham, 2010) as well as the rise in patient activism through forms of patient organizations which describe the role of the patient as an active client in the healthcare system (Patient empowerment: See case study on the medicalization of Morgellons Disease, Fair, 2010). The proletarianization argument on the other hand focuses on the relationship between professional control over medical practice, and state control with

regards to standardization of healthcare service delivery – emphasis being placed upon the loss of medical autonomy due to the changing qualities of professional work within large organizations. The proletarianization of medicine asserts that the autonomous qualities of the medical profession – determining the content of medical practice, the manner in which it is carried out, and what the goals of professional work should be – are diminished (Freidson, 1984). Proletarianization rests on the concept of the bureaucratization of professional work in large organizations whereby the evolution of managed care, quality assurance schemes, and standardization of medical practices has diminished the control of the medical profession over medical practice (Salmon et al., 1990). These controls have in turn created a rise in a managerial elite charged with bureaucratic oversight of physicians, their existence and control over the practical components of healthcare delivery further undermining medical autonomy regarding both self-regulation and individual clinical decision-making (Calnan & Spyridonidis, 2011; Kennedy, 2015). This process is also known as bureaucratization – "healthcare systems are policed as bureaucratically managed social needs hemmed in, distorted and constrained by state administration, fiat pricing and budget constraints, underpinned by the ideological architecture of 'cost-benefit 'analysis: in short, by the politics of money" (Kennedy, 2015, p. 214), or corporatization – described as extensive control over medical practice initially aimed at standardization of work to limit excessive differentiation among practices, but consequently reducing the work of doctors to line workers on the medical factory floor (Light, 2010; Light & Levine, 1988). Corporatization is seen as the result of the decline in fee-for-service models of healthcare service delivery, and a move towards a trend of doctors becoming salaried employees (McKinley & Marceau, 2002).

In a provocative article, Freidson (1984) challenges and defies both these argument, first dismissing deprofessionalization claims by stating that although medical knowledge may be increasingly accessible to the lay public, deprofessionalization would only hold true if this knowledge was not constantly evolving. Freidson claims that the constant development of novel medical technologies means that the medical profession will "thus continue to possess a monopoly over at least some important segment of formal knowledge that does not shrink over time, even though both competitors and rising levels of lay knowledge may nibble away at its edges" (Freidson, 1984, p. 8). Turning to the critique of the proletarianization thesis, Freidson first claims that although the tendency of moving from self-employment to employment by the state is clearly visible in the case of doctors, this cannot be seen as a devolution of medical autonomy, but rather that the medical profession is embracing the normal circumstances of all traditional professions (medicine, law, the military, the clergy, and teaching), for which self-employment was never a defining characteristic. Addressing the rise of the supervisory managerial elite Freidson does not claim the opposite, but as to hijacking medical self-regulation and self-supervision, criticism is found in that the study of the bureaucratization of medicine in formal organizational settings has left scholars of this theory blind to the fact that the managerial elite is still born of the profession of medicine. The positions that execute control over the work

processes of physicians are still filled by members of the profession namely; other physicians. As a result, the bureaucratization of medicine as understood to be external administrative control over the profession of medicine, is actually the formalization of professional controls which strengthens professional domination over medical practice, as opposed to the claims of its demise. “While the nature of professional control has changed, it remains largely dominated by the professions themselves, although it is limited, as is always the case, by the resources allocated to the support of professional work by the state, by the governing boards of firms and other institutions, by managers, and individual clients.” (Freidson, 1984, p. 13)

The arguments surrounding the loss of professional control over the content and execution of professional work are far from conclusive, however Freidson’s assertions are echoed within sociological inquiry which states that although there are challenges to medical autonomy the profession of medicine has, and seems to retain despite external pressures, the ability to adapt and preserve its autonomous nature. The organized profession of medicine has since the 2000s, “mounted campaigns to restore their professionalism and lost trust” (Light, 2010, p. 270) basing this on the reinstatement of the culture of Hippocratic medicine and thus remaining a focus in sociological analysis.

How then is it possible that in the face of government restrictions, bureaucratization and the emergence of the more autonomous patient, medicine remains steadfast but is seemingly so easily influenced by the economic incentives of the pharmaceutical industry? The discussion above has illustrated that despite the restrictions and reinterpretations of medical autonomy within modern healthcare systems, the medical profession still shows incredible resilience to external controls. However, the sociology of medicine has left the relationship between the profession and the pharmaceutical industry, and the effects of this relationship on medical autonomy, on the sidelines of inquiry. Relman’s (1980) framework of the “medical-industrial complex” chose to eliminate the study of the effects of private companies on the practice of medicine. This was perhaps due to industry being taken to fall outside of the sphere of the evolution of organized medicine, since pharmaceutical companies are market-driven entities which, at first glance, have nothing to do with the professional status of the physician organization. “They [pharmaceutical companies] have been around for a long time, and no one has challenged their social usefulness” (1980, p. 963).

The elimination of the effects of the pharmaceutical industry on the profession of medicine is quite a curious stance, especially due to the incredibly vital role that the industry played in the eventual solidification of professional autonomy in the “golden age of doctoring”. With the discovery of penicillin, and mass production of antibiotics, the profession of medicine established its professional dominance, but also established its relationship with the pharmaceutical industry. The age of antibiotics was the beginning of the unity *between* industry and medicine, as well as the importance of

industry *in* medicine, and initiated the age of "miracle drugs" in the 1940s, with a "marriage between science and marketing" (Timmermans & Oh, 2010, p. S100). Among the first companies to research, develop, and mass produce antibiotics were Abbott Laboratories, Lederle Laboratories (Pfizer), Merck & Co., E.R. Squibb & Sons (Bristol-Meyers Squibb), and Glaxo (GlaxoSmithKline), and were the companies that contributed to the research and development of what would be known as the greatest breakthrough in modern medicine (Quinn, 2013; Aldridge et al., 1999). The potential of the pharmaceutical sector regarding its large-scale role in medical service delivery became solidified when physicians increasingly turned to clinical research for scientifically-established medical practice (Light, 2010; Bothwell et. al., 2016). "From the development of insulin in the 1920s, through the "wonder drug" revolutions of sulpha drugs, steroids, antibiotics, tranquilizers, antipsychotics, and cardiovascular drugs in the ensuing decades, the American pharmaceutical industry had come to play a dominant role in the public understanding of medical science, the economics of patient care, and the rising politics of consumerism" (Greene & Podolsky, 2012, p. 1481).

It has, however, occurred that the role of the industry within medicine remains confined to the idea that industry produces and sells drugs, while the medical profession retains its professional control and discretion over the production of medical knowledge and its application in clinical care (Kitsis, 2011). This designation of roles of industry and medicine in healthcare service delivery is arguably not valid anymore. The rise of the pharmaceutical industry in the provision of medicinal products has affected the functional tasks of the profession of medicine. Being an intermediary between the industry and the public, the medical profession should maintain the interests of the public in the face of a market-orientated industry. In its very basic form, the pharmaceutical industry pursues the goal of profit accumulation by way of developing, manufacturing, and selling its products, while the intermediary position of the medical profession means that physicians retain an additional role as being the breaks within the profit-driven healthcare market. Light (2010) describes this role whereby the profession of medicine, through professional power, monopoly, autonomy, and ethical conviction, should be the stopper on capitalistic endeavours of the pharmaceutical industry. The analysis of the "profession-and-markets" in relation to medical autonomy, authority and ethical conduct has remained neglected compared with research on "risk, illness, and treatment" (Light, 2010, p. 270) and seen as a result of the sociological tendency to focus on the "powerless rather the powerful" (Busfield, 2006, p. 299). Additionally, one of Freidson's 3 myths of medicine (I argue) also contributes to a hesitance when analysing the profession of medicine; the myth being that doctors are the only ones capable of stating anything of validity about their practice and the healthcare system, because only they are in possession of the specialized knowledge required for analysis (Freidson, 1983). Social scientists thus may be fearful of evaluating physicians and the intricacies of the hard sciences. The vast literature available on industry influence over medicine can be found predominantly in scientific medical journals, and quite a few of the publications are

written by those with an MD qualification. It is certainly daunting to pass judgement on a profession, which I also found difficult to do, however I shall elaborate on this in the methodological chapter.

2.5. EDGING TOWARDS A THEORY OF ORGANIZATIONAL CRIME

> "*In the medical profession, which here is used as an example because it is probably less criminalistic that some other professions, are found illegal sale of alcohol and narcotics, abortion, illegal services to underworld criminals, fraudulent reports and testimony in accident cases, extreme cases of unnecessary treatment, fake specialists, restriction of competition, and fee-splitting*". (Sutherland, 1940, p. 3)

Sutherland (1940) revolutionized the study of criminology by stating that researchers should include in their repertoire of inquiry the study of white collar criminals – respected and high-status individuals whose crimes are conducted with the use of, and/or during the course of, their legitimate occupations (Sutherland, 1940, 1945, 1983). Sutherland challenged class-based explanations of criminality (Shapiro, 1987; Braithwaite, 1984) and the association of misbehaviour with low income and little social status. Seeking to develop a general theory of criminality, Sutherland claimed that behaviour, even that which is criminal, is learned through social interaction, thereby infusing deviance with favourable connotations (Brooks, 2016). Sutherland's argument was challenged as an abuse of the position of criminologist and as entailing the arbitrary demarcation of anti-social conduct as criminal (Tappan, 1947), spurring further questions of whether white collar crime should be considered as set-apart at all, its qualities bearing much resemblance to organized crime (Croall, 2001). Nelken highlights the "seven ambiguities" surrounding the subject of white collar crime research – focusing on the definitional flaws of the white collar crime concept, whether it should be seen as crime at all, insufficiencies of motive explanations (greed and power), congruence with traditional criminality, lack of sanctions and institutional response, whether white collar crime is an indicator of social change, and ensuing problems regarding the extent of white collar crime control strategies (Nelken, 2012, pp. 627-651). The reason I accept the criminal label for white collar criminality (despite lack of criminal law enforcement or consideration of outcomes as such) is due to Nelken's (2012) assertion that these white collar crimes are not new crimes produced by capitalism, but that the capitalist system produces new *ways* of committing old crimes.

Despite the daunting task of researching a phenomenon so fragile in its conceptual, definitional, and theoretical basis, criticism and scepticism did not stifle the attention to, or necessity of, studying crimes committed by powerful, privileged, elite or professional actors (Liazos, 1972), even if additional fine-tuning of Sutherland's original definition was needed (Clinard & Yeager, 1980; Braithwaite, 1985; Shapiro, 1987, 1990; Kramer et al., 2002; Ball, 2006; Slapper & Tombs, 1999). White collar crime, despite its disputed state, is used today as an umbrella term for crimes

committed by legitimate organizations, their occupational professional members, governments, and powerful individuals; "at a minimum" white collar crime includes the study of corporate crime (crimes committed by an individual to benefit the corporation, their person, and crimes of the corporation itself), occupational crime (crimes committed "within the context of a legitimate, respectable occupation"), governmental crime (crimes committed by government officials, agencies, and the government itself), state-corporate crime (a white collar "hybrid" crime involving the actions of government, corporate, and occupational crime), and residual white collar criminality (enterprise, contrepreneurial, techno- and avocational crime) (Friedrichs, 2010, pp. 6-7).

With attention to crimes of the powerful comes an approach which debates another fundamental question of white collar and corporate crime not addressed sufficiently by Sutherland, namely the question of whether the unit of analysis ought to be either the organization as an actor or the behaviour of people within it. Sutherland spoke of white collar crimes, but then took to analysing corporations, and described companies as criminal recidivists (Sutherland, 1983). The study of corporate crime, however, acknowledges that there are cases in which the identification of one individual as criminal (i.e. the white collar or occupational) is impossible. Take the cases of Nick Leeson and Bernie Madoff as examples of individual white collar criminality (Nelken, 2012), while the sinking of the Herald of Free Enterprise (Goulielmos & Goulielmos, 2005) and the Challenger spaceship disaster (Vaughan, 1996, 1997) reveal the inability to single out one culpable individual. "Corporations don't commit crimes, people do" (Martin, 1985 cited In: Cressey, 1986, p. 43). Some authors consider it a weakness of corporate crime research that without a conscious mind there can be no intent to commit crime, without a body there can be no criminal action committed. This is an important question with regards corporate criminal liability, since criminal law relies on *mens rea* and *actus reus* as a basis for culpability. Colvin (1995) categorises 2 approaches, the nominalist – which sees the corporation[2] as a collection of individuals who are criminal and corporate blameworthiness as a myth, while on the other end of the spectrum the realist approach argues that corporations can be found guilty in ways that are very different than that of individual guilt (see also: Stewart, 2012; Gómez-Jara Diez, 2011; Gobert & Punch, 2003). Coleman (1982), however, argues an important point for corporate crime, in that individual culpability would hold true were it not for the "irrelevance of persons" in large organizations. It is not people but positions, and the ability to fulfil the requirements of an occupation that are necessary, making individual personality the lesser requirement (Coleman, 1982, pp. 103-104).

[2] Corporation is a term used to denote companies, multi-nationals predominantly in the US. However, here corporation should also be taken to mean organization as Hall (1999, p. 30) describes it to be "a collectivity with a relatively identifiable boundary, a normative order (rules), ranks of authority (hierarchy), communications system, and membership coordinating systems (procedures); this collectivity exists, on a relatively continuous basis in an environment, and engages in activities that are usually related to a set of goals; the activities have outcomes for organizational members, the organization itself, and for society".

Individual-orientated approaches produce other limitations in the study of white collar and corporate crime; the neglect of studies evaluating organizations as victims, research concerned only with the large, for-profit entities, a failure to analyse how an organization itself produces criminality, too much focus on the study of organizational control from solely the perspective of enforcers and regulators, and the treatment of administrative transgressions as criminal law infractions (Reiss & Tonry, 1993). With regards to medical malfeasance, crimes within the medical profession are described as criminal actions perpetrated by the medical professional within the confines of his/her capacity as a physician (Jesilow et al., 1985). These acts of criminality include conduct such as; prescription violations (prescribing unnecessary drugs or treatment so as to reap additional financial benefits), conducting illegal abortions, fee-splitting (referral to medical specialists based not of competency but willingness of a physician to split the fees of specialist treatment with the doctor who referred the patient) and Medicare and Medicaid abuse (insurance fraud) (Sutherland, 1940; Jesilow et al., 1985; Hoffman, 2009; Price & Norris, 2009; Miller, 2013). There is less inclination to study medical unethicality, deviance, or crime in the context of the professional organization, the institution of medicine. Perhaps due to the incredible amount of individual autonomy possessed by a physician, or the lived experience of medical practice being limited to the doctor-patient relationship in a clinic, the medical profession is rarely approached as a unit of analysis, as a professional organization, a system, or an institution. Although the crimes of doctors listed above are committed by a single person or a small group of colluding physicians (and thus explain the focus on perpetrator and action) an approach which extends to the analysis of physicians' crimes in the context of the healthcare system may provide more insight into motives other than individual malice.

It is this train of thought that scholars have followed to divert focus away from individual versus organization conundrums in an approach that examines criminality as a product of the environment within which individual action is conducted and reproduced. Organizational criminology takes such a stance. Already touched upon in Coleman's (1982) explanation of the unimportance of individuals in large organizations, organizational criminology focuses on organizational qualities that potentially coerce, facilitate, neutralize, or moralize behaviour. Scholars have taken to assess the organization itself as providing the means, motive, and opportunities for its members to commit crimes, and espouse organizational characteristics as crime instigators. The complexity (organizational size), culture (individual identity, depersonalization, coveting of risk-taking, recklessness, leadership and offensiveness), and emphasis upon the attainment of organizational goals (pressure to perform, neutralization, rationalization, and promotion of amorality) are some of the organizational traits that provide the means-motive-opportunity triangle for criminal conduct (Punch, 2000, pp. 254-275). Organizations may also be viewed as "metaphors"; tools to produce a certain outcome (machine metaphor), the organization as an organism (the fight for survival), as a cultural system, a psychic prison, or a

continuously changing entity (Robbins, 1990, pp. 6-9) which will implicate the behaviour, duties, and expectations of their members.

These studies suggest goal attainment to produce an organizational culture within which certain behaviours are expected. Criminality is thus redefined as simply normal behaviour within an organizational context (Benson, 1985; Nelken, 2012). The goals of the organization are seen to prescribe and justify the means by which they are attained, and criminal conduct is easily translated into normal, necessary, and even ethical behaviour within the confines of the organizational context. Needleman and Needleman (1979), however, propose that while criminal conduct may be an expected mode of organizational goal attainment, normalization of otherwise criminal conduct is not a necessity. The authors describe "two models of criminogenicity" in which legal transgressions are recognized as criminal (eliminating neutralization, rationalization, or denial of wrongfulness) but are either desired (crime-coercive organizations) or tolerated (crime-facilitative organizations) forms of behaviour. Analysis of organizational policies, practices, and hierarchical as well as collegial relationships between members sheds light onto organizational norms and behavioural expectations impressed upon its members, and reveals how the supra-individual organizational culture may determine behaviour. In some cases it is the permitting of creative means for realising rigid goals that may produce deviance. Lippens (2001) suggests that organizations are today less bureaucratic, not controlled by formal and impersonal rules, but are transitioning into a post-bureaucratic age, wherein informal rules and decentralization allows for more dynamic and creative thought. As such, organizational moralities become loosely defined – "which are exploited according to the context of specific tactical performances" (Lippens, 2001, p. 326).

Organizational expectations and behavioural norms of goal attainment outlive the individuals themselves, and organizational criminology challenges the focus upon individual responsibility, especially in cases where the criminal outcome is the product of multiple actions of distant individuals separated in space and time, and allows for further developments of organizational culpability. The dangers, however, are imposition of complete culpability to the organization solely. For this research white collar crime and corporate criminality inform an approach that sees crime as not confined to legislative doctrine, as well as the view that criminal conduct is committed by powerful and legitimate occupational actors. Organizational criminology then advocates a supra-legal assessment of crime without blaming solely the individual actor. However, in this thesis there is additional twist: the study of influence in the profession of medicine, within the structure of industry-medicine relationships along the medicines delivery chain. The medical profession is the focus of this research but it must be assessed as to its relationship (context) with industry, and how professional goals are impeded from realization. As I discussed earlier, the delivery of healthcare, of medicine to the public, begets stages of interaction between industry and medicine. Thus these collisions between industry and medicine, and how the practice of medicine is thus shaped as regards its societal duty, are central to this thesis.

CHAPTER 3: THEORETICAL ELABORATION AND CONCEPTUALIZATION

> "*After many years of spirited disagreement, sociologists now agree to disagree about the appropriate definition of white-collar crime.*"(Shapiro, 2005, p. 279).

The definition of white collar crime has outgrown Sutherland's initial conceptualization; however, as illustrated in the above quote, there is still much contention as to the exact definition of the term itself. Although the continued focus on the phenomenon of white collar crime has resulted in a diversification of typologies of "crimes of the powerful" (Barak, 2015) white-collar, occupational, corporate, state-corporate, technocrime etc. (Friedrichs, 2010), the vehement focus on the qualities of the potential perpetrators (Shapiro, 1990) reproduces the same problems of Sutherland's original white collar crime definition – "The requirement that a crime cannot be a white collar crime unless perpetrated by a person of "high social status" is an unfortunate mixing of definition and explanation, especially when Sutherland used the widespread nature of white collar crime to refute class-based theories of criminality" (Braithwaite, 1985, p. 3). This type of offender-centric definition leads us to question whether it does not inadvertently result in the same kinds of generalized and stereotypical associations – such as the link between poverty and crime – among powerful actors i.e. power and money lead to crime, all those on Wall Street are criminals, all politicians are crooked, etc.

The offender-based allocation of criminality typology is not unfruitful, but does prove hazardous, especially for adaptation of such definitions to different organizational or professional contexts. This research will draw from white collar and corporate crime research, but will be attentive to the problems of offender characterization which reduces crimes and points fingers of blame to individuals and their actions and motives. Since this research focuses on the weakness of the medical profession in maintaining its professional interests in pharmaceutical-industry relationships, it is important to emphasize an embedded approach to explaining behaviour, lest we misunderstand the intention of this research and simply turn our pitchforks away from pharmaceutical companies to doctors.

3.1. SACRIFICING HOMO-RATIONALE FOR EMBEDDEDNESS

> "*I seem to be thinking rationally again in the style that is characteristic of scientists. However, this is not entirely a matter of joy, as if someone returned from physical disability to good physical health. One aspect of this is that rationality of thought imposes a limit on a person's concept of his relation to the cosmos*."
>
> – John Forbes Nash, Jr.

Shapiro advocates an approach to studying white collar crime not from the perspective of the offender as per individual or organizational qualities, but rather to focus on the actions themselves. In her article "Collaring the crime, not the criminal", Shapiro intends to "liberate" (1990, p. 346) the concept of white collar crime from the very approach that reproduces class-bias in both the legal system and systems of social control. This liberation comes with the focus on the "fiduciary duties of those in position of trust" (Shapiro, 2005, p. 279) and the abuse of this trust by fiduciaries as the core identifier of white collar crime.

Today one cannot execute all tasks and achieve all goals without requiring some form of additional outside help to be called upon. Obligations of law, economy, desires, and duties of citizens in post-industrial societies have produced a rise in the service industry; the requirements to execute multiple tasks and meet several obligations sometimes simultaneously, has produced a need to seek out and employ the services and knowledge of others to accomplish these goals – in a sense producing a society of middlemen. Our daily functioning as individuals, as a collective, or organizations depends on the structural networks of other individuals, collectives, organizations, that execute tasks on our behalves. A social relationship ensues between a **principal** – that which requires execution of a task or achievement of a goal, but lacks the capabilities or knowledge to do so – by investing "resources, authority or responsibility" in an **agent** – that which acts on behalf on the principal – for the attainment of the desired task or goal (Shapiro,1987, p. 626).

This description of social interaction is based on Granovetter's (1985) proposition that social behaviour cannot be interpreted outside of social relations, interaction and context. Accordingly, the ignorance of context and dynamic social relations leads to under- and/or oversocialized explanations of behaviour. An undersocialized view asserts that man's sensitivity to what others think of him, results in a consensually-formulated general (moral) norm which is internalized to the extent that obedience to it is not considered arduous. An oversocialized veiw of man assumes behaviour to be a product of individual self-serving motives and as such can only be controlled through the use of "institutional arrangements like contracts or authority structures" (Shapiro, 1987, p. 624). Both the undersocialized and oversocialized explanations are based on an "atomized" depiction of man. "Actors do not behave or decide as atoms outside a social context, nor do they adhere slavishly to a script written for them by the particular intersection of social categories that they happen to occupy" (Granovetter, 1985, p. 487). Behaviour must be seen from the approach of embeddedness which views behaviour to be a product of dynamic and mutable social relations.

Embeddedness asserts that behaviour and social action relies on social exchange, initiation of which is based on familiarity, referral, consistency, reciprocity – in short: trust. Trust is not clearly defined by either Shapiro or Granovetter, but intentionally so, for the literature on trust would place the authors at a crossroads as to assuming either the psychological definition of feeling and/or emotion, or defining trust as

property (formal obligation) of either interacting party created via reciprocity and consistency of exchange (Shapiro, 1987). Granovetter argues that trust is produced through continued, proven, constant interaction, and is a necessary baseline characteristic for social interaction to ensue. Even when two actors do not have trust as produced by familiarity, the agreements (contracts) drawn up between them are functional substitutes of this familiarized trust (Granovetter 1985). Shapiro (1987) however takes trust in the 'Granovettian' sense (common networks as the basis of behaviour production) as a sufficient motive but not a necessary prerequisite for interaction in principal-agent relationships. Reasoning that knowledge and information asymmetries between principals cannot always be bridged by familiarity, and that the knowledge and information asymmetry that plagues the principal renders monitoring of the agent impossible, trust is located in a fiduciary obligation of the agent towards the principal (Shapiro, 1990, Newhouse, 2014). Explanations of behaviour as embedded in the social network structure and the necessity of principal-agent engagement to bridge the gap between task and capability formulate the basic approach of this study, which sees the relationships between pharmaceutical companies and medical professionals as a necessity born of knowledge and capability asymmetries. Since research focuses on how this relationship affects the behaviour of medical professionals, this research further proposes that the behaviour of medical professionals can be explained as embedded in the social and organizational structures which characterize the professional medical relationships with pharmaceutical companies.

Agents, being providers of services to execute a task are complex players, entrusted with furthering their own interests, as well as being entrusted with furthering the interests of multiple principals, attracting principal investments – principals being "one-shotters" and agents being "return players" (Shapiro, 2005, p. 267). Additionally, the role of principal and agent is also complex in that the role of agent and principal are not static, especially in complex organizational relationships, or in hierarchical chains where the execution of a task is a process accomplished by more than one actor, the realization of which requires an approach that negates simple interpretations of behaviour as a cause and effect scenario between 2 actors – "The assumption that complex organizational structures and networks can be reduced to dyads of individuals is one of many assumptions—regarding efficiency and equilibrium, that individuals are rational and self-interested utility maximizers prone to opportunism, etc.—that are off-putting to other social sciences" (Shapiro, 2005, p. 266). As such, multiple interests, as well as simultaneous roles of being agents to one and principals to another, characterize these relationship networks. This is where the importance of trust and fiduciary obligation come in as a paradoxical element, since knowledge asymmetries induce interaction, but also present the opportunity for abuse to emerge. This is the crux of trust, simultaneously oiling interaction, as well as making the waters murky. Return on invested resources is not instantaneous, and the time these returns (goals) take to be attained, as well as how they are attained, are not necessarily within the comprehension of the principal. The opportunity for an agent to stray from the

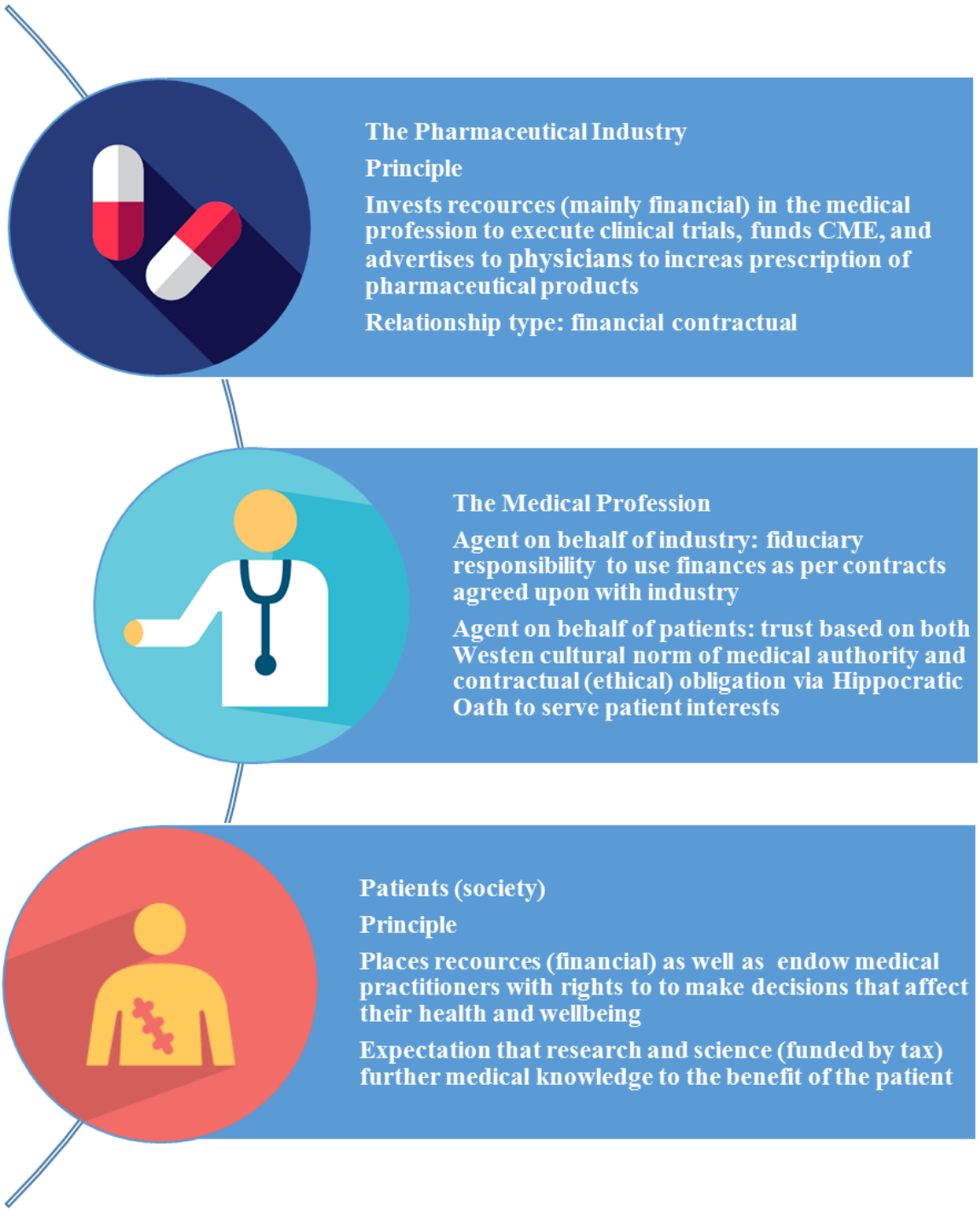
commitments made to the principal may arise, remaining hidden from view of the principal. The abuse of this trust and exploitation of its concealing properties is what Shapiro identifies as white collar crime (Shapiro, 1990; Vaughan, 1999)

Of course the argument about whether an interest should or should not be represented presents another question to address: which interest should be pursued, and is the pursuit of one interest nobler than pursuit of the other? Shapiro (1990) cites the whistle-blower as an apt example – the whistle-blower who is caught between the interests of the organization within which s(he) fulfils a role and obligation, and the society of which s(he) is a part i.e., a 'Snowden perplexity'. Without (for the time being) defining which interest should be furthered, taking interest as a neutral artefact Shapiro highlights requirements of interest attainment which must be present for trust be produced and maintained in a fiduciary relationship – 1) disclosure, 2) disinterestedness, and 3) role competence – the violation of which manifests the violation of trust. A further specification of violation of trust criteria is pragmatically evinced in the crimes of lying (misinterpretation, deception, exaggeration, omission, distortion, fabrication, falsification) and stealing (misappropriation, self-dealing). Corruption is listed as a crime, and defined as an "alternative form of theft" by way of renting out and selling positions of trust to outsiders. Role conflict is also listed under crimes of stealing, but is described rather as an inductor of theft in that conflict of interest ultimately comes with the pursuit of multiple interests by an agent, and as an "intrinsic vulnerability that gives rise to stealing" (Shapiro, 1990, pp. 352-353). Again, for the moment treating interests as neutral artefacts, I will take to describing the interests embedded in the healthcare delivery system.

3.2. PRINCIPAL-AGENT RELATIONSHIPS BETWEEN INDUSTRY AND MEDICINE

For this thesis, the principal-agent relationship is vitally important when placing the medical profession into the context of its relationship with pharmaceutical companies, its role as a profession, and its duties to patients. In this research the core question addressed is how industry is capable of influencing the medical profession, and why influence is successful, while simultaneously challenging explanations that would blame singular medical professionals as being susceptible to varying degrees based on their individual convictions to (medical) ethical ideals. As I approach this question, the profession of medicine must be placed into context. Identified by the literature on actors within the medicinal (pharmaceutical) delivery chain, the following actors present the backbone of this delivery structure: the pharmaceutical industry, the medical profession, and patients. The reason for allocating these actors specifically is due to the prior assessment of industry-medicine relationships taken to be crystallized in industry funding of medical research, industry funding of CME, and advertising via pharmaceutical sales representatives, as discussed in the literature review. It is not for perpetrator allocation but for identification of relational networks in the pharmaceutical product supply chain that these actors are specified, and for the

illustration of principal and agent roles. Patients, not the focus of research (fieldwork), are included in the theoretical elaboration, for they are the principals whom both medicine and industry serve, from a medical, ethical as well as service/product provision aspect.



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This visualization provides a simplified example of how the medical profession and its role as an agent manifests in the pharmaceutical product delivery chain. This research is limited to assessing the role of the profession of medicine as agent, although as Shapiro (2005) notes, the roles of agent and principal are not static, and both roles may be fulfilled by all actors depending on the knowledge and information symmetry that is to be bridged with regards to the goal that is pursued. For example the pharmaceutical industry may also fulfil the role of agent for the patient, since the monopoly of industry over pharmaceutical product research, manufacture, and distribution, means that expectations of the patient such as medicines safety, efficacy, accessibility and affordability must be met. Similarly, the research and development of products that address unmet medical needs is also a valid patient interest expected to be fulfilled by medical scientists and pharmaceutical industry R&D endeavours. Although alleviated from direct analysis and incorporation into the research sample, patient interests (societal obligations) form the wider independent contextual variable, within which this study of industry-medicine relationships is placed. It is also important for claims as to the fiduciary obligations of the profession of medicine, which I shall elaborate on in the coming sections, which are the basis of trust, autonomy, and authority of professional medical conduct, and the conceptualization of the theoretical framework for this research.

As Shapiro claims and as is illustrated here, we can speak of interests as multifarious, and in their most comprehensive form are the profession of medicine's mandate to further the contractual and reciprocal expectations of industry, providing a return on industry investment (research funding, CME support, and advertising), while simultaneously furthering the interests of provision of care to alleviate, manage, or mitigate the disease burden of the patient (research, self-education, and delivery of informed and good care). Given that principals cannot oversee the actions of the agent for reasons of knowledge and information asymmetry, principals may employ methods of agent restriction, such as: choosing to avoid agents (jack of all trades), choosing to engage with personal networks (colleagues, friends, family), drawing up legally-binding contracts, requesting reports by agents, monitoring their activities, offering the agent a stake in a successful outcome, or spreading risk and maintaining insurance coverage for agent deviation (Shapiro, 1987, 1990). However, there are limitations to these methods of restricting agent discretion, since too many restrictions may impede principal goal attainment by the agent. Additionally, since agents are return players, and if relationships are episodic, principals vary while agents remain the same, allowing agents to dictate many of the rules of engagement (Shapiro, 1990, p. 349). Agents are also in physical possession of principal property, and agency services are often difficult to restore to their original state e.g. surgery (Shapiro 1987, p. 635). For this research, it will be interesting to keep in mind that undue influence would suggest that despite the agent's supposed power to dictate the terms of agreement, the profession of medicine, according to the literature previously discussed, is unable to do so. This begs the question of: why? Shapiro argues that principal-agent relationships are rife with interest divergence, explaining that the service provision

business of agents pits their survival on continued principal investment, and as such they seek to attract continued investors who all seek interests of their own. While principal-imposed limitations may protect one interest, furthering interests of other principals simultaneously may lead to unavoidable interest collision. One cannot outright state that the interests of pharmaceutical companies and the interests of patients inherently diverge, but prior literature has shown that the economic interests of the industry, and the interests of patients, similarly cannot be said to coincide entirely. This is what Shapiro defines as an inherent conflict of interest in principal-agent relationships, and why the profession of medicine should act as mediator between industry and patients.

An approach that favours embeddedness as opposed to the under- or oversocialized explanation of action, declares the need to analyse conduct, behaviour, and decision-making as the products of social interaction. Social interaction is induced by knowledge and information asymmetries present in the principal-agent relationship. And an embeddedness approach views trust as both the base of proper, ethical, as well as improper, unethical or deviant conduct. I have discussed how the medical profession in this research is taken to be assessed from the position of agent, and have roughly outlined what interest the profession of medicine must further, based on the fiduciary obligations it has to patients and industry alike, as well as discussed how the requirements of disclosure, disinterestedness, and role competence ensure that trust is maintained – the violation of which would constitute white collar crime. Shapiro lists these crimes as lying and stealing, encompassing corruption as a form of stealing and role conflict acting in opposition to one's fiduciary duties.

There is, however, an element of white collar crime research which appears in Shapiro's approach, and is also common in white collar and corporate crime studies, which I propose unintentionally reroutes the argument of embeddedness, and "relational approaches" (Jancsics, 2014) in white collar and corporate crime studies, back to the atomized interpretation of human action. This I find to best understood in explanations as to why investigation and prosecution of these "crimes of the powerful" (Barak, 2015) are so elusive. The most prominent of these explanations, one which is probably the most difficult to overcome, is the characteristic of being hidden behind closed doors (Croall, 2001; Nelken, 2012), describing white collar crime acts to be encased in a quasi hidden bubble; inaccessible and evasive. This bubble is indirectly suggested to be impermeable, especially by theories that argue the existence of a "corporate culture" and a "criminogenic system" that is "crime facilitative or crime coercive" (Needleman & Needleman, 1979, see also Chapter 2). Being invisible and inaccessible to outsiders, the corporate culture is described as promoting, expecting, or facilitating legal transgression, deviance, and/or unethical conduct which becomes ingrained in normal everyday functioning of organizational members. It is assumed that if organizational members detect, anticipate or intend to engage in wrongdoing, techniques of neutralization (Piquero et al., 2005) will be used to individually or collectively mitigate the wrongfulness of behaviour. These techniques of

neutralization are said to be both provided by the organization or the organizational culture, and employed by the individual – rationalizations and explanations used to downplay or excuse criminal, deviant, or unethical behaviour. This view, however, requires individual and/or collective awareness of all consequences of actions, and especially deviant outcomes of actions.

The view of "disconnected dots" (Doty & Kouchaki, 2015) claims the opposite; emphasizing the inability of organizational members to see their actions as part of, or affecting the functioning of an organization as a whole. This produces "commitment drift" in individuals – a deviation from organizational mission statements. In short: organizational members lose sight of the so-called goals of an organization, but become preoccupied with the execution of their own daily work routines, unable to place their actions in the context of larger organizational outcomes. Disconnected dots are as much a characteristic of large corporations as they are of research into industry-medicine relationships. By studying a singular event of undue influence, restricting analysis to a specific, isolated instance limits the understanding of influence as a dynamic process, diminishes its continuity, and downplays its characteristic as a continuous and constant phenomenon operating within a system that facilitates its existence. In my view, although a study of corporate culture and impressions on the behaviour of organizational members is important for circumventing simplistic explanations of individual culpability, theories of neutralization and rationalization of criminal conduct, facilitated by the corporate culture, still presupposes individual rationalization of action, or at the very least, split personality disorder: the good everyday citizen, and the normalized, neutralized organizational actor.

This is slightly counterintuitive within an embeddedness approach to the explanation of white collar crime. Additionally, these theories would further assume that there is some indication as to whether crime or conduct is wrong or right (oversocialized view) and/or that the individual(s) engaging in the act will adopt, or be provided with a strategy of neutralization (undersocialized view). I have reservations about whether it is possible to achieve an embedded/relational approach by simply combining under- and oversocialized theories of behaviour. Following this thought, Braithwaite (1984) suggests focusing not on the perpetrator or individual motives behind the commission of white-collar crime, but rather on the 'how'; focusing on the modus operandi of action. This perspective may yield more beneficial data for white collar crime studies. Nelken explains that criminal qualities are often attached to outcomes of certain actions; they are "secondary or collateral features, both in priority and the succession of events, of an undertaking pursued for other legitimate purposes" (Nelken, 2012, p. 639). It is thus arguably more beneficial to study actions as a process that may lead to criminality, as opposed to concentration on the motives behind a criminal action of a singular individual, as many actions are criminal only when considered within the chain of events that leads to harmful outcomes. Ruggiero (2007) highlights the importance of attention to the "legal-illegal continuum", wherein white collar crime may be given *in medias res* position, bordering on the definitions of legal and illegal

actions. Albanese (1984) argues that, for example, the actions of a loan shark and a banker are not in fact different if considering the service they provide. It is but "the (often arbitrary) demarcation of legitimacy in interest rate" that differentiates the criminal or non-criminal status of each (Albanese, 1984, p. 17). I argue for a procedure, or systems approach, which scrutinizes the source of principal-agent interactions, their manifestation in concrete action, the inherent conflict of interest in principal-agent relationships, and the structural determinants of role conflict which lead to fiduciary obligation abandonment adopted in this research.

3.3. STRUCTURAL CONFLICT OF INTEREST AND INSTITUTIONAL CORRUPTION

Taking a turn again to the intrinsic ancillary characteristic of multiple interest representation by an agent, an "axiomatic approach" would take to define "the state of incompatibility of goals of two or more actors" (Axelrod, 1967, p. 87) as a conflict of interest. In medicine, and in relation to the medical profession, a conflict of interest is described as a "condition in which professional judgment concerning a primary interest (…) is unduly influenced by a secondary interest (…)", the primary interest of the profession of medicine being the "health of patients" (Thompson, 1993, p. 573). A secondary interest is not automatically one which is contradictory to the first; in fact it can be considered covetable, or requisite in achievement of the primary interest. The key in this definition is in the term *undue influence*, which can only really be assessed in relation to the "relative weight" of the secondary interest over the primary (Thompson, 1993, p. 573). There is not necessarily a need to eradicate the existence of a secondary interest, but rather to maintain primary interest domination. The inability or unwillingness to do so is where I deem Shapiro's definition of white collar crime to manifest itself, since the primary interest representation is the fiduciary obligation, the basis of trust in the medical profession. Here I start answering the question of which interest should be primary in industry-medicine relationships. I have argued an embeddedness approach, and this requires my analysis to dismiss the idea that primary interest abandonment is a conscious, rational decision made by an individual calculation of benefit-maximization (undersocialized view), or that a primary interest has been rephrased in organizational or institutional policy so as to interpret secondary interest as a sanctioned norm (oversocialized explanation). The theory of "Institutional Corruption" (Lessing, 2013) provides an embeddedness approach, of undue influence of a secondary goal over the first without singling out the individual or the professional organization explicitly as the unit of analysis wherein primary interest diversion must be sought. Institutional corruption is defined in the following;

> "Institutional corruption is manifest when there is a systemic and strategic influence which is legal, or even currently ethical, that undermines the institution's effectiveness by diverting it from its purpose or weakening its ability to achieve its purpose, including, to the extent relevant to its

> purpose, weakening either the public's trust in that institution or the institution's inherent trustworthiness." (Lessing, 2013, p. 553)

There are many elements of this theory that need to be addressed, and which Lessing himself does attend to. First and foremost a particular emphasis must be made as to the use of the word corruption, and the difference between institutionalized corruption, and institutional corruption. "Norm enforcers" easily deem corruption to equate to bribery (Heidenheimer, 2002, p. 141), the most commonly accepted definition – corruption as the abuse of public power for private gain (TI GCR, 2006; Dawood, 2014) involving the exchange of money in return for an undue advantage. The definition of corruption changes, however, if viewed as a legal definition, viewed as the effect that corruption has on the public, or viewed as the public's opinion about corruption (Gardiner, 1993). Financial exchange or financial interest is the most commonly cited form of corruption (Heidenheimer, 2002) not because this is the only mode of its manifestation, but because it is easy to identify, measure, and subjugate to regulation (Thompson, 1993). Corruption in Lessing's vernacular breaks away from the confinement of a legal conception, limitations to the political (public versus private) sphere, and financial exchange, evoking Hellman's (2013) view that corruption is a derivative, not a general social norm of right and wrong but that "(…) a conception of corruption depends on a theory of the institution involved" (Hellman, 2013, p. 1421). In opposition to institutionalized corruption (Shapiro, 1990; Nelken, 2012) which presupposed a normalization of criminal action in concert with legitimate action, institutional corruption theory claims a more nuanced interpretation that sees an inability to achieve the institutional purpose (primary interest) as corruption of the institution, meaning that behaviour and action itself may be very much legitimate, legal, and even ethical. This is imperative, and eloquently formulates what Nelken (2012) and Vaughan (1996, 1997) have advocated previously, in that criminality is hidden within a chain of actions, each of which independently viewed are not criminal, but may produce criminal outcomes.

The element of systematic and strategic influence is also important yet not taken to mean that intentional influence is evil. It rather evokes Shapiro's explanation, that since principals are limited in their ability to monitor agents, tactics of agent control are implemented by principals to ensure certainty in interest delivery, selecting agents via familiarity and referral, interest harmonization, imposition of contractual limitations, exercise of policing measures, offering incentives, insuring themselves, or spreading risk (Shapiro, 1990, p. 348). These limitations protect principals, and ensure agent self-interest is abdicated. In the sense of institutional corruption, weakening, rendering unable, or diversion of institutional imperatives (fiduciary obligations) diminishes trust in that institution, and produces the so-defined phenomenon of white collar criminality. Thus institutional corruption theory requires many of the mainstream understandings of corruption, influence, and institutional purpose to be assessed in a more neutral light. It is only in Hellman's (2013) conception of institutional representation when one can begin to ask the question of whether or not

this institutional corruption is wrong. In the following, I shall address the limitations of institutional corruption theory, as to its original intended application as a general theory of organizational deviance, but maintain that it is applicable for the study of undue pharmaceutical industry influence in the medical profession. I will also further conceptualize the institutional purpose of medicine from which it is diverted from by pharmaceutical companies, and realize a theoretical framework within which this may be studied.

3.4. FILLING IN THE GAPS OF INSTITUTIONAL CORRUTION THEORY: CRITICISM, COMPLIMENT, AND CLAIM

Lessing does not explicitly define what an institution is, but to analyse industry-medicine relationships requires definition, because this will be the focus of analysis for the research. The pharmaceutical industry is generally understood as the collective of legal entities (companies) which specialize in the "provision, distribution, and consumption" (EC Study, 2013, p. 15) of "any chemical substance intended for use in the medical diagnosis, cure, treatment, or prevention of disease" (Directive 2004/27/EC Art. 1 In: EC Study, 2013, p. 40). Medicine, however, is more commonly referred to as a profession than an organization or institution. Although Hall's definition of an organization (footnote 2) would see the medical profession as an organization, others see a stark difference between an organization and an institution, seeing the former as formally (regulated by laws) and the latter as informally (ideology or belief based) defined establishment (Khalil, 1995). Giddens' view, however, would seem to contrast the idea that rules are either doctrine (formal) or ideological (informal), but rather that these rules spoken of can be seen as the "structure" of social systems. "I treat structure, in its most elemental meaning at least, as referring to such rules (and resources). It is misleading, however, to speak of 'rules of transformation' because all rules are inherently transformational. Structure thus refers, in social analysis, to the structuring properties allowing 'the 'binding' of time-space in social systems, the properties which make it possible for discernibly similar social practices to exist across varying spans of time and space and which lend them 'systemic' form" (Giddens, 1984, p. 17). Thus Giddens sees rules as "structural principles" which are functional for the "reproduction of societal totalities". This must not be misinterpreted as rigidity, but that social systems (relations) have "structural properties" rather than existing as rigid structures. The reproduction of practices across time and space, considered to be the societal totalities, are "Those practices which have the greatest time-space extensions (…)" (Giddens, 1984, p. 17).

The profession of medicine and the reproduction of medical practice across space and time – the Hippocratic ideals, formal codes of ethical medical conduct, and the evolution of modern medical practice – are what constitute the reproduction of such totalities and thus systems "(…) can be referred to as institutions" (Giddens, 1984, p. 17). The theory of structuration provides the analytical base for the view of the profession of medicine as an institution in the transformative reproduction of medical

practice. Although prescribing to Giddens' view of an institution, I shall in this thesis use the term institution and organization to define the medical profession. Institution as the social system which reproduces behaviour is, in my interpretation, linked very much to the goal of a collective, while the term organization is the modus operandi of achieving a goal – perhaps it is plausible to see institution as motive and organization as means. For the moment and for the validity of institutional corruption theory, we must first address criticisms which span both the concepts of institution and organization.

One criticism of institutional corruption theory is the undefined but underlying assumption that an institution has an identifiable purpose (goal), enabling measurement of deviation from that purpose manifest in the alignment or divergence of institutional output from that baseline purpose. Public institutions – such as the American congress for which the theory was first developed, by Thompson (1993) – have an obligatory purpose, which private sector institutions do not – "Because private organizations do not coerce us, they are not generally obliged to act for the state's public purpose" (Newhouse, 2014, p. 555). Accordingly, this critique challenges the application of institutional corruption theory to non-public institutional analysis. In her analysis of the application of institutional corruption theory, Newhouse identifies 4 phenotypes of institutions labelled as institutionally corrupt by researchers: Fiduciaries, Frauds, Fiends and Fools, and singling out Fiduciaries as retaining the characteristics of institutional corruption as was defined by Thompson in an analysis of legislative ethics; "a state of affairs in which political benefits – such as campaign contributions, endorsements, organizational support, or media exposure – are made available to lawmakers under conditions that, in general, tend to promote private interests at the expense of the legislature's public purpose" (Thompson 1993 In: Newhouse, 2014, p. 557). **Fiduciaries** have obligations imposed on them by their principals, and breaching the pursuance of fiduciary (obligatory) duties constitutes institutional corruption. **Frauds** are institutions which have in place incentive structures which push members to engage in fraudulent behaviour. **Fiends** are institutions whose incentive structures recklessly endanger or damage the safety and security of the general public. **Fools** employ faulty business strategies in pursuit of client interests, doomed to fail not for intent, but lack of competence. These latter 3 institutions accordingly break no public or fiduciary obligation. The reason this critique is important to address, is that some forms of pharmaceutical industry-medicine relationships are seen by Newhouse to fall into the category of Frauds – research misconduct by scientists – or Fools – condoning doctors' acceptance of free gifts from industry which decreases their ability to remain impartial – and thus falling outside the scope of institutional corruption analysis (Newhouse, 2014).

The second critique refers to Lessing's application of institutional corruption to explain the corrosive effect of campaign financing in the US. Lessing argues that congress is institutionally corrupted (diverted from its mandate to serve the public) by the improper financial dependency it fosters with private institutions for campaign

success (Lessing, 2011). Similarly to what was said in the previous critique, and Thompson's view that political benefits tend to promote private interests, Lessing describes improper dependency as influence that draws actors away from "the influence intended" (Lessing, 2011, p. 264; Dawood, 2014, p. 111). Dawood's (2014) criticism is whether improper dependence is correctly deemed to be corruption itself, as Lessing would seem to purport that improper dependency (conflict of interest) is corruption already. Dawood's question is supported by Thompson (1993) in the reiteration that secondary interest existence cannot be defined as fulfilling the criteria of wrongfulness automatically. For this reason Lessing's argument is problematic, since a conflict of interest preceding action is a Schrödinger's cat, simultaneously dead and alive but not yet established– the feline's mortal state as being good or bad can only depend on the goal that one wishes to attain: good if you're rooting for the mouse, bad if you're rooting for the cat.

These criticisms are worthy of further exploration, especially since the adaptability of institutional corruption theory as applicable to any and all institutions bears limitations without the consideration of which will, in Newhouse's (2014) view, render it a theory of 15 minutes of fame. Criticism here is particularly useful since we can assess the difference between institution (motive) and organization (means), in that Newhouse critiques the existence of motive as an inherent attribute, while Dawood's criticism is closer to the means i.e. the existence of a (financial) dependency. Contrary to Newhouse (2014), I argue that industry-medicine relationships will fall under the category of fiduciary relationships, one which she does not see, but perhaps because her analysis would break down the medicines delivery chain into stages isolated from each other (medical R&D as unrelated to physicians' reception of gifts). On the other hand, Dawood (2014) does raise a particular point in that conflict of interest in itself is not yet corruption (or white collar crime for that matter) since the opportunity to break a fiduciary duty does not predetermine its breach. However, Dawood's criticism could go unchallenged if a conflict of interest (or improper dependency) was obvious, singular, and identifiable as such. However, as stated previously, upon a long line of sequential events, one *conditio sine qua non* is rarely the cause of a criminal outcome. Interactions between industry and medicine are made up of many dependent stages, and one outcome may require multiple tasks to be executed, and a variety of relationships to form. Thus for the study of the relationships between the pharmaceutical industry and the profession of medicine, and subsequent institutional corruption of the medical profession, an institutional purpose is seen as the obligation of health provision, protected by national and international law, and mandatory with regards the duties of the medical profession. The argument of improper dependency being institutional corruption itself may induce a debate, however, I will argue a fuller picture which does not stagnate argument at the precipice of conflict of interest, but which will engage in conversation about the embedded, structural reasons as to why (motivation) and how (means) an interest is identified and pursued. The study of how institutional corruption manifests in the medical profession is a complicated one, and one must ask the question; what then, are the institutional norms that the medical

profession is being diverted from i.e. the impediment of behaviour reproduction as to the basal requirements of ethical medical practice (adding my own criticism of Newhouse's critique). To begin, it is necessary to seek an understanding of what the components and norms of the medical profession are. The medical profession distinguishes itself from other occupations and so these distinguishing elements need to be identified and evaluated for this research to have an appropriate baseline of institutional purpose. This baseline represents the basis of trust, since the fiduciary obligations, and the ability to meet them, render the profession of medicine trustworthy for patients.

3.5. THE PROFESSION OF MEDICINE: TRUST, AUTONOMY, AND ETHICS

There are certain truisms we do not necessarily seek verification for. One of these is that we trust our doctors. According to global market research data, doctors remain and continue to be among the most trusted professions (GfK Verein, 2016). Trust, earned as it may be through individual experience, is also a necessary component of knowledge diversification in society, which produces a dependency on those who possess the knowledge and/or capabilities we do not, to execute a task or achieve a goal we desire, or provide a service we rely on (Shapiro, 1987). Trust is based on many societal and interpersonal factors; however, when it comes to the extraordinary amount of trust we place in doctors, it boils down to two main components which are derivatives of each other – 1) the autonomy and authority of physicians based on specialized knowledge, 2) which in turn is legitimized by a commitment to ethical and moral standards of conduct and decision making, roughly understood as the Hippocratic tradition. These two characteristics are separate in concept, but mutually reinforce each other – they are conditional determinants of the trust we place in physicians. Let us then discuss what a profession is, how its autonomy manifests, and how ethicality serves as autonomy's determinant. Here we establish the institutional norms of the profession of medicine, because it is these that the profession of medicine is being diverted from (its institutional purpose) due to systematic and strategic influence exerted by the pharmaceutical industry within industry-medicine relationships.

3.5.1. MEDICINE AS A PROFESSION: THE COMPONENTS OF AUTONOMY AND AUTHORITY

Autonomy is the freedom to act in accordance with one's own moral framework, independent from external constraints, the right to self-government. With regards to the medical profession, the qualities of self-determination of professional work, the possession and regulation of skill and knowledge, and the commitment to provide a societal need or service in line with a professional ethical code are what define the autonomous nature of the medical profession (Hoogland & Jochemsen, 2000; Warzynski & Noble, 1976; Wilensky, 1964). In a study discussing medical autonomy

in the UK, Harrison and Ahmad (2000) divide the components of autonomy within a tri-level model, establishing that medical autonomy is demonstrated in micro, meso, and macro levels of medical practice.

Micro level autonomy manifests within the clinical autonomy of physicians. Clinical autonomy is comprised of the professional control over 1) the diagnosis and treatment decisions in patient care, 2) control over the evaluation of the care provided to patients, 3) command over the amount and nature of tasks executed, and 4) the maintenance of contractual independence from employers. Expressed by Kendel (1990, p. 1115) this pertains to the microscopic autonomy of medical professionals through the possession of a "unique and complex body of knowledge" which cannot be understood, executed or appreciated by those who are outside of the profession. As such it is the autonomy expressed in individual clinical practice.

Meso level autonomy describes the "institutionalised relationship between the profession and the state" (Harrison & Ahmad, 2000, p. 131). The meso sphere of autonomy identifies the self-regulatory nature of the profession as granted by the state in self-licensure, as well as the recognition of medical organizations and associations that mediate the interests of the medical profession. The recognition of licensure, as well as professional registration databases, the coordination and accreditation of medical education, as well as medical boards and ethics committees, development of medical guidelines, the freedom to regulate professional members, to define acceptable and ethical conduct, as well as the right to discipline, punish, or expel members (Kendel, 1990; Timmermans & Oh, 2010) all belong to the execution of the meso level of autonomous practice of medicine.

Lastly, being that the medical profession is claimant to a unique body of knowledge (regarding the human anatomy and the pathologies it may suffer), as a profession it possesses the singular competency of defining the scope of its field of work (what belongs to medicine and what does not) as well as the way in which it approaches diagnosis, treatment, and management of disease. **Macro** level autonomy manifests in the biomedical model – an approach to the practice of medicine that emphasizes the importance of diagnosis of an ailment and definition of the ameliorative intervention.[3]

This model defines what autonomy means practically and translates the abstract notion of medical autonomy into 'autonomy in practice'. It is also enlightening as well as important for this thesis in that we are able to study medical autonomy as multi-

[3] The biomedical model sees disease or illness as a biological deviation within the body from the healthy or 'normal' state. The biomedical model rests upon 3 assumptions; 1) "an illness has a single underlying cause", 2) "disease (pathology) is always the single cause", and 3) "removal or attenuation of the disease will result in a return to health" (Wade & Halligan, 2004, p. 1398). The biomedical model has been criticized in that it reduces the patient to an object, or a series of quantifiable symptoms that excludes social and economic, not to mention emotional factors, the "lived experience" of illness that also effect the overall state of health (Borret, 2013, p. 497). The WHO definition of health challenges this narrow definition, recognizing the complexity of illness; however, it is still a determining view in medical science.

componential, and procedural as we shall see in the analysis of institutional corruption of medicine. Similarly the model alludes to the autonomous practice of medicine in the clinic to be the end result of prior autonomous actions; an accomplishment preceded by macro and meso level autonomy. I shall elaborate in due course, however it is important to note that autonomy rests on an additional component of the medical profession, without which such high degrees of self-determination of work cannot be carried out. Reverence for the medical professional stems not solely from the possession of knowledge of the complicated structure and functioning of the human body. Specialized skill alone does not denote a professional status, since every type of work has its own set of skills that those outside the occupation do not necessarily understand or cannot, without a licence, rightfully practice. Although skill and knowledge are components of autonomous practice, what differentiates the professions from other highly skilled occupations is the requirement to execute this knowledge in the spirit of altruism and ethical conduct, which should trump self-interest (Freidson, 1970, 1984; Sullivan, 2000; Timmermans & Oh, 2010). The professions emerge in response to a pressing social need. Looking at the medical profession, it is the functional manifestation of providing, enabling, and prolonging health, a basic human need.[4] Thus there is another element of professionalism, which relates to its function as being bound to act in the interests of this social expectation – the element of subjugation of medical practice to the interests of society maintained by a commitment to ethical conduct.

The legitimacy of the autonomous functioning of medical practice is rooted in an ethical duty to remain relatively unrestricted by other interests (healthcare budget, legal tradition, infrastructure etc. pose inherent limitations on medical practice). What makes medicine ultimately a profession is that it is executed in the "service of others", the members of the profession governed by "codes of ethics and a professional commitment to competence and morality, altruism, and the promotion of the public good within their domain". (Cruess, et. al., 2004, p. 75) In other words, this provides the social contract between the profession of medicine and society. It is the code of the medical profession that both guides physicians in their practice, as well as legitimizes their claim to authority and autonomy. "Professional knowledge and expertise are at the core of contemporary society" […] "…the social basis of the extraordinary grant of occupational authority and independence to professionalized occupations such as medicine and law has been a social contract between the profession and the public" (Sullivan, 2000, p. 673). The notion of the social contract manifests in the relationship

[4] **The Human Right to Health is protected in:**
Article 25 of the Universal Declaration of Human Rights
Article 12 of the International Covenant on Economic, Social and Cultural Rights
Article 24 of the Convention on the Rights of the Child
Article 5 of the Convention on the Elimination of All Forms of Racial Discrimination
Articles 12 & 14 of the Convention on the Elimination of All Forms of Discrimination Against Women
Article XI (11) of the American Declaration on Rights and Duties of Man
Article 25 of the Convention on the Rights of Persons with Disabilities

between the professions and the public; society granting the professions dominance and authority in specific fields, in return for the protection and promotion of health and quality of life (Timmermans & Oh, 2010). In the case of the medical profession, authority and dominance are granted by way of the specialized knowledge of human biology held by physicians, trust in the commitment of the professional to the ideals of medical practice grants the physician autonomy, the enablement of the right to practice medicine according to the interests of the patient.

3.5.2. THE BASIS OF AUTONOMY: A CULTURE OF ETHICS

Traditionally the ethics of medicine are held to be described in the Hippocratic Oath, a document that originates from somewhere between the 5th and 4th century BC, the Classical Era of Ancient Greece. Although it is agreed upon that it was not Hippocrates himself who authored it, nor that it was considered of any particular importance other than as one of the many Oaths that surfaced at the time, it has become the defining symbol of the fundamental ideals of (western) medicine today (Rocca, 2008).

The validity of the Hippocratic Oath in written form has been and continues to be debated, and one can easily find version upon version of it, modernized refurbishments of the ancient text. Critics challenge the necessity or even the appropriateness of swearing upon an oath in medical school claiming the Oath is something of a hollow vow, more to please the young physician, and even more, the lay patient (Loewy, 2007) Others see it as a reaffirmation of the duties of the physician, and that the culture of the Oath itself establishes physicians' moral resolve and commitment to integrity (Sritharan et al., 2001). The Hippocratic Oath, as an actual document comprising the ethical requirements of the profession upon which physicians swear conveys "(…) the core principles of the ethical system of the Western medical tradition". However, the Oath, or the action of taking a vow, reinforces the physicians' sense of belonging to an "unbroken Hippocratic line of succession" (Rocca, 2008, pp. 25-26).

The Hippocratic Oath, as it stood 2400 years ago, is, for modern medicine, out-dated. A vow to the Gods, the prohibition of euthanasia, abortion, and surgery, are some of the striking examples of ideals and prohibitions that do not hold fast for the practice of medicine today. This, as well as the fact that the necessity of the Oath itself is debated renders it more appropriate to speak of a Hippocratic *Culture*, or rather the Oath as a symbolic manifestation of the idealism that medicine is an "art, not a trade; a calling, not a business" (Quote by Sir William Olser In: Karanth, 2010, p. 637) – a *culture* of ethical and moral commitment. Swearing upon the Hippocratic Oath is most commonly done by medical students upon entering university, or part of the completion ceremony of their medical training, albeit not all medical schools require this to be done. It is a way of reaffirming the *spirit* of Hippocratic Medicine, which evokes the notion that the practice of medicine requires its practitioners to subordinate their mental and physical capacities to ethical and moral ideals, and to execute their

professional practice with a high degree of *altruism*; the only acceptable interest being that of the promotion of health and well-being of the patient.

The universality of the Oath is a more recent development than one would expect. Again, despite being subject to some controversy as to its necessity as a formal document to be sworn upon, the culture of Hippocratic medicine has in Europe become vital, especially after the horrors of World War II. In 1948, the World Medical Association (WMA) adopted the Declaration of Geneva as a response to the atrocious acts committed by physicians in Nazi Germany, and reinstated, in light of these crimes, the need to re-establish the values of the Hippocratic culture of medicine (see Hippocratic Oath in the Declaration of Geneva, 1948 as it stands today at Annex 1).

The WMA boasts a total of 111 National Medical Associations globally, including the Hungarian Medical Chamber (MOK), and the Royal Dutch Medical Association (KMNG). United under the aegis of the Oath, the medical profession is seen, probably now more than ever before, as a profession bound by universally defined ethical norms. The Oath, as important as it is, must however not be read alone since it has evolved to encompass Medical Codes of Conduct which translate the Hippocratic culture of ethics into the everyday practice of medicine to suit professional practice in a local context. These Medical Codes of Conduct which, although founded upon these universal principles, retain features and aspects of medical practice that are defined by national law. This will be important in the later sections of this thesis and I shall return to what is addressed by these Codes of Conduct in the legal and analytical chapters, since they represent textual codes of baseline medical institutional purpose. However, this section has aimed to describe the origins and qualities of the ethics of medicine, and the ethical culture of the medical profession as they pertain to the basis of trust upon which autonomy and authority can be claimed. As mentioned before, the possession of skill and medical expertise legitimizes authority, and necessitates autonomous practice. The permission to do so is maintained by a promise to place societal (patient) interests above all else, and establishes the enormous amount of trust we place in the medical profession.

The question of whether quality healthcare provision is a duty to be performed to the public, is not always simple: factsheet 31 of the Office of the United Nations High Commissioner for Human Rights and the World Health Organization explicitly state that "The right to health is NOT [sic] the same as the *right to be healthy*" (Human Rights Fact Sheet 31. 2008, p. 8). The human rights approach assesses the duties of the state in healthcare provision, but the state does not physically attend to the patient; the state provides the infrastructure for healthcare access such as healthcare budget, insurance, or concrete infrastructure, including providing licensure and protecting the autonomy and authority of the medical profession to execute healthcare provision. The obligation of the medical profession is to strive for the provision of the highest standard of medical care to patients that medical knowledge, science, and experience is able to provide – its fiduciary obligation in exchange for state protection of licensure and

autonomy. A violation of fiduciary obligation constitutes criminality, as is the case with medical malpractice. For these reasons, I perceive the duty of healthcare provision to the highest standard as the basic professional institutional imperative of the medical profession, pragmatically expressed in the control (autonomy and authority) over medical knowledge.

In the next section I will describe the theoretical framework for this research which assesses the institutional corruption of the medical profession, understood as the profession of medicine being diverted or weakened in its ability to pursue its institutional purpose by way of pharmaceutical industry influence within the 3 spheres of medical autonomy and authority over medical knowledge – strictly within the scope of medical knowledge regarding pharmaceutical products.

3.6. AUTONOMY OF MEDICAL KNOWLEDGE AND THE ANALYTICAL FRAMEWORK

> "Too often scholars and policy analysis from different specialities look at different aspects of a large and complex problem. The cumulative result is too often resembles the portrayal of an elephant as a horse built by a committee."
> (Reiss & Tonrey, 1993, p. 10).

I have discussed the components of medical autonomy and authority of the profession of medicine, as well as its basis in an ethical, normative and Hippocratic culture. To enable the analysis of the institutional corruption of medicine, I shall turn to the construction of an analytical framework. I have taken to rely on the insights of medical sociology both in defining as well as structuring the institutional imperatives of medical practice: provision of health through autonomous practice, guided by a Hippocratic ideal that promotes altruism and subsuming of self-interests to the interests of the patient. Drawing on this structure, I will analyse what was identified as industry-medicine relationships in the literature review and assess medicine as a countervailing power (Light, 2010) to the influence of the pharmaceutical industry via the autonomy of medical knowledge at the macro, meso, and micro levels. For this thesis, medical autonomy is based primarily on monopoly over medical knowledge, and is the basis for individual autonomous practice. I shall begin with macro level autonomous practice, and illustrate how meso and subsequently micro level autonomy is built in sequence which follows from a deductive approach.

Macro level autonomy is established in the claim of the medical profession over the production of medical knowledge vis-à-vis delineation of what constitutes *medical* knowledge, and how this knowledge is applied. Science, or the production of knowledge, rests on autonomy and impartiality, "the disinterested search for truth" (Lewis et al., 2001, p. 783), the analysis and application of fact devoid of personal or economic interests. As with the definition of the biomedical model as an approach to disease, the approach to medical treatment insofar as it is related to pharmaceutical products, is the knowledge produced about a medicine (Busfield, 2006). The basis of

drug production is drug research and development, which begins in the laboratories and medical research centres. This thesis will address the role of the pharmaceutical industry in the development and production of medical knowledge regarding pharmaceutical products.

Medical knowledge must not only be produced, but it must be communicated throughout the corpus of the professional medical organization. Harrison and Ahmad (2000) see meso level autonomy as the control over the accreditation and licensure of doctors, the right to self-regulate, and to construct and control the content of medical practice. Maintaining membership within the practice of medicine requires continued self-development and education – the interpretation and application of produced medical science into practice. This is done through Continuing Medical Education (CME), and the implementation of medical guidelines and protocols that translate produced knowledge about a medicine into medical practice. In this thesis, meso level autonomy in relation to the pharmaceutical industry will analyse the role of industry in medical education and medical knowledge interpretation.

Micro level autonomy is a critical point, in that while macro and meso level autonomy provide the basis for a collective body of scientifically-verified medical knowledge, as well as standardization in education, diagnosis, and treatment protocols, the autonomy of individual practice is still recognized as a necessity, due to the individuality of illness and disease (case-by-case treatment). The meso and macro provide a structured guide for medical knowledge and its standard application; however, the individual doctor still maintains the right to practice individual application of medical knowledge, as is his/her duty to the patient. The role of the pharmaceutical industry as it pertains to interactions with doctors in the clinical setting shall be the final level of analysis.

These levels of analysis are important for the analysis of empirical data, and shall be reflected in the structure of this thesis. Embeddedness provides the relational approach, understanding that social and organizational networks are an imperative contextual backdrop to the study of behaviour. Shapiro's principal-agent relationship assigns goal identification to act as orientation in explanations as to principal-agent roles, and in this case, the profession of medicine is the target of study. Applying the notion of a fiduciary responsibility for providing healthcare with pharmaceutical products, I view trust to be maintained by promotion of the highest standard of knowledge, disinterestedness, transparency, and role competence in all levels of medical autonomy. A breach of these standards constitutes a violation of trust (i.e. Shapiro's white collar crime). The meso/macro/micro framework provides a structure for both inquiry (investigation in the field) as well as a division into analytical chapters, but must still be seen as linked on a consequential string in practical terms – a *condiciones sine quibus non* each level of interaction, and each component of medical autonomy built upon each other (structural conditional determinants), the destruction of one rendering the others impotent.

CHAPTER 4: THE METHODOLOGICAL AUDIT TRAIL

"From inside a tradition of objectivity and scientific detachment, the lines of legality and illegality, of morality and immorality in research, may seem straight and clean. But as many criminologists know, these lines quickly become tangled and uncertain in the field."

(Ferrell & Hamm, 1998, p. 26)

In this chapter, the methodologies used in researching industry-medicine relationships will be introduced. Descriptions tend to scan the methodology from the technical plane, describing the toolkit of the researcher. However, in addition to the enumeration of a methodological apparatus, this chapter will also include a theoretical reasoning as to the methods used and the nature of the data so gleaned, substantiating the need for a reflexive analysis of the way in which this data was accessed, collected, and compiled. Methodologies are generative of data in themselves, wherein a description and a reflexive stance on the part of the researcher already place both the researcher and the researched phenomenon into context. The generation of data starts already in the preparation and execution stages of qualitative analysis of social phenomena and continues throughout.

The delineation of the boundaries of the field within which I aspired to conduct research focused primarily on the medical profession itself, respondents constructing relationships with the pharmaceutical industry, and providing explanations as to how and why the industry influences the practice of medicine. While correlations drawn between the number of industry-medicine interactions and changes in prescription practices of doctors may provide evidence for existence of the phenomenon of influence, it lacks explanations as to why such relationships are influential as communicated by those who are part of the industry-medicine relationship. Mostly, the common understanding is that the financial incentives of the pharmaceutical industry make it a corporate goal to influence susceptible physicians, changing prescribing habits to boost sales. The statement would be appropriate if not for the fact that doctors are highly autonomous, and express their own agency as well as their abilities to self-regulate as a profession. Research has chosen not to engage in the analysis of medical autonomy, or its corruption via the pharmaceutical industry. Speaking to doctors and actors within the pharmaceutical product delivery system allows for these explanations to emerge.

The question I sought to answer was whether industry-medicine relationships institutionally corrupt the practice of medicine, not limiting analysis to individual morality but seeing deviance as embedded and produced in the system of industry-medicine relationships in the pharmaceutical product delivery chain. This research placed the profession of medicine at the centre of inquiry; however, it required that modes of influence be placed in the context of industry-medicine relationships. Given

that this is a dynamic process of interaction, the system which promotes collaboration between industry and medicine also presenting opportunities for undue influence, the field of research had to be flexible, to incorporate those actors, organizations, and institutions that respondents identified as important for answering the research questions. Thus data collection was driven not solely by my own understanding of the published literature on the subject, but by the respondents themselves. The participants that I included in this sample evolved to comprise doctors, pharmaceutical industry respondents, lawyers, economists, pharmacists, journalists, regulatory authority representatives, and pharmaceutical industry associations.

To understand how doctors – trusted and respected professionals – contribute to the harmful actions of pharmaceutical companies (Gøtzsche, 2013), it is important to direct attention to the interpretations of industry-medicine relationships as to the roles that industry plays in medicine along the knowledge production, interpretation, and application activities of physicians. To presume industry influence over the medical profession is to presume the existence of an organizational culture that trumps the culture of medicine. It presumes that one culture – or set of norms and values – is corrupted (Lessing, 2013) to accommodate the expectations of another culture. Within this process, looking at meaning and interpretation of actions is pivotal to understanding the process of distortion of values, and how interpretation serves to mask the deviant nature of behaviour. "Crime and deviance constitute more than a simple enactment of a static group culture" (Ferrell et al., 2008, p. 3). The idea that crime is a dynamic interpretation of meaning attached to a specific relationship is portrayed within this research, and the study of industry-medicine relationships as the driving force behind the institutional corruption of medicine necessitated an interpretive-constructionist stance to be upheld throughout the compilation and analysis of data, as well as employing an ethnographic sensibility.

The ability to study behaviour requires the ability to incorporate the study of the meanings given by a subject to his/her own actions. Common to anthropology is the ethnographic method of inquiry which encourages the researcher to take a position of observation within which the distance between the observer and the observed is minimized. This requires the researcher to immerse him/herself within the environment of the subject under scrutiny; requiring the researcher to be present within the contextual arena of behaviour and action; to be *in situ* (Noaks & Wincup, 2004). Cultural criminologists promote research within the "immediacy of criminal experience", suggesting – to some extent – the immersion of oneself within the domains of criminal conduct. One must be present to be able to assess the interpretations of a specific action at a specific time. Hence the idea that "understanding the world requires regarding it on its own terms" (Ferrell et al. 2008, p. 175) presumes that the researcher must take a stance within the specific behavioural arenas of the phenomenon that one wishes to investigate. It is through applying a "criminological verstehen", the ability to appreciate the emotional, behavioural and verbal context of those under study that enables comprehension of action. In a sense, cultural criminological research requires a certain degree of sympathetic participation,

guided by an ethnographic sensibility wherein the researcher must "come to share, in part, the situated meanings and experiences" (Ferrell & Hamm, 1998, p. 27) of those investigated. This ideological stance I have come to understand as the manifestation of Becker's "underdog sociology" (Becker, 1967; Hammersley, 2001, p. 92), which is interpreted to mean that the task of the researcher is to study those social groups that are marginalized, or in some way, oppressed by a powerful other. This idea may be traced back to Becker's labelling theory (Becker, 1963), suggesting that 'crime' and 'criminal' are but labels given to certain actions and certain individuals by a powerful entity (i.e. the state). The task of the social researcher is to scratch the surface of the given label to expose the true dynamics underneath; to test the validity of centralized definitions of criminality. As such, criminological inquiry is able to reinterpret conventional ideas and explanations of criminality, going beyond the boundaries of textual definitions and pre-defined theories of criminality itself. It is here that the importance of ethnographic study in relation to researching the institutional corruption of the medical profession should be emphasized. As with underdog sociology, which sees deviance to be a construct of powerful actors used to supress the powerless, the principle holds important for investigating crimes of powerful actors; going against the grain and reflecting their own constructs of criminality back onto them – *uno specchio deformante*. The abstract nature of definitions of white collar, corporate and crimes of the powerful is not seen as a hindrance, but as an opportunity to explore the source of ambiguity of normal and legal behaviour that causes harm.

4.1. THE NETHERLANDS AND HUNGARY

This research was executed in Hungary and The Netherlands and choosing these two countries for analysis was motivated by 3 fundamental considerations. Firstly, the corrosive effect of relationships between the pharmaceutical industry and the medical profession enjoys a far more comprehensive study in American research than European. There is a tendency to "Americanize" the crimes of the pharmaceutical industry, or see corporate crime in the pharmaceutical industry as an American phenomenon, something echoed among respondents in the field. The intention of this research was to direct focus to the European context, and more specifically, to execute research within the European Union. This was done in consideration of the harmonization of medicines regulation, as well as recent implementation of European transparency requirements regarding payments from pharmaceutical companies to physicians and healthcare organizations (discussed in detail in Chapter 5). A study of industry-medicine interactions in Europe is also made interesting by the fact that contrary to the United States and New Zealand, Direct to Consumer Advertising (DTA) of 'Prescription-Only Medication' (POM) is prohibited. In this sense, although DTA of 'Over the Counter' medication (OTC) is allowed, the market uptake of POM is highly dependent on advertising to and informing physicians directly. For industry, the relationships they have with doctors in Europe are essential.

Secondly this research was an exploration into the question of whether institutional corruption is a phenomenon that varies in manifestation on a local level, or whether it is independent of country borders. This question was based on the knowledge that the pharmaceutical industry is a global industry, and as such, it is questionable whether industry-medicine relationships take on different forms in the two countries under analysis, and whether national borders shape industry-medicine relationships or perceptions as to emerging deviance. This consideration was based on corruption perception reports, and that corruption in general as a problem that disrupts normal societal functioning is deemed more prevalent in Eastern and Southern EU member states than in the countries in the Western and Northern EU regions (Transparency International Corruption Perception Index). This assertion was further supported by the European Commission EU Anti-Corruption Report (2014).

The following table is taken from the Transparency International website, where the 2016 corruption perception index (CPI) rankings and the scores for the preceding years till 2012 are provided. The Likert Scale type ranking places respondents' perceptions of corruption in their country on a numerical scale of 0: "highly corrupt" to 100: "very clean".

2016 global ranking	Country	Score 2016	Score 2015	Score 2014	Score 2013	Score 2012
8th	Netherlands	83	87	83	83	84
57th	Hungary	48	51	54	54	55

Data source: Transparency International website
https://www.transparency.org/news/feature/corruption_perceptions_index_2016
#table

This research thus took the Netherlands and Hungary as being on two opposing ends of the corruption scale, providing the opportunity to reflect on whether the CPI rankings held constant in respondent accounts, and whether CPI rankings were reflected within industry-medicine relationships.

Finally, the decision to choose Hungary and the Netherlands specifically was also technical in nature to ensure points of access such as engaging in a language which both the respondent and I could use with proficiency, and the availability of personal contacts within the field of medicine. Modes of access were fundamental in conducting fieldwork, since many of the obstacles to access were either my lack of medical education and medical titles (there are some places that only qualified employees can physically enter), obstacles to entry in bureaucratic structures or access (physical and verbal) limited by company trade secrets, as well as overcoming unwillingness to participate due to the sensitivity of the research subject, and the ability to build rapport via referrals from a friendly face or trusted colleague.

4.2. SAMPLING

4.2.1. DEFINING THE FIELD THROUGH SAMPLING

As I described in Chapter 2, the profession of medicine goes far beyond the boundaries of clinical practice, and as such, the study of its institutional corruption by the pharmaceutical industry requires that the field follow the manifestations of industry-medicine relationships as opposed to searching for the phenomenon within a set of defined respondents. Basing fieldwork upon a standard set of qualities, such as all respondents be doctors, or all respondents work at a particular institution or company, would only reproduce general (outsider) constructions of the professional medical field – what activities doctors engage in, where industry-medicine relationships manifest – or restrict the interviews (their contents and analysis) to my own interpretations. Thus, the boundaries of the 'field' – namely which institutions I would end up contacting, and who would eventually become respondents in the sample – was continuously shaped by the respondents, and referrals constituted data for this research as much as the contents of each interview. What constituted 'the field' of research took on an interpretive- constructionist approach, and sought to contribute to the production of knowledge regarding the inexplicable world and complex system behind the limiting vernacular of a single industry-medicine relationship.

Snowball - also known as chain or respondent-driven sampling – invokes the use of social networks. This methodological tactic of gaining access incorporates the basic idea of a dynamic social word, already in the beginning stages of research. Respondent-driven sampling is based on two fundamental notions: firstly, that social knowledge should be viewed as "primarily dynamic, processual and emergent" (Noy, 2008, p. 329; Nader 2011); and secondly, that social knowledge should also be interpreted as the product of relations of power exercised between both researcher and respondent, as well as *between respondents themselves*. Knowledge is not simply information that should be elicited, but it is the product of the very process by which we come to interact with others. Thus it is a procedure that in itself generates knowledge about the group. This idea is best expressed by Max Wertheimer's Gestalt psychology, which invokes the ideology that "the whole is greater than the sum of parts" (Holloway & Jefferson, 2000, p. 306). Snowball or respondent-driven sampling, and the knowledge gained by documentation of the mode of access achieved during research thus invokes the Gestalt perspective in that analysis includes the study of the dynamic of entry within a social group. In this sense, it is not just the individual that is studied, but the societal context within which the individual is situated, again reiterating that respondent-driven sampling rests on the networks that form the basis for social interaction.

Immersion within a certain social setting may be interpreted not only to mean 'being in the right place at the right time'. This expectation implies a certain degree of static encounter: as if groups of people are to be penetrated as in penetrating a sphere, and once inside, the researcher may then sit and takes notes about what ensues.

Characteristics of the 'medical culture' can be gleaned by documenting the ways in which entry is acquired, such as the use of informal networks as expressed by Danzinger, attesting to the rich data gained from documenting her efforts to access doctors. She states that via an assessment of means of access: "I had also gained invaluable knowledge about the structure of medical care settings" (Danzinger, 1979, p. 517). For this research the eclectic qualities of respondents, where they worked and what organizations they belonged to, informed my understanding of the pharmaceutical product delivery system.

4.2.2. KNOWLEDGE-DRIVEN RESPONDENT TRIANGULATION

Snowball sampling was also necessitated by the qualities of the medical profession itself – a result of the division of labour within the medical profession. Shapiro's description of the division of knowledge and labour (Shapiro, 1978, 1990) is not only important for the theories behind trust relationships in society, but it has a very real manifestation within the field itself. Knowledge asymmetry was not only represented in my position as an outsider, but was also a constant and omnipresent characteristic of the respondents in the field. Being that individuals are predominantly concerned with information that directly affects them as individuals, similarly the respondents I interviewed were also restricted in their own knowledge, which was generally bound to the borders of their own work. Thus it was not only that I saw my respondents as the "knowledgeable other", but that respondents also had their own "knowledgeable others" to whom I was referred if my questions overstepped the boundaries of their own understanding. The respondent turned out to be not 'just' a respondent, but a potential *key* to specific *information* about their professional worlds by what they said, and complemented by what they *did*, or who they *knew*. "An individual's working intelligence is never "solo". It cannot be understood without taking into account his or her reference books, notes, computer programs and data bases, or most important of all, the network of friends, colleagues, or mentors on whom one leans for help and advice" (Bruner, 1991, p. 3). Thus, respondents were not arbitrarily selected, but rather they were accessed as a result of a process of building and constructing the phenomenon of institutional corruption. The 'borders' of 'the field', were thus subject to a high degree of plasticity.

As a result of such a means of inquiry, I was able to construct an interactional chain of industry-medicine relationships from drug discovery and research, to clinical testing and development, to market authorization, to how knowledge of approved medication is then transported to clinical doctors and implemented into practice, and then identify how industry is present within the chain of pharmaceutical drug delivery from conception to clinical application. This will be revisited in the analytical chapters as it forms part of the data collected, and will provide the basis for describing industry-medicine relationships along the pharmaceutical product delivery chain. Prior literature did inform my initial search for respondents, seeking out those whom I interpreted to be present in the 3 platforms of industry-medicine interaction: clinical

research, medical education, and advertising to physicians (Lexchin, 1993). However, what began as a pursuit of doctors became a triangulation of a variety of respondents, to account for professional information asymmetries and the verification of respondent claims.

A variety of respondents made up the population sample, resulting in a total of 83 interviews that were conducted with 84 respondents (one interview in the Netherlands comprised of 2 respondents being present). 43 respondents working in Hungary and 41 respondents working in the Netherlands, were interviewed between April 2015 and April 2017. 2 respondents in Hungary, and 2 in the Netherlands, were interviewed twice, due to the interview being cut short, or due to respondents' particular willingness to discuss the subject further, and/or if they had very detailed and lengthy experiences in multiple sectors impossible to cover in one interview. In Hungary, interviews were conducted in Hungarian, which I translated into English. Interviews in the Netherlands were conducted in English.

The categorization of respondents is done arbitrarily for simplicity's sake into: Physicians, Pharmaceutical Industry Respondents, Regulators and Associations, and Other Respondents. These categories reflect the sector in which respondents were employed, or were active in, at the time of research, mainly because the majority of respondents were certified doctors yet they did not all work in medical practice. Additionally many respondents employed in the pharmaceutical or regulatory sectors had previously worked as practicing physicians – one respondent for example had worked as a clinician, a sales representative, a hospital director, and a therapeutic area specialist at a pharmaceutical company. This type of multi-sector experience was very common among respondents, their prior experiences adding to the richness of interviews. The category of Physicians is also nuanced, as some doctors worked directly with patients in the clinic, while others worked in a hospital environment but were purely active in laboratory research, or some engaged in a combination of clinical practice, hospital administration, and medical research.

Respondents under the category of the Pharmaceutical Sector worked at innovative and generic pharmaceutical companies, but some were also active in the biopharmaceutical sector (preclinical research) or employed at clinical research organizations which sell clinical trial services to pharmaceutical companies. These respondents held degrees in medicine, law, economics, pharmacy, or marketing. Under the category of Regulators and Associations I placed national medicines regulatory authorities, inspectors, and members of medical ethics committees, as well as medical associations, and pharmaceutical industry associations. The reason for doing so again pertained to the activities (sector) of these bodies: ensuring compliance with legislation and regulation, as well as providing self-regulation, codes of ethics and medical guidelines.

Finally, the last category of Other Respondents was a product of fieldwork in the Netherlands. The Dutch media is particularly critical of pharmaceutical companies, and I was referred to journalists as being specialized in subjects of healthcare

criminality, having investigated particular cases of industry crime in the Netherlands. Some respondents had published books on industry criminality, or were directly involved in European studies into healthcare corruption and were considered experts in certain subjects. Finally, in the Netherlands there were Non-Governmental Organizations, which are focused on specific consequences of industry-medicine relationships, aiming to achieve financial transparency, creating awareness as to medicines' risks among patients and doctors, and aiming to minimize over-prescribing of medications by physicians. The general categories of respondents are provided below as regards sector. The details of respondents can be found in Annex 2.

Medicine	Clinical Doctors Academic Medical Researchers Administrators
Industry	Innovative Pharmaceutical Companies Generic Pharmaceutical Companies Clinical Research Organization Biotechnology Companies
Regulators/Associations	National Medicines Regulatory Authorities National Medical Associations Clinical Trial Ethics Committee Pharmaceutical Industry Associations Pharmaceutical Industry Self-regulatory Foundation/Committee
Other	News Media Medical Journal Healthcare Economy Expert Healthcare Non-Governmental Organizations

In addition to the variety of respondents I came to interview, their accounts and descriptions also led me to a respondent account driven search of legal, self-regulatory, and medical codes of conduct assessment. These formal documents will be listed in Chapter 5, as they provide not only formal and informal codes of ethical behaviour for both pharmaceutical companies and medical professionals, but also aid in formal documented verification and understanding of the wider system of pharmaceutical product delivery. Interviewees sometimes mentioned areas of disease, medication, or specific personal experiences regarding undue industry influence in medical practice. Following up on these experiences led to specific case studies being uncovered during this research, and these will be described in the analytical chapters. Document analysis and ensuing case studies were not adopted as a formal method in this research. Document searches and following-up on what respondents said via desk research was

initially used as a mode of respondent claim verification, while secondary case study analysis was planned to serve as illustration of abstract hypothetical scenarios described by respondents. However, in combining the interview content, and the documents used for verification, specific instances emerged that proved illustrative, original case studies for this thesis. These are all products of the respondent-driven sampling and the appreciation of method as data generative.

4.3. ACCESS

4.3.1. INVISIBILITY

The snowball sampling method was originally devised as a mathematical model (Goodman, 1961, p. 148) aimed at increasing randomization in participant selection, but its subsequent implementation in the social sciences was done with the particular intention of achieving identification and access to hidden or hard to reach populations. These populations are difficult to access in that they are not directly visible within the general population and both their location as well as size of these groups is unknown. These populations choose to be hidden or are forced to hide themselves due to a variety of reasons – stigmatization, illegality, intolerance, fear of persecution etc. (Heckathorn, 1997). Inaccessible due to their marginalization from the larger society, these populations group together to form organizations of subterranean values, creating what social learning theorists and cultural criminologists refer to as the "underbelly of society" (Henry & Einstadter, 2006; Topalli, 2005; Ferrell et al., 2008). Medical professionals, pharmaceutical industry employees, or members of formal and self-regulatory authorities can hardly be considered hidden in the traditional sense of hidden populations. The respondents in the sample are not stigmatized, illegal, or deviant, in fact they are upstanding citizens, a part of the healthcare system, and advertise their presence and activities. The legitimate professions have traditionally been associated with ease of access, but I found during research that this is only true in theory.

Being visible, does not directly translate into accessible, for the world of industry-medicine relationships is protected by bureaucratic mazes, corporate trade secrets, and the functional status of respondents. Although respondents may not always be hidden from view, they are protected from being accessed – visible, but inaccessible (Thomas, 1993; Gilmore & Kenny, 2014) and "hidden-by-choice" (Noy, 2008, p. 331). Potential respondents were identified and contacted using several tactics which were determined by the resources and accessibility opportunities available in fieldwork countries. Mode of contact, as well as access strategies, had to be constantly reformulated in relation to their efficacy in leading to respondents. In both countries snowball sampling and referrals from one respondent to the other was not only the fastest means of gaining access to respondents, but also one that ensured the highest response rates to requests for interviews both regarding agreement to participate as well as declination. Looking for doctors, members of medical associations, regulatory agency personnel, or

pharmaceutical industry employees through a central institution (the organization where the potential respondents work) proved to contain numerous barriers to outsiders.

4.3.2. CONTACTING RESPONDENTS

The power of referrals was integral to the success of access, since it built rapport, while simultaneously reproducing a culture of favours, whereby some of these respondents explicitly mentioned that they were only really willing to meet me because the referral was given by a friend, a superior, or a specific colleague, and as such personal networks were incredibly important in the beginning stages of contacting respondents. There is criticism with regards to using personal networks, such as running the risk of respondents referring the researcher to people who think alike (respondent bias), or that personal ties with respondents may cause tension when asking sensitive questions, especially posing questions about corruption, crime, unethicality, or professional integrity. However, I experienced that these criticisms had little validity in the sampling procedure. I used personal contacts for initial access, however this was combined with contacting respondents without referrals (cold calls), so as not to rely completely on personal networks. Respondents sometimes would sometimes 'tip me off' and tell me to contact a certain person while stating explicitly that I should not use their names as a reference, meaning that opinions which opposed that of the referee were not purposefully circumvented, but actually promoted by respondents themselves, invested in my exposure to opposing descriptions of a similar phenomenon (also an intention of respondent triangulation). Respondents also had a tendency of preferring referrals to singular individuals rather than referral to more than one person. If probed for further contacts, respondents were partial to suggesting organizations to contact, in which case I was usually told to search for specific departments via organization websites as opposed to specific individuals. Cold calls were thus not simply a conscious decision to minimize respondent bias, but were also an unavoidable means of contact.

4.3.3. DISCLOSURE AND ANONYMITY

All respondents were made aware that interviews were undertaken for the purpose of PhD research, and that this data would be used for data analysis and published in a thesis. The respondents were informed of this in written (email), or verbal (telephone) form, and were told of my intention to record interviews, either in the email, and/or once again before the interview started. It was important to be completely open about my status as an academic researcher, and thus the purpose of this data collection. In emails or via telephone, respondents were asked to participate in a PhD project that aimed to study the role of industry in medicine, and industry-medicine relationships. Respondents were generally open to being approached by a researcher, but the fact that I was a criminologist specifically, was omitted after the first few contact attempts, and left to the end of the interviews referring to myself as a 'social scientist'. The

reason for this was necessary, because the fact that I am a criminologist ended up barring access to respondents. The following email excerpt provides an illustration of this, after I had forgotten to remove the automated email signature containing the name of the Doctoral Program:

"Thank you for your mail and interest in my opinion. From (XXX) I did not understand that your doctorate is on Cultural and Global Criminology. This gives me the impression that you are looking for criminal activities of medical industry in relation to medical profession. If so, I don't feel I have relevant issues to discuss." (Email excerpt: October 9, 2016)

In a research project concerning interactions between doctors and patients during childbirth, Danziger (1979) explains how the medical profession (as a professional organization) is generally hostile towards outsiders who wish to gain entry, especially if the purpose of entry is to scrutinize their professional practice. This resistance is described as the "myth of experience" (Freidson, 1983, p. 213) which claims a professional belief that only the medically trained are capable of truly understanding, and thus legitimately evaluating professional medical conduct. Conducting criminological research usually had the effect of dissuading potential respondents from participating entirely. The subject of the role of the pharmaceutical industry in medicine is already a loaded subject in that respondents from all sectors are very much aware of criticisms towards industry-medicine relationships. Cases of pharmaceutical industry deviance, or doctors accused of being influenced or bribed by pharmaceutical companies, has been picked up and debated in the media, as well as being the subject of numerous books (see Chapter 2). Respondents were willing to speak to me knowing that I was a social scientist, but if the subject is studied by a criminologist, then participants would make the assumption that I am looking for criminal conduct, or have an intention to criminalize conduct. Participants did not take kindly to having legal conduct being labelled as criminal, which was not my intention, but taking into consideration public and academic debate on the subject, there were a certain number of obstacles in terms of preconceived assumptions that had to be considered when approaching respondents. Thus I had to constantly negotiate with myself, regarding how much information I should disclose about the criminological quality of this research before interviews commenced, finding a balance between being as open as possible, as well as lowering the chances of respondents declining to meet me based on their interpretations of my research intentions.

The sensitive nature of the research subject created a cautious air in respondents' – an unwillingness to speak on behalf of an entire profession, the fear of anonymity being comprised by the fact that 'everyone knows everyone', contractual obligations regarding what may be spoken about and what may not (trade secrets and employment contracts), as well as scrutiny towards the necessity or validity of this research. These fears of participating were addressed with guarantees of anonymity, the option to withdraw participation at any point until the thesis submission, and if the respondent wished, a copy of the interview transcript upon request. Once the interviews were

concluded, and if conversation allowed, I divulged the field of this research. Not once did I experience dismissal or concern if I gave this information after the interview was concluded.

Respondents were all guaranteed anonymity, which included the concealment of: names, age, place of work, and any other information capable of identifying them personally. I requested that I be allowed to reveal their profession, medical speciality or at least the sector within which they worked. All respondents are given codes to signify country, sector of employment, and a numerical identifier.

Country codes	The Netherlands (NL) Hungary (HU)	
Sector	**Medical**	Physicians (DR)
	Industry	Pharmaceutical Companies and Clinical Research Organizations (PH)
	Regulator/Association	Government Regulator (REG) Medical Association (MA) Pharmaceutical Industry Association (PA)
	Other	News Media (JO) Medical Journal (MJ) Expert (EX) Other Organization (OO)
Numerical identifier	01, 02, (…) etc.	

[COUNTRY] [SECTOR] [ID]: e.g. **NLDR01**: Dutch practicing physician. **HUPA01**: Hungarian Pharmaceutical Industry Association.

The detailed code key for each respondent, their medical specialization, sector, or organization of employment, as well as interview dates, can be found in the Annex 2.

4.4. INTERVIEWS

4.4.1. SEMI-STRUCTURED INTERVIEWING

Institutional corruption of the medical profession theorizes (in short) that through systematic and strategic influence, which is legal and ethical (even necessary), the medical profession (or institution of medicine) is diverted, restricted (or made incapable) of achieving its institutional imperatives. To assess the veracity of this presupposition, the interview method was chosen. Although institutional imperatives are to be seen as described in documents such as guidelines, codes of conduct, policies,

and legislation, research aimed to investigate whether these codes of conduct are (1) expressed or represented in accounts and whether a knowledge of, or commitment to these institutional goals is expressed (how organizational goals are described or translated into practice), (2) whether these are limitations to the achievement of organizational goals and how institutional purposes are compromised in the practice, (3) what explanations may account for compromise or deviation from institutional imperatives, and (4) whether explanations reflect individual coping strategies (opinions) related to industry influence, or institutional normalization i.e. institutional goal deviation?

Building on the idea that information is not just something to be elicited, but created through mutual dialogue, a constructivist approach was adopted in the interview technique. Knowledge cannot be seen as an object to be excavated from the mind of an individual, but rather as something that is constructed both within the process of access and the very moment of interaction (Nader, 1972). "The modernist bias in such cases is hard to overcome, and is particularly acute with regard to sampling procedures, which seem to be inextricably associated with the term 'statistics.' When learning how to interview, too, students typically ask how should the interviewer 'extract,' 'persuade,' 'lure,' 'obtain,' or at the very least 'elicit' information from research subjects" (Holstein & Gubrium, 2004, pp. 144–145).

Eliciting answers to pre-defined questions, and confirming or disproving ideas based on simply reading an abundance of theoretical and empirical studies, will reproduce information that has already been constructed, rendering the interview as such a corroboration of literary deduction. Holloway and Jefferson (2000) describe the deficiencies of controlled interviews (question-answer formats) illustrating how this method is 'researcher-centric', wherein the researcher forces his/her own reality onto the research subject. The question-answer type of interview imposes upon the content of the interview: (1) pre-selecting a subject of discussion; forcing the respondent into a specific reality of the researcher's own construction, (2) answering a limited set of questions, requiring the respondent to manoeuvre within a reality that is not his/her own, and (3) asking questions that have been worded according the researcher's own interpretations of the respondent's reality, ultimately disregarding the respondent's own vocabulary and invested meaning . Achieving the most accurate account of someone else's reality requires the ability to give control over to the respondent. "Storytelling stays closer to actual life events than methods that elicit explanation" (Holloway & Jefferson, 2000, p. 304). Achieving reliability and representativeness through reproducibility of research diminishes agency, and reinstates the fallacy that behaviour is a predictable response to a certain stimulus. Analysis of narrative interpretation of one's own reality however touches upon an intrinsic human characteristic that cannot be reproduced through controlled interviews, and that is: "we organize our experience and our memory of human happenings mainly in the form of narrative – stories, excuses, myths, reasons for doing and not doing, and so on" (Bruner, 1991, p. 4).

As with respondent-driven sampling – requiring the researcher to immerse him/herself within the reality of respondent networks, analysis of narratives follows the same approach; immersion within the verbalizations of the reality of another. With the use of in-depth interviews, Gauthier (2001) illustrated how techniques of neutralization and rationalization were used by veterinary professionals when behaving in ways that "violated the sacred trust" between professional and client. According to Gauthier, in-depth interviews allowed insight into the motivations and situational circumstances behind these "professional lapses" and described as the most appropriate to investigate a phenomenon in which "conflicting goals of patient care and profit" (Gauthier, 2001, p. 469) could be analysed. My method of questioning took to incorporating semi-structured interviews, and reactionary questioning. Initial questions were needed to begin an account, but as interviews ensued, the pre-constructed questions were abandoned in favour of reactionary questions, asking respondents to elaborate on, further discuss, explain, or give examples of their statements. The written questions were returned to if the account strayed to irrelevant subjects (e.g. family, politics, pets etc.)

4.4.2. CO-CONSTRUCTIONISM IN RESEARCH

> "By offering the respondent an absolutely exceptional situation for communication, freed from the usual constraints (particularly of time) that weigh on most everyday interchanges, and opening up alternatives which prompt or authorize the articulation of worries, needs or wishes discovered through this very articulation, the researcher helps create the conditions for an extraordinary discourse, which might never have been spoken, but which was already there, merely awaiting the conditions of its actualization."
>
> (Bourdieu et al., 1999, p. 614)

A phenomenological approach to interviewing requires that the researcher take on a neutral position as listener only, and uses probes to coax, or support the respondent to go on with his/her descriptions or line of thought. The relationship between interviewer and respondent is described as being similar to student (researcher) and teacher (respondent), where the student seeks to learn about a phenomenon through "sensitive questioning" (van Maanen, 1990 cited In: Roulston, 2010, p. 17). This stance I take to be presumptuous of the power of the researcher, especially taking into consideration my position as a medical-pharmaceutical layperson. This research relied not solely on eliciting information, but learning from respondents the technicalities, jargon, and complexities of the pharmaceutical product delivery system. As such, questions had to be posed, and in fact, discussion had to be initiated by me, answers relayed back to respondents, clarification requested, and hypothetical scenarios given, to which further answers were provided, serving simultaneously as data, as well as verification of information collected from multiple sources. In this sense, all interviews were a constant deliberation and re-examination of definitions of ethical/unethical conduct and the interactions that may or may not be perceived as posing a threat to medical

autonomy and integrity in relation to industry-medicine relationships. I did in fact take on the position of student, but the student was not one that was passive and all accepting, but one that wanted to understand a phenomenon, and interpret it, as well as challenge the explanations provided by the respondents.

The need to challenge respondents' answers was necessary for two important reasons. Firstly, although prior study of the literature may produce theoretical and empirical reproduction of pre-constructed understanding, a way of testing this knowledge is to actively seek the reaction of the respondent by bringing these ideas, theories, and debates into the interview. Secondly, challenging respondents, or reflecting together on what had been given as a response, was necessitated in that professionals tend to value 'professional scripts'. When there is a status quo, or widely accepted truism, e.g. doctors save lives, they are responsible, autonomous, important, high in status, and trustworthy, the respondent will approach answers from that status quo. Especially for these respondents, governed by ethical codes of conduct and business practice, the scripts of that occupation tend to guide the respondent, and produce answers that are in line with images of the profession projected to the public. Co-constructionism breaks professional scripture – the automated responses that stem from a position. The constructionist approach to interviewing puts emphasis on the importance of both the social interaction as the construction of data, as well as looking at the resources people use to construct and describe their world to us.

The researcher as an active participant is described through the "Socratic-hermeneutic interpre-view" approach (Dinkins, 2005) in which the researcher and respondent enter into a dialogue, whereby data is co-constructed within the conversations between them. The added value of such an approach is that while taking a 'passive' approach may protect the researcher from being judged as asking leading questions, taking an active (conversational, interactive) approach to interviews provides a means for "immediate reflection for either the researcher or the participant on the ideas that emerge within the interview. Such immediate reflection is more likely to occur when the researcher creates a dialogue and is thus able to probe deeper and deeper into the respondent's beliefs that shape her understanding of the phenomenon of interest" (Dinkins, 2005, p. 2). Although contradictory to expectations of value-free research (Weber, 1949), this technique not only acknowledges subjectivity, but aims to make use of the strengths of subjective awareness – constant reflection upon our personal values and biases must persistently be applied, which allows for proper interpretation (Gouldner, 1962). As such, this method of interviewing allows for reflection through conversation and co-construction.

Researching undue influence, and the institutional corruption of the medical profession through relationships with industry is a highly sensitive subject, and as such, the conversational, co-constructivist approach serves not only to generate data in a fashion that allows respondent accounts and academic definitions to be consolidated, but alleviates the hostility that respondents feel when a researcher enters their world, raises uncomfortable questions, and then leaves to interpret what they said in his/her ivory

tower. Roulston (2001) describes the application of a Socratic-Hermeneutic Interpreview method as an interview scenario in which the researcher and the respondent *co-construct* data generating "situated accounts" (Roulston, 2010, p. 50) whereby the researcher provides possible ways of discussing a subject, and together with the respondent seek to understand a phenomenon. These unstructured interviews are viewed as accounts – "a linguistic device employed whenever an action is subject to valuative inquiry" (Scott & Lymann, 1968, p. 46) – rather than as explorations into the ethical psyche of the respondent, or merely a collection of individual experiences, which Brinkman calls "Qualitative Opinion Polling" (2007). This method of inquiry tries to break the boundaries of the interview method, using it as a tool to produce knowledge and not simply fishing for facts.

4.5. DATA COLLECTION, RETENTION, CODIFICATION, AND ANALYSIS

As a curse of the working world, personal time (meaning before or after work, or the weekends) was not easily sacrificed by respondents. As such, fieldwork required flexibility to meet a respondent at the time and place that they allocated. Rescheduling was many times not always an option and ill-advised, as rescheduling often resulted in postponing interviews for weeks or even months, and even loss of respondent willingness to participate. In addition, interviewees were all accustomed to being given an exact amount of time regarding interview length – respondents were partial to sacrificing roughly an hour of their time. The time limitations are incredibly important to be aware of because many respondents felt that by giving me an hour, they had done enough, and usually would not reply to a request to conduct a second round of interviews. The time restrictions required familiarization with the medical jargon used as much valuable time is lost if a respondent has to delve into anatomical definitions. Additionally, respondents sometimes became slightly agitated if they had to explain what to them was considered basic knowledge.

Excluding 3 respondents who did not allow for sound recordings to be made, all interview transcriptions were done using Express Scribe Transcription Software. Interviews were accompanied with field notes, used as reminders of interview scenarios and reflexive data. Interview analysis was executed in NVivo 11 Qualitative Data Analysis tool.

Analysis of interviews was done using a coding methodology, i.e. coding or "tagging" words, sentences, and paragraphs within interviews under separate keywords. The analysis revealed the nature of industry-medicine relationships as they formed and progressed along the pharmaceutical product delivery chain. The interviews reflected the conceptualization of medical autonomy described in Chapter 2; industry-medicine relationships as manifesting in micro, meso, and macro level medical autonomy. Thus coding was not only important for interview analysis, but also adopted in the structure and chronological order of the analytical chapters.

Coding of interviews formed the basis of interview analysis. As stated prior, semi-structured interview techniques were employed in a manner that initiated conversation about specific subjects. Before interviews were conducted, a topic guide, consisting of open questions was devised. Interviews followed a standard schema; beginning with a request towards the respondent to introduce themselves and describe their line of work for reasons of (1) respondent self-identification as physician, academic, journalist, lawyer, sales representative etc. and (2) as an attempt to reaffirm the respondent that it was their personal experiences and opinions that this research aimed to document.

The specific topical questions took as their basis the literature on industry-medicine relationships, condensed into 3 main discussion subjects: (1) relationships between industry and medicine in medical research, (2) relationships between industry and medicine in medical education, and (3) relationships between industry and medicine in the clinical setting specifically with regards descriptions of relationships with pharmaceutical representatives. The 3 categories, albeit generic guides, helped orientate discussions, but if respondents had particularly in-depth insight or experience in a certain discussion topic, the open questions would be set aside, and the interview would take on a degree of spontaneous conversation in which the goal was to allow richness of descriptions, and the excavation of potentially new, and important features of industry-medicine relationships.

Interviews concluded by asking respondents to reflect on industry-medicine relationships, i.e. what they thought about the role of industry in medicine. Closing interviews in this way was done with the purpose of "zooming out" so to say, to evaluate specific descriptions from a birds eye view and allow for a general evaluation of industry-medicine relationships, as well as ensuring a smooth end to the interview.

Once interviews were recorded, all were transcribed word for word, from opening introduction, to the final goodbye and imported into docx files, and subsequently imported upon completion into Nvivo. The Nvivo tool shows each interview as a document, which if separately opened can be coded. Coding is highlighting words or sections of the interview which are then filed under a node (code/tag/keyword). Nodes were assigned to sections according to a core subject of what was being described by the respondent. Initial coding resulted in circa 90 nodes, which were then grouped together under more encompassing nodes; e.g. nodes such as "job description", "reason for choosing profession", "educational background", "prior experience" were grouped together under a larger node named "introduction". Following the method of grouping nodes, larger subject areas were identified. Listed below is an overview of grouped nodes under larger nodes for the reader to get a sense of grouping and sub-grouping of nodes hierarchically.

1. **Introduction**
2. **Role of industry in medicine**
    a. *Industry in Medical Research*
        i. Preclinical research

1. Industry in academia, technology transfer, spin-out, biotech

ii. Clinical research
    1. Industry funding of clinical trials, Clinical Research Organizations

iii. Post Marketing Trials
    1. Seeding trials
    2. Medicines approval process, regulators

b. Industry in Medical Education

i. Evidence Based Medicine
    1. Medical Guidelines
    2. Key Opinion Leaders
    3. Continuing Medical Education

c. Industry in Clinical Practice

i. Continuing Medical Education sponsorship
ii. Sales representatives
iii. Transparency and disclosure of direct payments

3. Closing (general remarks)

The above is a bird's eye view of the larger grouping of nodes, which shows how the content of interviews followed the pharmaceutical product life cycle from pharmaceutical product research to clinical use of a medicine. Interview analysis in this way was not only revealing as to the rich descriptions, but revealed the procedural, and consequential nature of industry-medicine relationships, and how influence manifests within micro, meso, and macro level medical autonomy, showing industry influence not as isolated events but as a process.

The coding hierarchy is the skeletal structure of the forthcoming analytical chapters, within which interview descriptions and accompanying documents research and assessment (triangulation of sources) will ensure.

4.6. CONCLUSION

Researching the crimes of respectable people and professions is not only difficult due to the absence of criminal definition, but it is made more so because it requires studying institutions that we are usually ambivalent about. We do not always entertain much curiosity about the structures, organizations, or bureaucracies that govern our daily lives, unless those structures negatively affect us directly. The banality of everyday life and its acceptance – it's just the way things work – promotes unawareness, limiting societal engagement in the systems that control their lives. This in turn perpetuates control over definitions of right and wrong, legal and illegal behaviour within this less visible arena, to the organizational actors themselves (Nader, 1972; Gusterson, 1997). Healthcare and the monopoly of the medical profession over provision of health is, to the citizen, a faceless mechanism, one that does not open

itself up to questions and explanations beyond that of the actual situation wherein a patient is treated by the doctor. Seldom do we spend time thinking about the entire mechanism, the institutions of healthcare, the complex public and private machinery, and the constant battle of competing interests that precede the actions of a physician filling out our prescriptions for a particular drug in the confines of the clinic. A qualitative approach to this field of study evokes a curiosity and a mode of inquiry that strives to connect and understand these 'backstage performances' that we may not ever see or realize.

The methodological chapter has thus aimed to introduce not only the modus operandi of gathering data, but also an overview of the constructionist approach necessitated by the complexity of the research subject, the qualities of the field, and the intention to use method as data generative. This research identifies the subject of the institutional corruption of the medical profession as a phenomenon to be investigated and described, but also takes the opportunity to use less traditional interviewing techniques which have been chosen with an awareness of respondent and researcher qualities, as well as the desire to add stories to the faceless system of pharmaceutical product delivery.

CHAPTER 5: MORE THAN A MANUFACTURER: THE ROLE OF INDUSTRY IN MEDICINE

"Pharmaceutical companies are increasingly looking to move beyond product to solution; to become a total partner rather than just supplier."
– Dr Uloff Münster, Managing Director of Merck
(Netherlands Pharma Report, 2011, S11)

The medical profession is only but one actor within the wider healthcare system. Krause (1999, In: Light, 2010) places the professions on one corner of a hypothetical triangle, the two opposite corners being the state and capitalism. The triangle is illustrative of the general frame of healthcare itself being an arena of competing institutional interests, with the profession of medicine as one countervailing power confronting the profit-driven pharmaceutical industry and the state. A system is "understood as an arrangement of parts and their interconnections that come together for a purpose". The Health System is then defined as a system whose purpose is the concern for the health of people (World Bank, 2007: Annex L). The World Health Organization denotes a "Health System" as the collective term for all organizations, individuals and activities "whose primary interest is to promote, restore, or maintain health".[5] The 'healthcare system' is a concept that incorporates any and all aspects that influence the health of a society including socio-economic factors such as poverty, education, healthcare infrastructure, as well as the extended political environment (World Bank, 2007) and are complex structures determined by the boundaries of the nation-state: the "political, historical, cultural, and socio-economic traditions" of each country they function in (European Parliament Working Paper, 1998, p. 5). In this chapter I will discuss the regulatory framework; international harmonization of pharmaceutical Research and Development (R&D) regulation, national medicines laws of Hungary and the Netherlands, pharmaceutical industry self-regulation, and the codes of conduct of the medical profession, to illustrate Krause's triangle (Light, 2010) in the regulatory playing field.

The profession of medicine claims an expansive arena of responsibility, and manifests its professional control outside of the boundaries of clinical practice, as in line with Freidson's (1970) explanation of professional dominance extending to all stages of healthcare provision throughout the health system. Looking at the framework of medical professionalism and autonomy, medical practice does not begin, but rather ends with individual (micro level) clinical decision-making. The role of the profession in the health system is apparent in the stages of medical knowledge production and development, which then defines the activities of other healthcare actors (e.g. disease identification, most pertinent healthcare policy initiatives, disease burden, diagnosis,

[5] http://www.wpro.who.int/health_services/health_systems_framework/en/

healthcare delivery, and so forth). Pharmaceutical products make up one of the vital components in healthcare actor decisions (which diseases should be researched, what treatment can be developed, how much treatment costs, etc.). Busfield (2006) describes 2 stages of the making of scientific facts of a pharmaceutical drug: (1) the pre-approval stage – all knowledge that is produced prior to market authorization of a pharmaceutical product, and (2) the post-approval stage – knowledge produced after authorization. The role of the medical profession is not restricted to clinical practice but extends to these fact-making stages; it is this that I shall describe in this section. Curious as to the accounts of doctors specifically regarding how they viewed pharmaceutical industry collaboration, I asked doctors what they saw the role of industry in medicine to be. The generality of this question was what made it so important, because it required that the respondent, as well as myself, discuss a role – i.e. a function that the pharmaceutical industry performs in medicine, and then assess how a role or function might manifest as a relationship between medicine and industry, and what form that relationship may take. The following quote from a practicing physician in Hungary sums up the role of industry in medicine.

"*(The role of the pharmaceutical industry) is very important of course. In essence, the pharmaceutical industry is the Maecenas, and (regarding) the different (medical) specializations it is the main driving force, (with respect to) what type of new medicines get (implemented) into practice, to what extent are there new, innovative products, because these (products) stir up (vitalize) the profession. Not just from the point of view of medical practice, but also indirectly, creating the possibility of organizing congresses, attending congresses abroad etc. So a person is able to take part in the international circulation (of information).*" [HUDR01]

With the description of the role of industry in medicine (a diversification of industry functions) comes a system of professional organization very much in line with the macro, meso, and micro levels of autonomy. Investigations into this role lead to the identification of the structure of the medical organization along the chain of pharmaceutical product delivery. This structure is supported by explanations from respondents in the field, as well as an analysis of the dynamics of the respondent-driven sampling technique. This thesis has thus adopted an analysis of industry-medicine relationships along the pharmaceutical product lifecycle – the stages of drug research, development, authorization/licencing, and distribution of information to physicians (advertising). I shall discuss the regulatory and technical-scientific requirements, and the harmonization processes that characterize the technical aspects of pharmaceutical R&D. I will then illustrate how stringency in drug research and development has redefined the meaning of "evidence" in medicine, and the phenomenon of evidence-based medicine, and how medical science is translated into clinical practice. Contingently, an enumeration of the regulatory framework in Hungary and the Netherlands shall be given as to what legislative, self-regulatory, and professional codes define and regulate industry-medicine relationships.

An overview of the regulation alongside the pharmaceutical product lifecycle is important for this research, since what is seen as ethical and proper scientific conduct is a product of historical development linked to both the fortification of medical professionalism, authority and autonomy, as well as the increasing role of industry as medical Maecenas. Medical research and development, evidence-based medicine, and informed clinical practice evolve from continued development of the roles, and ethical and financial responsibilities of industry and medicine. Additionally, the regulatory overview will show a binary division alongside Busfield's (2006) division of creation of scientific fact about a pharmaceutical product i.e. a regulatory framework for pre-approval stages of drug development (medical research, clinical trials, and marketing authorization procedures), and another for post-market authorization (marketing to physicians). This regulatory division weighs heavily on whether industry-medicine interactions are considered to be proper or "improper" (EC Study, 2013). Improper industry-medicine relationships which are considered to endanger the integrity of physicians – and which enjoy the most amount of regulation from an ethical perspective – are mainly considered emergent in the post-approval stage of industry-medicine interactions, undue advertising, and individual financial perks and gifts given to individual doctors. This type of regulatory focus promotes individual culpability, reinforces the understanding of corruption limited to bribery, enables respondents to categorize many unethical actions as proper conduct provided it happens pre-approval, and dismisses non-financial industry influence. Dualistic regulation also creates difficulty in understanding pre- and post-approval stages as different phases of the same system, especially from an ethical perspective.

I shall return to this assertion in the analytical chapters, evaluating respondent accounts of ethical and unethical practices alongside the contents of ethical and technical regulatory documents. To be able to do this, and see medical knowledge production, interpretation, and application embedded in a process within a regulatory context, the technical stages of the pharmaceutical product lifecycle and accompanying regulatory frameworks and standard requirements must be introduced in this separate chapter.

5.1. THE PHARMACEUTICAL PRODUCT LIFECYCLE

"*Yes, this is a large area. Large. It is not so transparent, especially seeing it from the outside, but even for those people who are on the inside*." [HUREG01]

Pharmaceuticals today are required to undergo lengthy and expensive clinical testing, which are all aimed at producing enough scientific evidence that allows for an evaluation of whether the drug in question is deemed both safe and effective to be allowed onto the market, prescribed by doctors and used to treat patients. The requirement to clinically appraise medicines was not always the norm, or at least not regulated to the extent that it is today. It was in fact due to the horrible consequences of Thalidomide in the 1960s in Europe which led to regulatory intervention in clinical research and the development of medicines for human use. Thalidomide was

discovered in the 1950s by the German pharmaceutical company Chemie Grünenthal, (also the first company to introduce antibiotics to the German market after the Second World War). Just as antibiotics were called "magic bullets" (a term used to describe the ideal medication: complete efficacy, and no side-effects), so too Thalidomide was a drug that was advertised as being without risk. Such was the belief in the safety of Thalidomide – sold as a sleeping pill or mild tranquilizer – that the drug was marketed as being able to relieve morning sickness and so prescribed to pregnant women. At the time, there were no universally accepted standards for what constituted enough or reliable tests to determine safety and Chemie Grünenthal relied on the clinical experience and "impressionistic testimonials" (Braithwaite, 1984, p. 67) of doctors, and short clinical trials with small numbers of patients. It was indeed the absence of stringent evidentiary requirements in Europe that made chief of the Division of New Drugs, and director of the Divisions of Scientific Investigations at the US Food and Drug Administration (FDA) Dr Frances Oldham Kelsey, sceptical about the safety of Thalidomide (McFadden, 2015; Hamburg, 2012). Her suspicions proved right when the horrifying side-effects of the drug came to light. Thalidomide was found to cross the placenta, and affect the unborn child still in the womb. These babies were born with a condition called Phocomelia, or malformation of the limbs. "Some of the thalidomide children have no arms, just flippers from the shoulders; others are without legs as well – limbless trunks, just a head and a body" (Braithwaite, 1984, p. 65).

In response to the Thalidomide disaster that swept across Europe, the United States Congress enacted the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act in 1962 (Greene & Podolsky, 2012), tightening the standards of clinical testing by requiring provision of evidence of both safety and efficacy of pharmaceuticals before their approval onto the market. Europe (EEC) and Japan were soon to follow this example, which has led to the global harmonization and standardization of clinical trial processes. Within the European Community, the first directive providing the regulation of medicinal products was enacted in 1965 (Council Directive 65/65/EEC), but it was not until 1975 that common standards for toxicology and pharmacological testing were devised (Abraham & Davis, 2013; Bothwell et al., 2016). Today, safety and efficacy standards for market approval of pharmaceutical products in the European Union are established by the European Medicines Agency (EMA), the central EU authority for medicines regulation and authorization. Requirements for the conduct of clinical trials are laid down in Directive 2001/20/EC (Clinical Trials Directive). As of May 2016, the Clinical Trial Regulation EU No. 536/2014 regulates the requirements for medicines approval in the European Union member states. The transition period since its implementation is still underway, but the directive sets forward the intention to continue harmonization of clinical trials and pharmaceutical authorization procedures in EU member states, which have their own medicines approval authorities, as well as market authorization review processes. Council Directive 2005/28/EC (The GCP Directive) establishes the criteria for Good Clinical Practice (GCP) in line with the International Conference for the Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP). Currently adopted in the

EU, USA, and Japan, ICH GCP standardizes clinical trial requirements both regarding ethical and scientific minimums. The ICH GCP guidelines have their origins in the Declaration of Helsinki – an ethical document produced by the World Medical Association for the medical community, which lays down the core ethical principles of conducting experiments on human subjects. ICH GCP guidelines maintain the well-being of patients that are enrolled in clinical trials, and serve as an assurance mechanism for the general public, that the rights and safety of trial participants will be respected at all times. It also serves to guarantee that the data derived from clinical trials are credible (ICH GCP, 1996, p. 1). Harmonization is an international endeavour, and the processes from drug research to subsequent development and finally market authorization go through the standard 4 phase model, known as the lifecycle of a pharmaceutical product, or product lifecycle process,[6] illustrated in the image below.

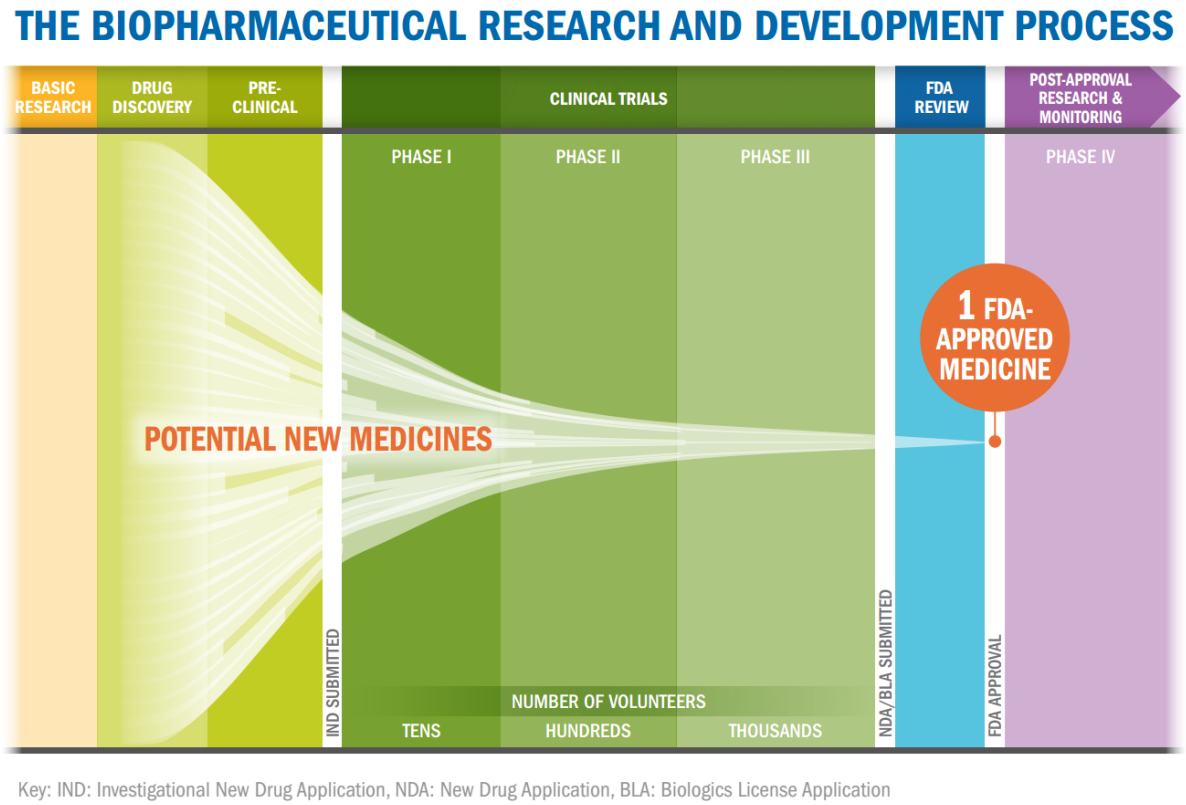


Image source: Pharmaceutical Research and Manufacturers of America (PhARMA, 2015) "Biopharmaceutical Research and Development. The Process behind New Medicines"

5.1.1. BASIC RESEARCH, DRUG DISCOVERY, AND PRECLINICAL RESEARCH

Drug discovery is the stage in which innovation begins. In the case of pharmaceutical products, the discovery stage is where molecular compounds are tested in a laboratory to see whether a compound might hold any beneficial effects against a disease. Enormous amounts of compounds are tested in the research setting, only few of which end up showing signs of efficacy, or potential use in the medical setting. This stage is

[6] https://www.fda.gov/ForPatients/Approvals/Drugs/default.htm

also known as “in vitro” testing, where the study of a compound is constricted to petri-dishes and test tubes. Research attempts to isolate a “lead compound” – a molecule that has a desirable effect on the disease target, and which may potentially become a pharmaceutical product (PhARMA, 2015). Once a lead compound has been identified by scientists, the preclinical phase of research begins, when the lead compound is tested for the first time in living organisms, also known as “in vivo” studies. Testing in animals aims to study the basic chemistry of a potential drug, focusing mainly on pharmacological and toxicological data – whether the compound is effective, and safe enough to be tested in humans. The majority of preclinical research is done in rodents, small mammals, and non-human primates (Novo Nordisk, 2015).

5.1.2. CLINICAL RESEARCH

If preclinical testing has provided enough evidence to convince scientists that a compound holds potential as a marketable drug, and would be safe to use in humans, the compound moves to the clinical research phase where it is tested for the first time in human subjects. Testing in humans is again divided into 3 clinical trial phases. As the image above shows, the 3 phases of clinical trials – Phase I, Phase II, and Phase III – in human subjects are also a further vetting process of the tested drug, showing that in reality, although many compounds are identified, only a small percentage ever end up becoming medicines.

Phase I clinical trials usually comprise of healthy volunteers, are conducted in a sample size of 20-100 participants whom are administered the drug over the course of several months. The main purpose of Phase I clinical trials are to test the safety of the drug, as well as the right dosage to administer. According to FDA data, about 70% of Phase I clinical trials make it to Phase II. In contrast with Phase I trials, Phase II trials test the drug in volunteers that have the targeted disease or condition. The length of Phase II trials are longer, taking anywhere from a few months to about 2 years, and includes a larger population size between 100-300 research participants. Phase II studies drug efficacy, and monitors side-effects, or adverse drug reactions (ADRs). The FDA estimates that 33% of Phase II drugs move on to the next step. In final Phase III, trials are the largest in participant size (300 to 3000 patients), as well as longest in duration (from 1 to 4 years). Phase III trials test drug efficacy and ADRs. The success rate of drugs moving to market authorization is estimated to be around 25-30%.

Although varying in trial duration based on medicine and disease, the general consensus is that it takes about 6 to 12 years for a drug to go from compound to clinically tested and approved medication. (www.fda.gov, PhARMA, 2015, www.efpia.eu)[7]. Lengthy trials are also expensive, and any entity that indulges in funding trials with such high risks is rewarded for doing so by the medicines patent system, which allows for the funding entity and product licence holder to be awarded patents to manufacture and distribute the medicine for up to 20 years, including the

[7] http://www.efpia.eu/about-medicines/development-of-medicines/clinical-trials/

years spent on clinical trials (Lehman, 2003). The entire innovative pharmaceutical industry makes its profits from the competitive patent system.

5.1.3. MEDICINES REGULATORY AUTHORITY REVIEW AND AUTHORIZATION

When all phases have been completed, the data derived is submitted (called a new drug application: NDA) to the relevant medicines regulatory authority which decides, based on the data, whether the drug is safe and effective enough to be given a market authorization. It is only once the complete cycle of clinical testing has been done, and only after review by the competent authority that a decision is then made whether a drug should be granted approval and can be sold to consumers.

5.1.4. POST-MARKETING SAFETY MONITORING, PHASE IV TRIALS

Finally, there are Phase IV clinical trials, or post-marketing research, which is conducted once a drug has been put on the market. The purpose of Phase IV research is to monitor the product as is used in real-life clinical practice – its rationale being that pre-authorization trials cannot provide data that is 100% conclusive since these trials are run in controlled settings, where research participants are chosen according to stringent inclusion and exclusion criteria, and cannot account for patients with comorbid illnesses, taking more than one type of medication, taking medication over much longer periods of time, or lifestyle choices that may interplay with the medication. Phase IV trials are continued pharmacovigilance studies noting ADRs, but are not as highly regulated as pre-authorization processes, since the medicine is already approved and trials comprise of using the medication in line with the approved use and indication.

These stages will be very important to keep in mind as we proceed to the analysis, because the relationship between industry and medicine is at its most potent in medical knowledge production. Too often these scientific stages are considered simply technical contexts, which are in danger of being dismissed as irrelevant for social scientific research. As I have said previously, however, the study of institutional corruption requires the understanding of these seemingly unexciting scientific processes, because as I shall assess, these technical complexities hide and confound unethical behaviour.

5.2. GOOD SCIENCE AND GOOD MEDICINE: ADOPTING EBM IN MEDICAL PRACTICE

How has harmonization in clinical trial regulation taken effect in the medical profession? In addition to the stringent requirements of clinical trials, another outcome of the Thalidomide scandal was the deliberation of what qualified as adequate evidence upon which decisions to approve drugs could be based. Alongside clinical trial quality

controls, the Kefauver-Harris Amendments (1962) addressed the need for clinical trials of pharmaceuticals to provide "substantial evidence" defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labelling or proposed labelling thereof" (Kefauver-Harris Amendments section 102, subsection e.). Subsequently adopted as the baseline for good evidence on the European continent, the amendment interpreted substantial evidence to be produced by way of using Randomized Controlled Trials (RCTs) in clinical research. RCTs were already used in medical research during the late 19th century and increasingly so during the "golden age of doctoring" when the profession of medicine adopted a scientific foundation upon which clinical practice was based. "By the early 20th century, innovators had introduced many clinical trial techniques to eliminate bias, including blinding, alternate assignment to trial groups, and statistical analysis" (Bothwell et al., 2016, p. 2175). From the 1970s RCTs were regarded as the gold standard in the production of medical knowledge. RCTs are performed by randomly assigning research participants into two or more groups where one group receives the treatment that is being tested, while the other receives a comparator drug or a placebo. Double-blind randomized control trials are conducted when neither the investigating physicians administering the medication, nor the participating patients, are aware of which group they are assigned to, not knowing if they are receiving the innovative drug, comparator or placebo. Double-blinding is a technique used to minimize the effects of bias in clinical trials, and is considered the most scientifically sound means of testing pharmaceutical drugs. Double-blind randomized control trials are the norm for clinical trials within the EU (Directive 2001/83/EC section 5.2.5.1)

The quality and veracity of evidence in medicine is paramount, and so it has led medicine to develop a "hierarchy of evidence" aimed to inform not only scientists but also clinicians as to the dependability of facts regarding pharmaceutical drugs. The reason this is discussed in this chapter is intentional for understanding that clinical R&D technicalities not only determine the practice of medicine, but further strengthen the symbiosis between the pharmaceutical industry and the medical profession not only in medical knowledge production, but knowledge interpretation and application. Clinical trial stringency produces a hierarchy of research designs and data that are considered more powerful than others. This hierarchy of evidence is presented below.

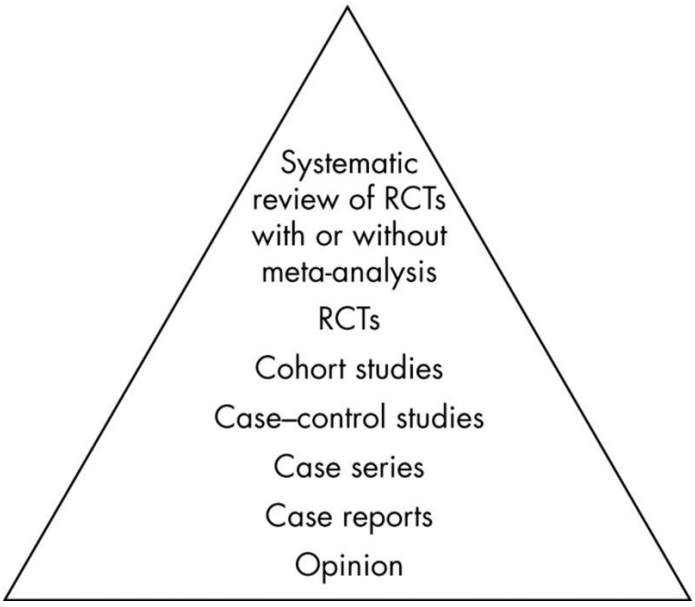


Image source: Akobeng, A. K. (2005) Understanding Randomized Control Trials. *Archives of Disease in Childhood*, 90(8), p. 841

Systematic reviews and meta-analyses are generally considered the crown of all evidence: systematic reviews being the collection of all available evidence aimed at answering one particular research question, while a meta-analysis is the use of statistical methods to summarize the results of multiple clinical trial studies. The placement of systematic reviews and meta-analyses at the top of the hierarchy has been scrutinized by some authors claiming that the heterogeneity of clinical trials constitutes a limitation in conducting meta-analysis, while systematic reviews may produce uncertainty as to the interpretation of results due to variations of analytical methodologies (Murad et al., 2016). Nevertheless the consensus remains that RCTs provide the strongest evidentiary power with regards to pharmaceutical products. As a respondent medical journal editor respondent stated: "*We give information about randomized, double-blind trials on drugs. We hardly ever write about un-blinded randomized trials, because they are flawed because the doctors and the patients know what they receive. (…) The highest level is randomized control trials, and the lowest level of evidence is the expert opinion.*" [NLMJ01].

The story we began with, the marriage between science and medicine in Chapter 1, has had enormous consequences for the standards of knowledge production of pharmaceutical products (clinical trials), as well as devising a hierarchical model for what counts as the strongest evidence on the efficacy and safety of a medical intervention (hierarchy of evidence). As I discussed previously, medicine solidified its autonomy in the age of antibiotics and rode the wave of success with the further burst of new medications that arrived in the 1950s. In addition, I spoke of the rise of the managerial elite within medicine, mitigating high degrees of variation among practitioners. Managerial oversight and governmental controls and regulation in clinical trials, led to the adoption of RCTs as the gold standard for medical knowledge production in the 1970s. This directly resulted in the development of evidence-based

medicine (EBM) in the 1980s (Timmermans, 2015). EBM, also known as evidence-based healthcare (Pearson et al, 2005) is a scientifically supported approach to healthcare provision where medical diagnosis and application of treatment is based on systematically and scientifically tested, verified, and reviewed evidence (Sackett et al., 1996; Sackett, 1997; Lambert, 2006; Timmermans, 2015). The 'hierarchy of evidence' triangle is – in addition to a "restratification of medical knowledge production" based on strength of evidence in the medical research setting (Timmermans, 2015, p. 314) – also used as a guide for physicians in individual decision-making processes revolving around diagnosis and treatment in the clinical context. EBM is the translation of medical clinical research and scientific development into the medical guidelines and protocols which determine the work of practicing physicians providing the scientific basis behind the art of medicine. Trials, of which the majority are funded by pharmaceutical companies, provide the strongest scientific evidence, which in turn determines the knowledge base for the medical profession, and is another vital consideration for the analysis of institutional corruption of medical knowledge interpretation.

5.3. REGULATION IN HUNGARY AND THE NETHERLANDS

Having discussed the role of industry in clinical trials, and its direct implications for the medical profession in the adoption of EBM, we come to the third point of the triangle in enumeration of national medicines law. The legislative plane will be complemented by industry self-regulatory documents and descriptions of medical professional codes of conduct. Citing a respondent from the Dutch innovative pharmaceutical industry association, laws provide an abstract framework of what areas are regulated, while industry and professional codes rectify for the generality of law [NLPA02].

In both Hungary and the Netherlands, European Union Directives and ICH GCP guidelines have been implemented into national law. Edict No 235/2009 (of 20 October 2009) of the Hungarian government sets out the rules governing authorization procedures of biomedical research, clinical trials with investigational medicinal products for human use, as well as with medical devices intended for clinical trials, and implements ICH GCP, while the Dutch equivalent is the 1998 Law on Medical Research Involving Human Subjects. As regards the national medicines laws pertaining to drug quality, distribution, and advertising, as well as the national medicines authorities responsible for legislative oversight and medicines authorization, differences arise in Hungary and the Netherlands.

5.3.1. HUNGARY

In Hungary, the National Institute of Pharmacy and Nutrition (OGYÉI) established on the 1st of March 2015, and appointed by Edict 25/2005. (II.25.), is the licencing authority for pharmaceuticals (www.ogyei.gov.hu). The establishment of the OGYÉI

was a result of merging the National Institute of Pharmacy (OGYI), and the National Institute for Quality and Organizational Development in Health Care and Medicine (GYEMSZI). In addition to the merging of these two regulatory bodies, the OGYÉI has also been delegated some of the tasks of the National Public Health and Medical Officer Service (ÁNTSZ), as well as incorporated the National Institute of Nutrition and Dietetics (OÉTI), originally an independent research institute, which now functions as a separate department within the OGYÉI (www.ogyei.gov.hu). The OGYÉI fulfils a dual task of being the drug controlling agency, as well as the methodological and research institute of Hungary. In sum the OGYÉI is responsible for:

- examining quality of medicinal products and monitoring of adverse drug reactions
- the authorization of medicinal products as well as market withdrawal of defective or dangerous medications
- authorization of the manufacture and distribution of medicinal products and parallel imports
- controlling goods manufacturing, distribution, clinical and laboratory practices regarding the development of medicinal products
- pharmacovigilance
- authorization of clinical trials
- monitoring off-label indications
- monitoring individual demand and dispensing of medicinal products
- since January 1st 2017, the OGYÉI has also been assigned the task of authorizing clinical trials for medical devices
- Enforcing the standards pertaining to advertisement of medicinal products as well as other informational activities

In Hungary the two main laws that govern medical product authorization, licencing, distribution, marketing, provision, labelling, and pharmacovigilance are the: Act XCV of 2005 on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products (GyTV) and Act XCVIII of 2006 on the General Provisions Relating to the Reliable and Economically Feasible Supply of Medicinal Products and Medical Aids and on the Distribution of Medicinal Products (GyFTV)

5.3.2. THE NETHERLANDS

Contrary to the example of Hungary, where one central agency is responsible for almost all aspects of monitoring of pharmaceutical products from research and development all the way to market authorization and pharmaceutical advertising, these tasks are divided among separate authorities in the Netherlands. For the purpose of this research, two authorities are of particular importance, these being the Dutch

Healthcare Inspectorate (IGZ) and the Medicines Evaluation Board (CBG/MEB). Both agencies belong to the Dutch Ministry of Health, Welfare and Sport.

In the Netherlands the national law for medicines regulation is the 2007 Dutch Medicines Act (GnW), which defines the responsibilities of the Dutch Medicines Evaluation Board (MEB-CBG website).The Dutch MEB is responsible for decision making, evaluation, and providing market authorization for medicines intended for human use. In addition the MEB monitors safety, efficacy, and the risks associated with authorized medicinal products. It maintains a database that contains information on all medicines authorized in the Netherlands, and also provides scientific advice to pharmaceutical companies related to NDA submission procedures.

The IGZ[8] is responsible for monitoring the quality and standards of healthcare delivery: safety and "quality of medical care, medicines, and medical products" (IGZ website). As part of its activities, the IGZ is increasingly looking at monitoring pharmaceutical company advertising "to prevent unwanted interference" or undue influence (Het doel is ongewenste beïnvloeding voorkomen. IGZ website).The IGZ accepts complaints regarding healthcare service and delivery, providers, or companies, and launches investigations, the legal basis for which is Article 36 of the Health Act (1956). Regarding pharmaceutical products, the IGZ monitors compliance with the 2007 Dutch Medicines Act (GnW).

5.4. POST-AUTHORIZATION AND MARKETING LEGISLATION

Due to the European Union's efforts towards harmonization across all aspects of the regulation of medicinal products (Lewis & Abraham, 1998), harmonization covers both the medicines authorization procedures (from regulation of clinical trial procedures to market authorization) as well as the provisions for providing information on pharmaceutical products to both the general public as well as those healthcare professionals who are "qualified to prescribe or supply them"[9]. Here we come to the regulation of knowledge produced about a pharmaceutical product after it has been given market authorization. These regulations are laid down in the Directive 2001/83/EC. The Directive 2001/83/EC focuses on the information provided to prescribers and categorizes them as either being informative or advertising. As a definition of advertising, the Directive 2001/83/EC defines advertising of medicinal products as including "(…) any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products." (Title VIII Advertising, Article 86). The text of the Directive

[8] At the time of fieldwork, the Dutch Healthcare inspectorate was known as the IGZ. As of October 1st 2017, it incorporated the Inspectorate of Youth Care, and is now known as the IGJ. (www.igj.nl)

[9] Notice that it is persons qualified to prescribe and supply, and not solely doctors or physicians. Prescribers and suppliers may be pharmacists, prescribing nurses, or any other healthcare professionals that are allowed to prescribe medication. The right to prescribe is detailed in national laws. For the purpose of this thesis, prescribers shall mean physicians and doctors who have a university degree in medicine.

2001/83/EC deems advertising to happen on 2 platforms: (1) direct to consumer advertising, and (2) advertising to persons qualified to prescribe or supply medicinal products. Advertising to prescribers manifests via the practice of

1) pharmaceutical companies employing sales representative to visit physicians,
2) supplying medical samples to physicians,
3) providing gifts, offers, promises, benefits or bonuses either financial in nature or in kind,
4) and financially sponsoring physicians' attendance and hospitality costs for medical congresses.[10]

The Directive 2001/83/EC, however, notes that advertising does in fact contribute to the entire body of information supplied to prescribers, an acknowledgement that the line between information and advertising is a thin one, and thus while advertising is inarguably done to *influence* prescribers, the necessity of providing information to prescribers still warrants advertising (Directive 2001/83/EC (47)). The solution to minimizing industry influence over prescribing is achieved by subjecting advertising practices to "strict conditions and effective monitoring" (Directive 2001/83/EC (47)), the mode of which is not explicitly stated in the Directive itself, but is subject to national regulation, stipulated in Council Directive 84/450/EEC of 10 September 1984 relating to the approximation of the laws, regulations and administrative provisions of the Member States concerning misleading advertising (Directive 84/450/EEC). As per advertising, member states are responsible for ensuring "adequate and effective means exist for the control of misleading advertising"[11] (Directive 84/450/EEC, Article 4 (1)). However, the Directive 2001/83/EC is important in that it identifies what kind of advertising practices are allowed, as well as roughly asserting the frame in which advertising may still be considered proper. This is important in that the Directive 2001/83/EC forms the basis of what is implemented in national law, as well as what is incorporated into the pharmaceutical self-regulatory framework which I shall discuss in a moment. As regarding the above 4 modes of common practice of pharmaceutical company advertising to physicians, Directive 2001/83/EC stipulates that:

1. Pharmaceutical sales representatives **"**have an important role in the promotion of medicinal products", and should be subject to "certain obligations". The provision of medicine samples to prescribers is deemed

[10] Not considered advertising is the information found on medicinal product labels, and accompanying package inserts (information on use of medication, dosage, warnings, and side-effects, correspondence that is accompanied by information of a non-promotional nature such as a need to answer a specific question in relation to the medicinal product, and "factual, informative announcements and reference material" that related to changes in the package insert, ADR warnings, trade catalogues, and medicines price lists, provided that they do not contain any product claims) (See Directive 2001/83/EC, Title VIII, Article 86/2).

[11] 'misleading advertising' means any advertising which in any way, including its presentation, deceives or is likely to deceive the persons to whom it is addressed or whom it reaches and which, by reason of its deceptive nature, is likely to affect their economic behaviour or which, for those reasons, injures or is likely to injure a competitor (Directive 84/450/EC, Article 2(2))

necessary, "so that they can familiarize themselves with new products and acquire experience in dealing with them" (Directive 2001/83/EC (51)).

2. Where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy.
3. Hospitality at sales promotion events shall always be strictly limited to their main purpose and must not be extended to persons other than health-care professionals.

Accordingly, all advertising to physicians in the European Union will be deemed acceptable should they meet the above criteria which requires that physicians be able to make decisions "objectively, without being influenced by direct or indirect financial inducements" (Directive 2001/83/EC (50)), and should have access to a "neutral, objective source of information about products on the market" (Directive 2001/83/EC (52)). It is here that national legislation, pharmaceutical industry self-regulation, as well as the profession of medicine is given freedom of interpretation as to where the boundaries of acceptable and unacceptable, objective and biased information are to be found.

Legislation in both Hungary and the Netherlands implement Directive 2001/83/EC as regards to what is considered advertising, what is permissible, what restrictions should be enforced, and what general standards should be maintained to ensure that the advertising activities remain within the realms of acceptable influence in the GyTV, GyFTV and the GnW respectively. In Europe, Direct to Consumer Advertising (DTCA) is only permissible for medication that does not require a prescription (over the counter medication: OTC). As such, advertisements of Prescription-Only Medication (POM) are allowed only to healthcare professionals who are authorised to prescribe and dispense medication. Prescribers in Hungary are physicians, dentists, and pharmacists, while in the Netherlands these are physicians, dentists, midwives and prescribing nurses. Due to implementation of EU law, the following general stipulations are found in the National laws of both Hungary and the Netherlands regarding promotion of medicines:

It is prohibited to advertise a pharmaceutical product for which a market authorization has not been given (GnW Art. 84/1, GyFTV Chapter II § 11/A). The advertisement must provide, and must be limited to its promotion for the indication for which it had been approved (prohibition of off-label advertising). Information should be balanced and objective, and may not be misleading. (GnW Art 48/2-4, GyFTV Chapter II § 11/B (1)-(2)). Free samples of products may be given to prescribers, provided that the label indicates that it is a free sample and may not be sold, and must be the smallest package available on the market. Only two samples are allowed to be provided per year. (GnW Art. 92, GyFTV Chapter II § 15, further regulated by Ministry of Health Degree 3/2009 (II.25)). Doctors are not allowed to ask for, or accept inducements, gifts, financial or

in kind, unless these are inexpensive or minimal value. Gifts of any kind must be that which the practitioner can use during the course of his/her practice or be beneficial for the patient. Hospitality agreements, financial sponsorship for participation of medical events are allowed, in so far as they are inexpensive, and that sponsorship is limited to strictly educational events (GnW, Art. 95, GyFTV Chapter II § 14(1)-(2)).

With slight variations, the legal provisions of advertising to doctors, provision of gifts, and sponsorship and hospitality agreement in the National Medicines Laws of Hungary and the Netherlands are quite similar. In Europe (and in Hungary and the Netherlands) the further specification of ethical and unethical marketing practices has adopted a system of pharmaceutical industry self-regulation which goes beyond the legal requirements that are stipulated in the National Medicines Laws. Pharmaceutical industry associations have designed and implemented their own Codes of Conduct regarding ethical medicines promotion, and incorporate the basic EU legislative and national legislative requirements. The Codes are adopted, implemented, and monitored by pharmaceutical industry associations.

5.5. INDUSTRY SELF-REGULATION AND CODES OF ETHICAL PHARMACEUTICAL MARKETING

Similarly to international and national laws which take on a hierarchical approach, pharmaceutical industry self-regulation also has its international, and national association codes. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) is the international body, a member of which is the European Federation of Pharmaceutical Industries and Associations (EFPIA). In concert these bodies issue general, international codes of conduct for ethical marketing practices. EFPIA then has as its members the European national industry associations, which build on EFPIA codes, and implement them in the national context. For Hungary, this is the Association for Innovative Pharmaceutical Manufacturers (AIPM), and in the Netherlands is NEFARMA.[12] The image below shows the hierarchical structure of both legislation and industry self-regulation in the international, regional, and local contexts.

[12] Known as NEFARMA at the time of fieldwork, it is as of September 2016 now known as the "Association of Innovative Medicines":
https://www.verenigginginnovatievegeneesmiddelen.nl/homepage

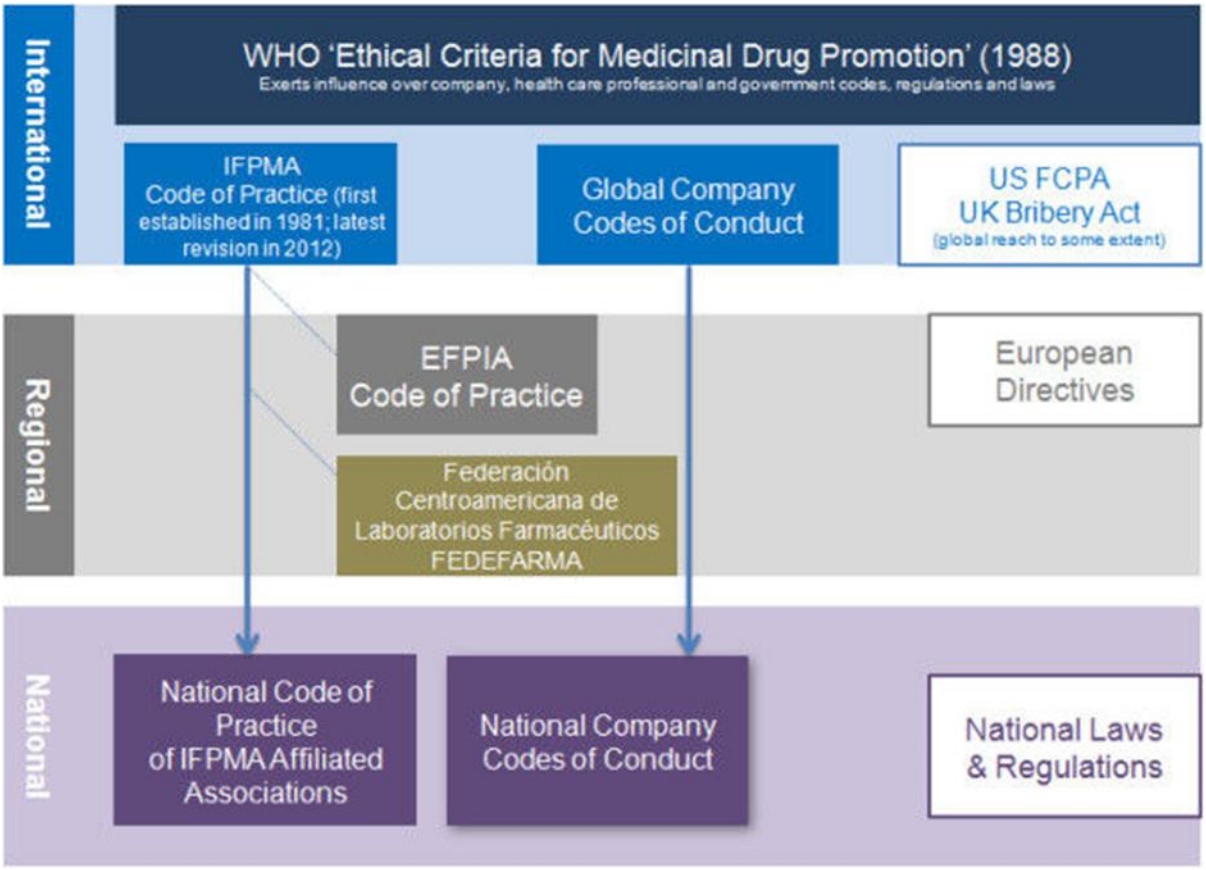


Image source: Francer et al. (2014) Ethical pharmaceutical promotion and communications worldwide: codes and regulations. *Philosophy, Ethics, and Humanities in Medicine*, 9(7), p. 2

Both the Dutch and the Hungarian industry self-regulation for ethical promotion are based on the EFPIA code on the promotion of prescription-only medicines to, and interactions with, healthcare professionals (Adopted 5 July 2007, ratified 19 June 2008).

5.5.1. HUNGARY

In Hungary, the Self-Regulatory Code of Conduct for Ethical Pharmaceutical Marketing and Communications (GyKEK Code, 2014) is adopted by the 4 Pharmaceutical Industry Associations:

- MAGYOSZ (The Hungarian Association of Pharmaceutical Manufacturers and Distributors)
- AIPM: The Association of Innovative Pharmaceutical Manufacturers
- GE: The Generic Pharmaceutical Manufacturers and Distributors
- (Vedettseg): "Immunity", The Vaccine and Immunobiology Product Manufacturers Association

The monitoring of compliance with the Code itself is executed by the Hungarian Communications Ethics Committee (KEB), a committee set up by the 4 industry associations, its members delegated from each.

5.5.2. THE NETHERLANDS

In the Netherlands the Foundation of the Code for Pharmaceutical Advertising (Stichting CGR) was founded in 1998, to oversee the implementation and monitoring of the Code of Conduct for Pharmaceutical Advertising (2014, amended in 2017). Its members are the following organizations:

- Nefarma (Association for Innovative Medicines in The Netherlands)
- Bogin (Association of the Dutch Generic Medicines Industry)
- Neprofarm (Association of the Pharmaceutical Industry for Self-Care Medicines and Healthcare Products)
- KNMG (The Royal Dutch Medical Association)
- KNMP (The Royal Dutch Pharmacists Association)
- V & VN (The Dutch Nurses Association)
- NAPA (The Netherlands Association of Physician Assistants)
- CBD (The Dutch Association of druggists)

5.6. TRANSPARENCY AND DISCLOSURE CODES

In 2010, the United States Affordable Care Act came into force, and with it section 6002, also known as the Physician Payments Sunshine Act (Sunshine Act). Due to increased public scrutiny over the extent of financial relationships between pharmaceutical companies and physicians, the Sunshine Act made it obligatory for payments by pharmaceutical companies to physicians to be subject to disclosure and available to the public. Such transparency made its way to Europe, and in 2014, the European Federation of Pharmaceutical Industries and Associations (EFPIA) adopted its own version of the Sunshine Act in the "EFPIA Code on Disclosure of Transfer of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations". This Code sets out the requirements for its members, the National Innovative Pharmaceutical Industry Associations, to make arrangements as to the disclosure of financial payments to healthcare professionals (HCPs) and healthcare organizations (HCOs).

For HCOs the code mandates disclosure of donations or grants in cash or in kind, contribution costs for organization of events, and any fees relating to consultancy or other services rendered. For HCPs disclosure extends to contributions made for participation in events (conference or education hospitality costs), and fees paid for service and consultancy agreements. It is the pharmaceutical companies that must disclose these payments either on the company website, or on a centralized platform. In Hungary, the implementation of the EFPIA HCP/HCO Disclosure Code made payments to HCPs and HCO available for the first time in June 2016. The obligation to disclose payments is only obligatory for pharmaceutical companies that are members of the Hungarian AIPM. The disclosure reports are available on the separate websites of each AIPM member company.

In the Netherlands EFPIA was of not much consequence, since disclosure of payments has been normal practice since 2012. Initiated by the Dutch Ministry of Health, Welfare and Sport, a transparency register was created by the CGR foundation, and became accessible in 2013 (Transparency register website), disclosing 7,500 financial payments made by industry to individual doctors. The total amount for payments made to HCOs and HCPs for the reporting years of 2013-2014 was 33 million euros. The centralized database is available on the "transparenieregister.nl" website. Contrary to Hungary, the disclosure requirements extend to all pharmaceutical associations.

5.7. MEDICAL ASSOCIATION CODES OF ETHICS ON INDUSTRY-MEDICINE RELATIONSHIPS

In addition to the national medicines laws, pharmaceutical industry self-regulation, and financial transparency, the profession of medicine, as part of its autonomy, provides its own ethical codes. This goes beyond the Hippocratic Oath, which provides the basic 4 principles of the medical profession; "*beneficence, non-maleficence, respect for autonomy, and justice*" [NLMA02/03] (Beauchamp & Childress, 2001; Beauchamp, 2007) but is complemented by Codes of Ethical Medical Practice. These Codes address the specificities of clinical practice, and are produced by the National Medical Associations of each country. Variations in the Codes of Conduct for medical practice follow national laws regarding the legalities of certain medical practices e.g. abortion and euthanasia.

5.7.1. HUNGARY

The Hungarian Medical Chamber (MOK) defines itself as the independent and democratic association of medical doctors in Hungary; its duties include the representation of the professional, ethical and financial interests of the medical profession (Hungarian Chamber of Medicine website). Being the autonomous representative of the medical profession in Hungary, the MOK is responsible for drafting, promoting, implementing and monitoring of the Hungarian Code of Medical Ethics (MOK Code, 2012).

As regard to the ethicalities of medical professionals when it comes to pharmaceutical industry promotion, the code states general points of consideration for medical professionals. Section II.7 specifies principles for conduct involving the ordering of medicines and/or medical devices, as well as relationships with pharmaceutical sales representatives. Section II of the code stresses the duty of doctors to prioritise patient interests during diagnosis and treatment, and especially points to the consideration of the financial situation of the patient when prescribing medication. Decisions to prescribe products should be made on decisions that have taken safety and efficacy into account, and this relates to the interactions with pharmaceutical sales representatives, in that any decisions should be based on the availability of professional, scientifically, and statistically based data. The doctor is responsible for

ensuring that all information received via a sales representative is complete and accurate. Sales representatives are only allowed to visit doctors at times where they do not disturb the clinical practice of medicine, meaning that sales representatives should not visit during clinical hours. A doctor is not allowed to accept gifts, financial or in kind, in exchange for prescribing the drug, or promoting its use to patients. Doctors are not allowed to advertise the use of medication for the purpose of increasing consumption, and are not allowed to advertise medication to patients. In addition, the physician is not allowed to refer to famous people or famous organizations so as to influence patient decisions about medications (MOK Code, 2012 section II.7)

5.7.2. THE NETHERLANDS

In the Netherlands the equivalent of the Hungarian MOK is the Royal Dutch Medical Association (KNMG). Apart from the KNMG, representation of the medical profession is further divided into 3 additional medical associations. These associations are the Federation of Medical Specialists (FMS), the Dutch College of General Practitioners (NHG) and the National General Practitioners Association (LVG). However, it is still the KNMG which issues the ethical codes of conduct for the practice of medicine. The codes of conduct are also multiple, culminating in the 2007 Code on Medical Professionalism, The Dutch Hippocratic Oath (KNMG Artseneed, 2010), The Code for the Prevention of Improper Influence due to Conflict of Interest (KNMG COI Code, 2012), The Doctor's Rules of Conduct (2013 version 3.1), and the Notes to the Code of Conduct for Doctors (2002). With regards to the ethicalities of relationships with pharmaceutical companies, the code on medical professionalism highlights the importance of doctors' "freedom to form an opinion without interference of third parties" and defines autonomy as "formation of an opinion free of influences from the state, church, market, employers, financial principals or, for example, financial incentives aimed at personal or shareholders' profit" (2007, p. 10). The KNMG COI Code (2012) describes rules specifically for those physicians that are responsible for creating medical guidelines to inform medical practice. The Doctor's Rules of Conduct (2013 version 3.1) make no specific mention of interactions with pharmaceutical companies apart from section VI (1): "The doctor maintains an open and integral relationship with business and prevents conflicts of interests which can harm the patient." The ethics of relationships with industry, the code states, are to be sought in the Industry self-regulatory code of ethics. This, however, is complemented by the Notes to the Code of Conduct for Doctors (2002), which explains in a summarized version the ethicalities of medicines promotion in the Pharmaceutical Industry self-regulatory ethical code of conduct for medicines promotion.

5.8. CONCLUSION

The goal of this chapter has been not simply regulatory enumeration, but also to show the legislative hierarchies in the international, regional, and national contexts, and how regulation itself has followed the developments of clinical testing of drugs, and the

solidification of medicine as a profession. Additionally, these regulations will continuously be revisited during analysis, being that they are what would constitute the legislative baseline for proper conduct. Also discussed was the division of regulation which concerns pre- and post- medicines authorization, and analysis will show the consequences of this as regards to respondents' perceptions of where corruption manifests and what it is perceived to be. Pharmaceutical product delivery is highly regulated, and this chapter has given a taste of the immense amount of laws and codes from governments, industry and the profession alike. Alongside seeing corruption as the distortion of the institutional imperatives of the medical profession via industry-medicine relationships, and studying its roots within the system of pharmaceutical product delivery, I will also show that the vast amount of regulation not only falls short in minimizing unethical conduct, but produces loopholes that eventually contribute to medicine's institutional corruption.

CHAPTER 6: INDUSTRY CORRUPTION OF MEDICAL KNOWLEDGE PRODUCTION

"*Regardless of whether we condemn the pharmaceutical industry, without them there are no studies, there is no progress, no development, and no science or medicine*."
[HUDR10]

To continue to provide good quality of life, medicine continues to develop, and aspires to find new and innovative ways of treating the ill, or even perhaps achieving a cure. Progress in medical science and the development of new and effective treatment is high on the medical agenda, as its mandate in society as a science-based practice is increasing disease understanding and research, applied and delivered through medical care. Treatment takes many forms but medicine today is increasingly executed through the provision of some form of pharmaceutical drug (Drews, 2005, p. 21). According to the 2014 OECD Report, *Healthcare at a Glance*, the consumption of pharmaceutical products has increased in European countries, and figures between 2000 and 2010 show that consumption of anti-hypertensive medication, diabetes medication, and anti-depressants rose two-fold, while the consumption of statins increased three-fold in the same period. But let us not forget the widespread consumption of medication used for a variety of other illnesses: painkillers, contraceptives, hormone replacement therapies, lifestyle medication for sexual dysfunction or obesity, and medicines for anxiety, stress, depression etc. Medicine has come far, and many of the diseases once considered a death sentence now become manageable. Daily inconveniences are overcome with ease. The age of antibiotics – miracle cure-alls and "magic bullets" – started the revolution in what was considered practical medicine, solidifying the marriage between science and medicine. To bring a product so high in demand by society, and so vital within provision of medical care, pharmaceutical drugs must be researched and developed – scientifically tested and evaluated – to then be put onto the market and benefit society.

The pharmaceutical product lifecycle is not only a complicated and very lengthy process, but one that is extremely costly, and this is where reliance on the pharmaceutical industry is incredibly important, since it is these large multi-national companies that essentially provide the majority of funding for medicines Research and Development (R&D). This is also the first arena in which studies of industry-medicine relationships see a potential for conflict of interest to arise. Critics argue that when the pharmaceutical industry is the dominant financer, the pressure to put a drug on the market and start creating a profit is so immense, that industry manipulates and biases the trial results to make their product look more favourable. That industry biases results, which are then published in medical journals and translated into clinical practice, is the process by which the pharmaceutical industry is capable of biasing medical knowledge completely (Lexchin et al., 2003; Lexchin, 2012; Lewis et al.,

2001; Angell, 2004; Abraham & Davis 2013; Rodwin, 2012; Brown, 2013; Gray, 2013b).

This is an incredibly critical and vitally important argument for the institutional corruption of medicine beginning with biasing medical research. I would first like to devote some discussion to what exactly R&D is, for the term is generally used as one, when in fact they are two very distinct and separate stages. This only became evident when conducting fieldwork, and by following the referrals and accounts of the respondents themselves because, like the literature on industry-medicine relationships, the tendency to place any and all medical research under the all-encompassing term of R&D masks the intricacies of the separate stages of Research and subsequent Development. Research itself (preclinical) is surely the chronological predecessor of pharmaceutical drug development, but the context within which drug research and discovery happens, and the relationship between medical science and the pharmaceutical industry has its own peculiarities, not generally debated with such nuance in the industry-medicine relationship literature.

The stage of discovery, also known as "basal/basic research" is considered the basis of knowledge production, and it is in this stage in which the "hallmarks of the academic mission" – the disinterested search for scientific fact – dominate knowledge production activities (Lewis et al., 2001). However, there are certain changes that have taken place, both in the pharmaceutical industrial sector, as well as academic medicine, that may call into question the independence of medical knowledge production. The following section shall discuss these developments, and I shall argue that commercial interests are in fact entering medicine already in the research (discovery) stages. The profession of medicine defines what belongs to the body of medical knowledge, as well as the mode in which study of, and attendance to this body of knowledge should proceed. This ability is the manifestation of the macro level of medical autonomy – the freedom and ability to define the scope of medicine and the approach to disease. While the pharmaceutical industry claims to support the interests of society in that it takes part in medical innovation, this claim is criticized in that the pharmaceutical companies fund research that focuses on diseases affecting high income countries, disease areas that are low-risk, and on drugs that can be brought to the market more quickly (Rodwin, 2012). The profession of medicine and medical research is ideally supposed to be the countering weight on the scale which has commercial interests of industry on the one side, and societal interests on the other. However, recent developments in both the pharmaceutical sector as well as academia rattle the basis of medical autonomy preceding the phase of industry-sponsored drug development. The first regards the innovative capabilities of the pharmaceutical sector, and the other regards the rise to prominence of basal research in academic medicine in the pharmaceutical marketplace. To understand this process, and my claim about diminished macro-level medical autonomy, I shall begin with an explanation of the research-based pharmaceutical industry, its basic functioning regarding its profit model, and then explain how it has turned increasingly to basal research to make up

for the struggle that it faces as an industry. In turn I shall evaluate how academia, having realized the extent to which the pharmaceutical industry has become dependent on medical knowledge, reshaped itself not only in its activities and how it views its mandate to further medical knowledge production, but also regarding its entrepreneurial activities in the pharmaceutical marketplace.

6.1. THE PHARMACEUTICAL INNOVATION CRISIS AND ITS CONSEQUENCES

The ultimate business of innovative pharmaceutical companies is to bring to market novel medications, also known as a New Molecular Entities (NMEs). An NME is a pharmaceutical product that contains an active ingredient (chemical compound or molecule), the likes of which have not yet been approved before either as one product, or as a combination product, classified as bringing a new therapy to the patient (FDA website definition). What makes the industry profitable is the patent system. Patents are given for NMEs for roughly 20 years, and until the patent expires, a company retains exclusive ownership of the NME, both in terms of manufacturing and selling it on the market under a protected brand name. Posing one of the most considerable pressures on the research-based pharmaceutical industry is the loss of patents for brand name medications. The rationale behind patent protection is that the period of market exclusivity grants pharmaceutical companies time and means to produce a return on R&D investments. The minute that a patent on a brand name medicine expires, other companies are allowed to copy and manufacture the original drug. These copied drugs are called generics, and are produced by generic drug companies. When an innovator drug company loses its patent, it also experiences a drastic drop in sales called the "patent cliff" (Song and Han, 2016). This drop in sales is mainly due to the fact that generics are sold at much lower prices, since they do not need to undergo the lengthy and expensive trials that prove efficacy and safety as innovative medicines do, but simply have to prove bioequivalence – evidence that the generic possesses the same active ingredient as the original, has the same dosage, is administered in the same manner, and exhibits no significant difference regarding the absorption rate of the active ingredient in the body (US FDA website,[13] EMA CHMP, 2010[14]). Between the period of 2010 and 2016, many pharmaceutical companies lost patent protection of numerous highly profitable products. To give an idea of what this means in terms of revenues; in May 2014 the UK-based pharmaceutical company AstraZeneca lost its patent for Nexium®, an acid reflux pill, which produced global sales of $3,994 billion in 2012.[15] In 2015, the American pharmaceutical company Bristol-Meyers Squibb and Japanese company Ostuka lost patent exclusivity to the jointly sold atypical antipsychotic Abilify®. The drug supplied Bristol-Meyers Squibb with $2.3 billion in 2013, 14% of its total revenue for that year, and accounted for a quarter of sales for

[13]https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm,
[14]http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf
[15] http://www.fiercepharma.com/special-report/top-10-drug-patent-losses-of-2014

Otsuka[16]. Pfizer lost patents to Lipitor®, a cholesterol lowering drug, in 2011 that produced $10 billion in annual sales (Wilson, 2011)[17], and it will also see the loss its patent for the 'little blue pill' Viagra® in December 2017. Used to treat erectile dysfunction and pulmonary hypertension, Viagra® brought in global sales of $2.05 billion in 2012.[18] The loss of patents for companies in 2016 alone is estimated to decrease revenues for brand name products by $172 billion,[19] the loss of patents for other medications such as treatments of multiple sclerosis, HIV and cancer also expired throughout 2017[20].

Innovative pharmaceutical companies have always relied on the "blockbuster" model of profit accumulation – a drug receives blockbuster status when it brings in annual revenues of $1 billion (Angell, 2004) – but the recent loss of patent protection of these blockbusters has not been complemented with more NMEs (Smith, 2006), leading to conclusions that there is indeed an innovation/productivity crisis that the pharmaceutical industry needs to address (Pammolli et al., 2011; Schuhmacher et al., 2016). In fact, the number of NMEs that have been approved by medicines regulatory authorities has been dwindling over the last 20 years (Gagnon, 2013; Light et al., 2013; Schuhmacher et al., 2016). As a respondent from a global top ten pharmaceutical company explained:

"*If you go back 30-40 years, when we had no medicines at all then the number of new medicines that came to the market were a lot more than they are today. There are a number of reasons for that. Firstly because here are a lot of medicines have been discovered and developed. Secondly the regulations around developing new medicines are much stricter. So what might have gotten approved 20 years ago probably won't get approved now. The hurdles to bring medicines to market are significantly more. Equally with some diseases (…) what more can you add to a number of diseases, things like hypertension? It's pretty much solved with the medications we have today. So there are a number of reasons why actually you are seeing fewer and fewer medicines being brought to market*" [NLPH06].

One way the industry has tried to keep its profits high is by flooding the market with so-called "me-too drugs" (Angell, 2004). "Me-too" is term used to denote medications that are slightly modified versions of already existing brand name medications. When a drug company loses its patent for a brand name drug, it modifies the brand name medication just enough to acquire a new patent, and will sell that drug under a new brand name. Critics describe me-too drugs as the pharmaceutical industry's strategy of extending patent protection, by simply placing a similar version of the same drug onto the market and "shifting users" to the newly patented product (Angell, 2004). The most notable example of a me-too patent extension strategy is the story of how drug

[16] http://www.fiercepharma.com/special-report/top-10-patent-losses-of-2015
[17] http://www.nytimes.com/2011/03/07/business/07drug.html
[18] http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales
[19] https://www.drugs.com/article/patent-expirations.html
[20] http://www.fiercepharma.com/special-report/top-10-u-s-patent-losses-2017

company AstraZeneca, just about to lose patent protection for its brand name heartburn medication Prilosec®, patented another heartburn medication, Nexium®. Although it was advertised as being an improvement over Prilosec®, Nexium® was just a slightly modified version of Prilosec. All the company did was to take the active ingredient in Prilosec® (Omeprazole), modify it and rebrand it as Nexium® (Esomeprazole), and successfully retain the monopoly without actually developing a new drug. (Angell, 2004, pp. 76-77). Me-too drugs are not more or less beneficial than their previous versions, and this is precisely the problem, because by being allowed to produce me-too drugs, the pharmaceutical industry is able to maintain its innovator status (and patent exclusivity) without actually having to innovate at all. This patent extension tactic, otherwise known as 'ever greening', is highly criticized and industry is turning to additional means of bolstering innovation. There are many strategies that pharmaceutical companies have been called upon to consider – from increasing R&D spending, to outsourcing some of their functions to other companies to decrease costs, or even the drastic step of implementing open source cooperation with the public (Hu et al., 2007). One trend that has been developing is the increased role of the biopharmaceutical sector in medicines innovation, and this is where academia has stepped in significantly compared to the past.

Like the opening quote to this chapter, the rhetoric that the pharmaceutical industry is the driver behind innovation in medicine was my own basis of understanding. Upon meeting with respondents with backgrounds in medical research, however, this axiom was dispersed as a general consensus came to light; innovation comes from basal research predominantly conducted in academic research institutes. The productivity crisis in the pharmaceutical industry has led to the development of a new type of innovation source process: out of the industry lab, and into the academic setting. A Cardiologist from the Netherlands with an extensive background in medical practice, medical research, academia, industry, and the biopharmaceutical sector, helped explain how exactly the innovation crisis in the pharmaceutical industry is changing both pharmaceutical R&D as well as the academic medical landscape. The "*Big Pharma Model*" of companies themselves researching new drugs in company laboratories is "*at the end of its line*", and being replaced by a "*new model*" which is seeking new products from the biopharmaceutical industry. Biopharmaceutical companies are smaller companies that are involved in the preclinical stages of medical science, and according the respondent, 40-60% of new drugs in 2016 came from these smaller biotech companies, their inventions then bought by large pharmaceutical companies [NLDR12]. These biotech companies largely originate from the academic sector, and are a result of academic and research institutions allowing researchers to start their own companies and patent their findings. This process is called technology transfer and translational medicine in academia, a phenomenon that has gained new importance for the organization and execution of academic research, as well as for industry-medicine relationships.

6.2. TECHNOLOGY TRANSFER: THE BIRTH OF THE ENTERPRISING UNIVERSITY

"*What I think is the truth, is that the great majority of the interaction (with industry) is bloody necessary. Academia would partly not exist without it and if you organise it right, it is actually great fun, right?*"
[NLDR13]

In many interviews respondents, especially those that worked in biotech, industry, and academia, spoke of the importance of bridging the gap or crossing the divide between industry and academic institutions. This bridging in practice is the evolution of a specific function in research institutions, which is called technology transfer. Technology transfer is described as the process of taking ideas and innovations that are based in the academic research setting, and transforming them into marketable products (European Investment Fund website). Technology transfer or translational research is also called "valorisation" in the Netherlands, referring also to the circulation (spreading) of knowledge (De Jonge & Lowaars, 2009), and K+F+I Activities[21] in Hungary.[22] Research drives innovation, and academia has always been a research-driven institution. Technology transfer traces its roots back to the 1980s USA Patent and Trademark Law Amendments Act or Bayh-Dole Act. In the US the Bayh-Dole Act was passed to allow researchers to retain property rights to government funded inventions, and then to seek out private companies which would then invest in development efforts enabling commercial exploitation of academic discoveries (Siepmann, 2004; Jacobs et al., 2006). The American model of exploiting academic research in business ventures has been slow to enter Europe where traditionally academic research had developed independently from industry, focusing its activities on pursuing academic prowess and publishing in high impact scientific journals, as opposed to focusing on commercializing their research results (Agres, 2002). In the United States, before the Bayh-Dole Act was implemented, a drawback of focusing purely on academic endeavours resulted in medical knowledge remaining inside of the scholarly community; discoveries were either never or only very sluggishly exploited to their full commercial potential. If they were, scientists and/or the affiliated research institutions derived no tangible or monetary rewards "other than perhaps increased enrolment or better quality teachers if the publications were well regarded and respected by scientific peers" (Siepmann, 2004, p. 214). The Bayh-Dole Act was the first step out of the academic trenches, and into the market place. It was in 2002 that the European Union addressed this discrepancy between US and European academic-industry partnerships in its *Report on Research and Development*, acknowledging that although Europe has what it takes to compete with the US regarding its intellectual knowledge base, simply the "supply" of skilled researchers is an "insufficient condition for a successful innovation system". One of the biggest conclusions for the

[21] K+F+I; Kutatás (Research), Fejlesztés (Developmnet), Innováció (Innovation)
[22] These concepts are also used in other areas of academic knowledge transfer not limited to the natural sciences.

report was that European countries were advised to improve systems of knowledge transfers between public research and private industry (EU WG Report on R&D, 2002, pp. 3-6)[23].

But what exactly does this mean? The divide between university research and industry does not mean that the two never cooperated in Europe. Industry always looked to potential marketable research in the academic setting, but the circumstances in which discoveries were licenced basically allowed companies to buy a discovery, and not only develop it and turn a profit on the market, but also claim intellectual property rights, meaning that medical scientists would end up losing control over the data and making it difficult for researchers to publish or further develop their ideas. A Dutch respondent with a background in Technology Transfer in medicine described the relationship between industry and academic research:

"*It was normal back then, that there was a pharmaceutical company, they had had the money, they said: "just test that compound for me, and here you have your money, and everything is for me". And then afterwards, some academics can do nothing anymore with what they found in the research because all the intellectual property has gone to the company*" [NLPA02].

While transferring knowledge developed in the academic setting and then handing that over to manufacturers to develop, mass produce, and sell was not an unknown practice , the circumstances of how this was done (handing over all information and IP rights to industry in exchange for funding the development process) was what needed to be changed, because prior to the implementation of technology transfer liaison, researchers would usually lose their right to the research data, limiting scientific freedom such as the ability to publish or present findings without consent from the company. This begrudging situation – inability to fully exploit academic research outside of the academic ivory tower, not meeting the demand of the public by increasing applicability of R&D productivity and results, and academia losing out on both financial returns and rights over information on research that would produce possibly further knowledge – led research-based academic centres in Europe to focus on implementing the infrastructure that enables smoother transition of innovation to the marketplace, emphasising the importance of applied science, and enabling intellectual property rights retention by research institutions (Novotny, 2013; De Jonge & Louwaars, 2009). Universities and research institutions have now in place Technology Transfer Offices (TTOs) based on the American model (Siepmann, 2004).

TTOs provide researchers with the services needed to identify innovative, applicable, and patentable discoveries, as well as to research market conditions within which their discoveries have the potential to be exploited. These TTOs liaise with private companies, and negotiate the patent and licensing agreements, so as to secure funding

[23] http://register.consilium.eu.int/pdf/en/02/st05/05402-r1en2.pdf [accessed May 2017 now unavailable] see also https://www.timeshighereducation.com/news/economic-policy-committees-report-on-eu-research-and-development-in-2001/166774.article

(investment) and possible royalties for the academic institution in the event that an innovation holds market potential, while retaining some of the IP rights so that scientists can publish and report on their findings. TTOs monitor the research activities of ongoing scientific research, and either upon their own identification, or by way of being approached by the researchers themselves, advise on whether to pursue IP protection and licencing or not. It is at this stage that a decision is made whether to licence the innovation to an established company and form a Public-Private Partnership (PPP), or whether the researcher will create a so-called academic "spin-out". (Lockett et al., 2003; Pirnay & Surlemont, 2003).

A PPP is an agreement between one or more public entities engaging in funding agreements with private sponsors i.e. a funding collaboration, whereas a spin-out is the process of forming an independent company. The definition of an academic or university spin-out company is not solidified, and is often used interchangeably with the term spin-off company. The spin-off/out companies are defined as a company whose innovation emerged from a university or research institution (parent organization), but is separate from it. The spin-out company must exploit the knowledge (innovation) that was developed within the academic/research institution, meaning that the spin-out company must endeavour to create a profit via the commercialization of the academically-based knowledge (Pattnaik & Pandey, 2014). The end result of the spin-out process is the creation of a profit-orientated company (Makra, 2013; Lockett et al., 2003; Pirnay & Surlemont, 2003)

Spin-out companies are active players within the biotech industry. Biotechnology companies are quite diverse in their activities, some have become big enough to go beyond discovery into preclinical, and some even to the first phases of clinical testing, but generally the biotech industry is dominant in the discovery phases of research. The European Union is in hot pursuit of promoting industry-academia and Public Private Partnerships (PPPs) and bolstering technology transfer within its Innovative Medicines Initiative (IMI) which represents the world's largest PPP between the European Commission and European Federation of Pharmaceutical Industries and Associations (EFPIA). The IMI is aimed at "initiating collaboration between key players involved in Healthcare Research, including universities, the pharmaceutical and other industries, small and medium sized enterprises, patient organizations, and medicines regulators." (IMI website) Thus, TTOs in the university setting is exceptionally important in bridging the gap between industry and medicine, ever more so in Europe. In Hungary and the Netherlands TTO activities were described during fieldwork as being relatively new functions, and took off between the mid-2000s and late 2010s. In the Netherlands numerous spin-out companies have formed, relying on venture capital funding, and then seeking industry sponsors for later clinical phases of drug development. The focus on technology transfer and the push towards exploitation of patents in the academic setting, establishment of technology transfer offices and support for formation of smaller companies as a focus for national policy, is more prominent in The Netherlands than in Hungary, although Hungarian developments are following a similar trajectory as regards the importance of promoting translational

research. In Hungary, spin-out activities do not hold as much popularity yet, but take the form of PPPs between industry and academic research groups, acquiring private investments to fund academically-based research (Novotny, 2013)

The Royal Dutch Academy of Sciences (Koninklijke Nederlandes Akademie van Wetenschappen: KNAW, 2014) survey on the utilization of intellectual property rights of the results of scientific research conducted at universities and research institutes, states that two thirds of patents produced through Dutch research go to companies. The survey investigated the question of how to make the best use of patents from the research setting, and the importance of TTOs "when launching start-ups and seeking investors" (State Secretary question raised in the Dutch House of Representatives, In: KNAW, 2014, p. 7). Connecting the dots we can see an interesting development – an EU-wide realization of the importance of basal, academic medical research market exploitation potential, and the possible lucrative opportunities that academic IP rights retention produces. A failing innovation model in the pharmaceutical sector makes academic medical research a prime candidate for future investment and innovation. Academic and medical research centres, presented with an increasingly interested industrial sector, advance on the opportunity to become academically and economically active. Ironically, this process for all its beneficial intentions relies not only on bolstering financial ties between industry and academic medicine, but gives academic inquiry a stake in the marketability of research. In the following I will elaborate how this distorts academic independence and research integrity.

6.2.1. A "SPIN" ON THE COMMITMENTS OF MEDICAL SCIENCE

"*If you have a good idea to improve something then you go to talk with industry. First they ask, is this a high volume product or a low volume product? Hmmm, we cannot earn any money with that. So we stop (negotiations). Maybe it's a very important improvement but you have to finance it and you have to find investigators, and so it's all dependent. It's all about money. Everything is finally about the money.*"
[NLDR18]

"*Lots of our scientists sold their products, for I wouldn't say a low amount of money, they sold it for a good price, but they lost a little bit of control over it or they took more money for less control or less money for more of control and things like that.*"
[NLDR14]

When the fruits of research hold potential for marketability, an opportunity presents itself: the ability to start a company and find investors to fund the research. This is the basic logic of the biotechnology industry. How much of biotechnology is the result of university spin-out is difficult to say since the definition of spin-out companies is imprecise. While some researchers leave academia completely to form an independent company, others keep a foot in academia, when the university maintains a certain percentage of licences. Speaking to a respondent with extensive experience in both

academic spin-out companies, as well as start-ups funded by venture capital, we approached this definitional headlock. Technically all knowledge is academic he said, but the route to the biotech industry is multiple. Some researchers may opt to start a company on their own and look for investors, while others are allowed by universities to create spin-offs, where the university retains some of the licences of the novel medical technology, and partakes in finding investors through the TTO infrastructure [NLDR12]. According to Reuters' interview with Francesco De Rubertis, general partner for Europe's largest life sciences investment firm Medicxi Ventures, 30 to 40% of drugs approved by the FDA were discovered in European academic laboratories (Hirschler, 2016).

Why enter into the biotech sector, or even consider a spin-out? Firstly, although smaller companies engage in research that has a higher chance of failure in developing a sellable product due to its focus on relatively under-researched disease areas, if they succeed, the financial rewards are incredibly high and particularly seductive. Secondly, large companies themselves are seen as just "*too large, too slow, and too bureaucratic*" [NLDR12], and forming smaller groups that take the shape of companies is one way of recreating that smaller, more focused, specialized research environment. Becoming a company is vital in that investments from third parties (essential in the face of difficult to attain and limited resources of government funding) relies on market potential. University spin-out companies engaging in the economic sector may bring in a hefty financial reward, as illustrated in the description of a spin-out veteran telling of how his first spin-out some 15 years ago resulted in an upfront payment of $10 million [NLPH03]. Universities stand to gain much if a spin-out company manages to put a drug on the market. However, it is not only an incentive for the university institution, but for researchers as well, where the potentials of such success are tempting; a Dutch gynaecologist described how a product that he is currently trying to get approved would financially settle him for life [NLDR18].

How has this affected the profession of medicine in terms of medical knowledge production? It is not noble to ensure that advances in medical research are materialized in products usable by patients? This fits in perfectly with the duty of science towards the public. The application of scientific discovery in practice strengthens the social approval of science. Applicability of scientific discovery translates complicated, abstract knowledge, unfathomable to the laity, into technologies and applications "that can be understood by all" (Merton, 1938, p. 261) thereby validating science as a socially acceptable activity. The duty of science is to further knowledge greatly, while basing progression upon the *self-constructed reward system* for scientific originality, which is achieved through the recognition, status, and acknowledgement granted by peers. This type of reverence by peers is constructive self-interest, since it is both a goal, as well as a motivation for scientists to continue knowledge production. The reward system is self-contained; meaning that it produces a closed sphere, in which both endeavour and reward are produced inside the scientific community, and as such, expunge the need for outside (non-scientific) modes of gratification. However,

introducing the competitive process of getting medical research out of the confines of the academic setting and into the market has unforeseen consequences, which undermine macro level medical autonomy, and may if not erode, certainly misplace the belief in an uninfluenced progression of medical science. Values, systems of reward, and "extrascientific criteria" that do not originate from the scientific community itself are considered as compromising the ethos of science (Merton, 1938, p. 260; Abraham, 1994), and should be viewed as endangering scientific autonomy.

It is important here to keep the motivational factors of knowledge development in mind, because the influence of the pharmaceutical industry is generally conceived as opinions being swayed for money. However, discussing the industry-academia relationship, a respondent from Hungary expressed his coming to terms with the fact that it is not simply a question of finance i.e. human desire for money that influences choices in medical research, but in fact the scientific reward system itself that has created an arena for industry presence to exert influence. Industry makes its presence in academia a necessity in that it promotes its presence under the guise of furthering the ethos of science. At fault, as the respondent saw it, is the scientific incentive structure itself – the stimulus of the academic world, the importance of publication and authorship, and the worthlessness of publishing findings of research that do not result in novelty – that creates compromise.

"*I thought it was the money, and the private (interests) but then I realized that is the bad incentive structure (of academia…) that creates turbulence.*" [HUREG02]

The turbulence here boils down to the decisions orientated around what to research, and while the emergence of TTOs enable researchers better IP protection for their discoveries, and do streamline the translation of academic research into clinically applicable knowledge, the drawback comes from academia becoming a stakeholder in the market-orientated research chain. The new roles of academia as providing a potential solution to the innovation crisis in the pharmaceutical industry takes seed in the scientific ethos, and I found that marketability and saleability of academic knowledge is not a "happy circumstance" (Merton, 1957, p. 293) or ancillary by-product of scientific knowledge development, but rather an emergent ethical criteria. Within the academic setting I asked researchers, principal investigators, as well as PhD researchers whether the market incentives and the lucrative opportunities that commercialization brings with it affects the direction of academic research. In a particularly defensive response, the question was turned on its head when one respondent made it a question of principle.

"*Many professors have studied their small fish or whatever thing they are studying from day one when they started and thirty years later they are still studying their small fish. So is that ethical? No I don't think that's good actually. I am not afraid to say that. Why? I mean who determines where research is going?*" [NLDR10].

Techniques of moral disengagement allow for a complete redefinition of a morally unjustifiable decision/action as one that is righteous. The "exonerating comparison" (Lanier & Stuart, 2010, pp. 181-182) contrasts the pursuit of the Mertonian form of "pure science" as not serving the public good. The pursuit of "small fish" illustrates how only research that places marketability as its goal can be considered ethical according to the above respondent. Others within the academic setting made similar formulations, another respondent taking a more active interpretation of the duties of medical science.

"*What does a sellable product mean? I mean some products to become sellable means that it's going to help people (…). So the idea of a sellable product usually means for us something that actually can help people, actually can improve the medical care that we can provide, not just the idea of money itself*" [NLDR14].

These examples are indicative of the larger organizational transformation taking place in academic medicine and research-based institutions. While there cannot be qualms about the general intention to provide the patient with a product they may benefit from in practice and not just in theory, De Jonge and Louwaars (2009) see the problem of translational research located in its emphasis on economic rather than social values, which would require academic researchers to realize the full capacity of their research agendas, and the larger societal implications of economically-orientated scientific endeavours. The pharmaceutical industry is interested in producing drugs, specifically sellable products, and medicines' redefinition of 'helping people' with product production begs the question of whether other, less marketable treatments are receiving due attention. An interesting example, and one that I challenged this particular respondent with, was a presentation I had seen on a TED talk channel. The speaker, Dr Mark Mattson, Professor of Neuroscience at the Johns Hopkins School of Medicine and Chief of the Laboratory of Neurosciences at the U.S. National Institute on Aging, explained how intermittent fasting has beneficial effects for those suffering from "diabetes, cancers, heart disease and neurodegeneration" (Longo and Mattson, 2014, p. 1), and may be an effective method for helping those with Alzheimer's disease (Sugarman, 2015). The presentation ends with Dr Mattson concluding that funding for this kind of research is non-existent, since drug companies only fund projects that produce a sellable drug (TEDx, 2014). The respondent was highly sceptical, and asked me to send him this video, because the world is full of quacks, and I had to be careful as to my sources of information. After sending the video and allowing the respondent to background check the speaker, I received the following email: "*Turns out fasting is beneficial. Wow!*" [NLDR14]. Since research and trials are funded by industry, it becomes increasingly difficult to subject all medical research to the costly process of scientific testing, especially those stipulations that offer treatment that endorses lifestyle changes such as nutrition choices and regular exercise over taking medication. Another physician illustrated this discrepancy.

"*We did recently a patient's survey from the pancreatic patient society and asked them "what do you think we should study?" and number one was nutrition. We did basically*

no nutrition research and we could maybe get bit more funding from the nutrition companies because there quite a few big nutrition companies. So in a way you are right (that industry funding of clinical research may influence what is being researched), but if there is a new product that pharmaceutical companies want to have studied then I don't see a problem with that, if they then pay also for the research." [NLDR10].

Two contradictions enter the conversation, the lack of funding for research and another more significant aspect, the divergence between what patients desire, and what medical research pursues. To answer the respondent's previous question – "*who determines where research is going?*" [NLDR10] – it is seemingly the funders, and not patients or researchers.

"Commitment drift" is the "perceived systematic breakdowns in keeping an organization's most important commitments to its stakeholders" (Doty & Kouchaki, 2015, p. 25). Although commitment drift is used in the context of for-profit enterprises, this process is indicative of the institutional corruption of the commitments of medicine to serve the interests of society. When market exploitation is part and parcel of the medical scientific commitment scheme it produces a foothold for rationalizing economically driven decision-making in the production of medical knowledge. Describing how translational medicine has transformed academia, the Ted talks-sceptic oncologist compared academia today to a magazine through which pharmaceutical companies can page through and decide what they want to invest in.

"*Academia became like a magazine in a way, you are going to the magazine and you are looking for what you want to buy. There is a lot of things that academia is producing and the company may be interested in one or two different things and that gives the freedom to the company to say "okay, we are not going to waste our money in to all kind of things that we are not interested in" but academia now has a portfolio of things that they are researching and companies can say "okay I am interested in this and this and I would like to fund this thing to keep on working on that*." [NLDR14].

While certainly beneficial for the pharmaceutical companies, in my interpretation the magazine status of academic and research institutions serves also to further motivate researchers to be chosen as a good investment. Thus research may tend to orientate itself towards what a company would likely fund, creating a commitment to please industry in hopes of sponsorship rather than address other social needs, such as researching rare disease areas, or effects of lifestyle choices which do not require pharmaceutical intervention. Although helping patients can be understood as creating a verified and efficacious treatment, this should not automatically mean solely the development of a pharmaceutical product. Additionally, this reasoning also rationalizes continued and growing dependency on the pharmaceutical industry funding of R&D, lessening critical evaluation of industry's vested interests in successful research. It is this that I shall further discuss, beginning with an illustration of just how much of clinical research is now under the financial control of industry.

6.3. HOW MUCH OF MEDICAL RESEARCH IS FUNDED BY INDUSTRY?

This section continues with the assessment and subsequent role of industry in drug development, which concern predominantly the clinical trial Phases I to III. Already in the discovery (research) phases we see the role of industry affecting the medical profession in relation to reinventing marketability from a possible end result, to an ethical component of medical knowledge production which continues in clinical development and reinforces industry funding as not an opportunity but a necessity. The commitment structure of medical knowledge production is redefined by respondents to include marketability but with the redefinition of the goal of medical knowledge production, comes also a redefinition of the acceptable means by which this is achieved – promoting prolific industry funding of clinical trials.

According to EMA data, about 4000 clinical trials are authorized to be conducted every year in the EEA, and since clinical trials are run in 2 member states on average, this means that there are approximately 8000 clinical trial applications each year (EMA website). Clinical trials run in the EEA must comply with clinical trial regulation of the European Union, laid down in Directive 2001/83/EC and Directive 2001/20/EC (European Union clinical trial legislation). Regulation of clinical trials, harmonization in the standards of clinical research, and adopting international guidelines (ICH GCP) serve to strengthen the verifiability and quality of clinical testing and in turn is seen as a guarantee for national medicines authorities to trust the results of clinical data that has been generated in different countries and in different clinical settings (see Chapter 5). The European Union has indeed followed a path similar to that of the United States FDA, leading to what Abrahams calls the "Europeanization of Medicines Regulation" (1997, p. 169) which began in 1965 with Council Directive 65/65/EEC. The intention was to create an "integrated EU wide pharmaceutical market" so as to strengthen European pharmaceutical companies in the global marketplace, but also to address the discrepancies in the availability of medicines to patients, as national medicines regulatory authorities were inconsistent in which medicines were approved on the national market, and which were not. Regulatory harmonization thus pursues equality in medicines availability within the EEA.

These efforts are undoubtedly necessary in the provision of good quality and effective medicines to patients across the European continent and globally, however increased surety comes with a hefty price tag – expansion of regulation leading to mounting costs of pharmaceutical clinical trials. According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), the estimated cost of bringing a new medication to the market is around 2,558 million, or 2,5 billion USD. This amount describes the cost of drug research and development in the period of early 2000s and mid-2010s – an amount that increased over two-fold compared to the previous decade. A surge in drug R&D costs is a general global trend and is not expected to recede any time soon (EFPIA website, DiMasi et al., 2001, 2016) especially since trials are now

conducted in many countries (multi-sited clinical trials), and involve larger numbers of participants.

The real cost of bringing pharmaceutical products to the market is a subject that has been heavily debated (Angell, 2004) and continues to be an incredibly important topic of concern today. The pharmaceutical industry has been criticized for providing overly inflated calculations of drug R&D costs which it uses as its argument for keeping the prices of innovative medicines high, thereby driving up government spending on new medicines and thus rendering many patients incapable of purchasing medications that are seriously needed. Indeed the pricing of new medicines is something of a black box, since companies do not disclose their actual spending on medicines R&D, and continue to profess that without high prices of medicines, they would not achieve returns on the billions of dollars invested in clinical research and development, which would halt future research and innovation. During fieldwork, the actual cost of running clinical trials was information that was not freely available. Asking respondents as to the costs of clinical trials, the information I received ranged from estimates, to a concrete number. A respondent in the Netherlands broke down the costs of drug research in USD, putting Phase I costs at $10 million, Phase II at $25 million, and Phase III at $750 million, totalling at $785 million. In Hungary, estimations were roughly around the same amount, but one respondent in charge of overseeing clinical trial execution in a hospital was more specific, claiming that the costs of clinical trials in 2015 was $1,3 billion "*exactly*" [HUDR20]. On the other hand, an industry-sceptic respondent asserted that the costs are more likely to be around $800 million [NLMJ01], far below the billion dollar mark cited in a recent study conducted with the use of figures derived from pharmaceutical companies (DiMasi, 2016). While the debate of validity of cost claims continues among those that are active in the subject of 'access to medicines' (being linked to medicines' pricing) it remains a fact that industry funding of medical research is omnipresent especially in the clinical development phases.

The numbers of clinical trials run across the globe, and information that reveals whether the sponsors are private companies, national institutes of health, or academic institutions is hard to come by – in fact there is no concise data available at all. With only 37% of all countries effectively able to produce publicly available data on clinical trial funding, and studies addressing this question varying greatly in research methodology, we are left with only rough approximations (Terry et al., 2014). In the United States, it has been estimated that 70 to 75% of all clinical trials are sponsored by pharmaceutical companies (Bodenheimer, 2000; Chopra, 2003). Additionally, while industry sponsorship is on the rise, funding by non-industry entities, such as national institutes of health, is decreasing (Ehrhardt et al., 2015). "In the EEA (…) approximately 61% of clinical trials are sponsored by the pharmaceutical industry and 39% by non-commercial sponsors, mainly academia" (EMA Website). Databases that contain trial information are numerous, the three main clinical trial registries are the US clinical trials database (ClinicalTrials.gov), the European Clinical Trials Register

(EurdaCT), and the World Health Organization International Clinical Trials Registry Platform (ICTRP).

Consistent and large scale data for industry and non-industry sponsored clinical trials across the globe are unavailable, as the authors of a recent study conclude. Atal et al. (2015) assessed the ratio of industry and non-industry sponsored clinical trials and the impact of global distribution of clinical trials by looking at 119,679 trials run in 177 countries registered in the WHO ICTRP database. Clinical trials are becoming increasingly globalized, larger population sizes increase the validity and applicability of research results, while also making it possible to find larger populations for research involving products for rare diseases. In addition, shifting clinical trial sites from high to lower income countries cuts down on clinical trial costs (Drain et al., 2014). These factors have a significant effect on clinical trial sponsorships, which are visualized in the graphs below.

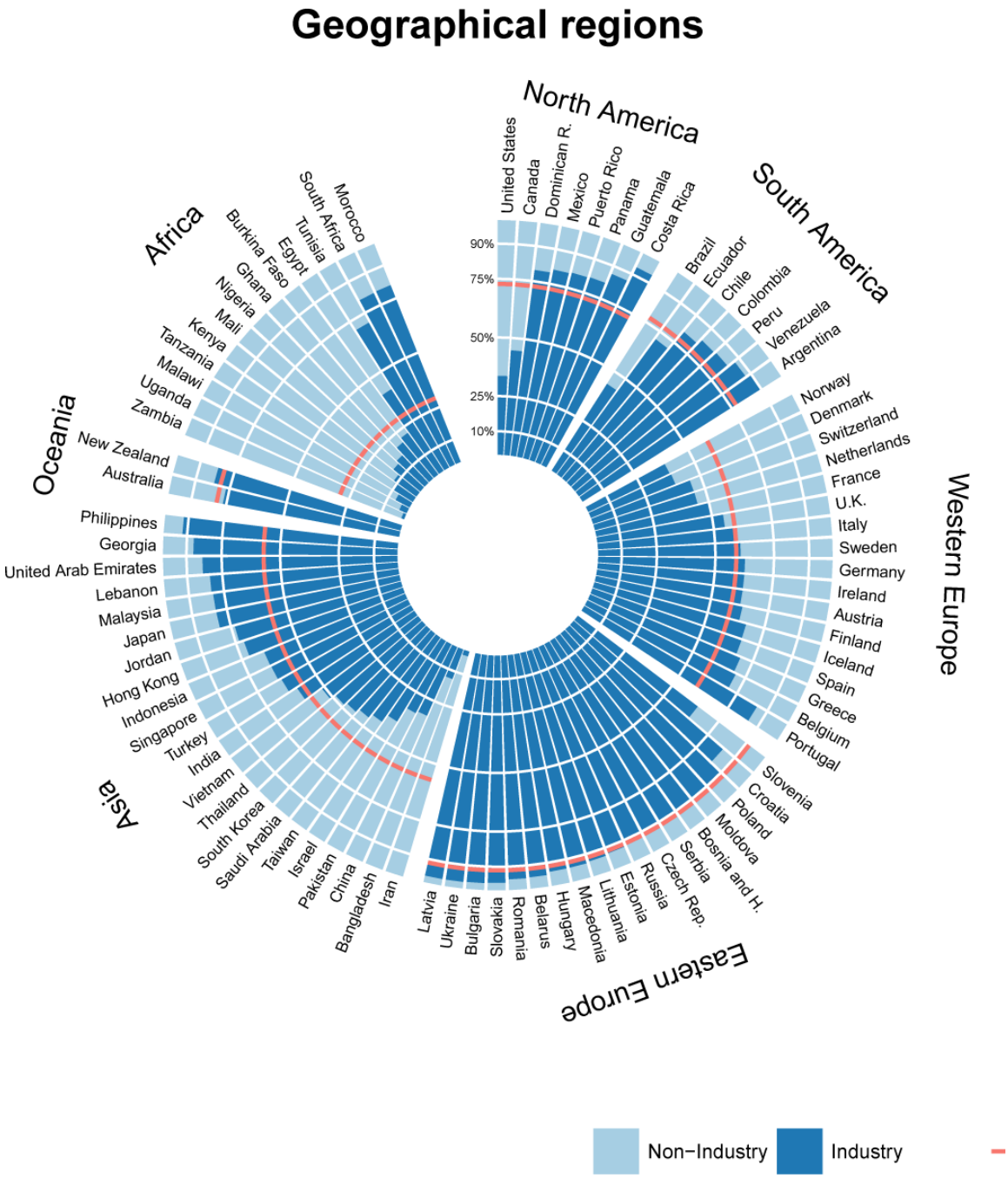


Image source: Atal, I., Trinquart, L., Procher, R. & Ravaud, P. (2015) Differential Globalization of Industry and Non-Industry-Sponsored Clinical Trials. *PLoS One*, 10(12)

Illustrated in the above, we can see the differentiation in ratios of industry and non-industry sponsored clinical trials as pertaining to geographical region. Especially interesting is the high concentration of industry funding of clinical trials in Eastern Europe, far more than any other geographical region, averaging around 90%. In Western European countries, industry sponsorship of clinical trial averages at just over 50%. According to respondents, the high concentration of industry-funded clinical trials in Eastern European countries can be explained by 2 factors. Firstly, clinical trials are cheaper to run in Eastern Europe [NLDR09]. Respondents in industry claimed that Hungary specifically is a cheap country in terms of clinical R&D expenditure, undercutting the costs of Western European clinical trials by at least a quarter

[HUPH11]. Developing countries may be an even cheaper option, but ethical concerns arise, since many developing countries may lack the institutional and regulatory infrastructure (ICH GCP Guideline implementation) that enables protection of clinical trial participants. Additional ethical issues concern the standard of healthcare at the local level, the availability of treatment once the clinical trial has come to a close (exploitation of developing countries to benefit rich countries), and the abuse of informed consent in that many times clinical trials are the only means in which patient populations can actually access treatment at all (Emanuel et al., 2004). Thus Eastern European countries may be more favourable in that the costs are lower, but regulatory oversight and standards of medical care are still in concurrence with those of Western Europe. Clinical trials for market approval are often multi-sited (run in multiple countries) and although the above graph shows less industry-funded trials in Western Europe in comparison with Eastern Europe, industry funding jumps to 90% in the West when the comparison is between trials that are single country run, or conducted in at least two countries, shown below.

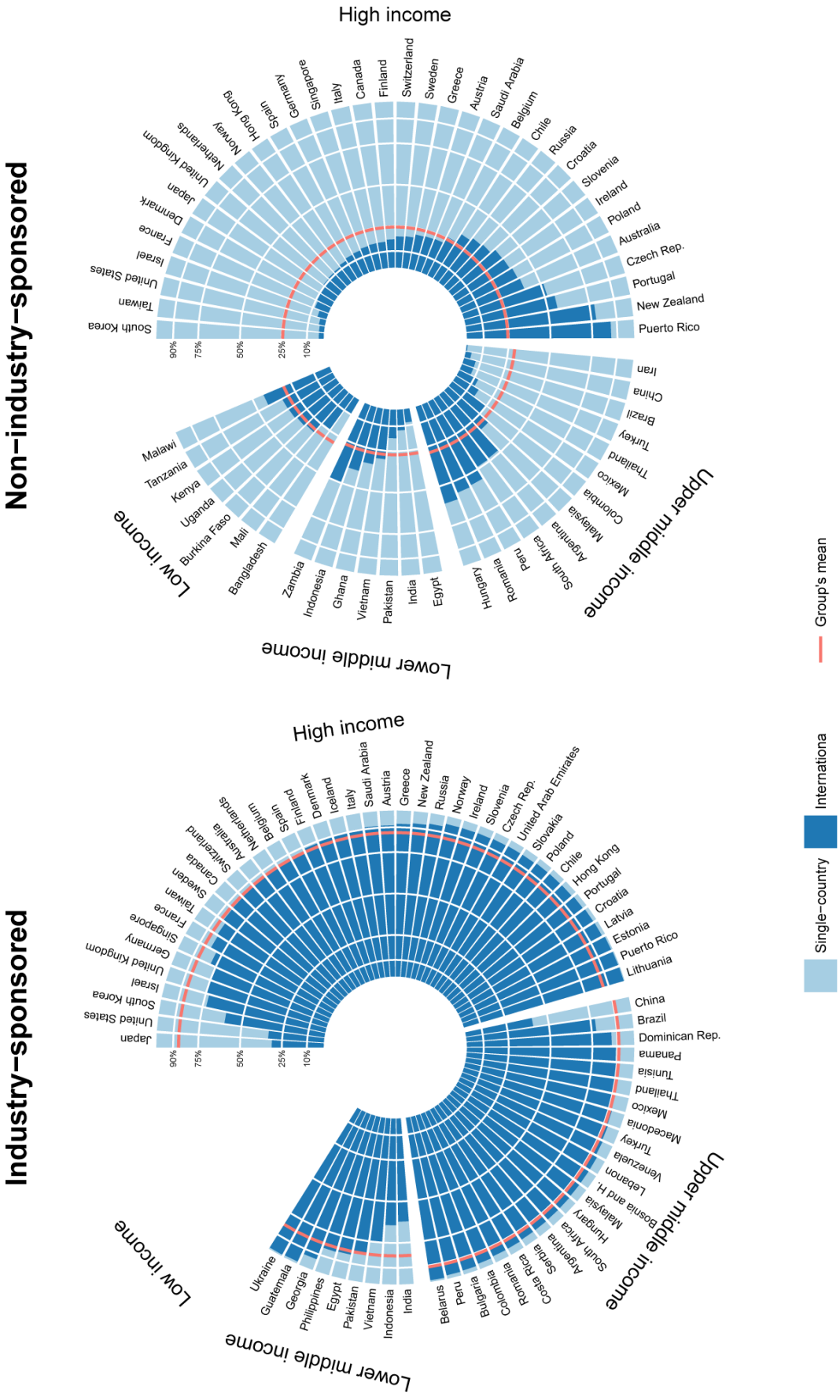


Image source: Atal, I., Trinquart, L., Procher, R. & Ravaud, P. (2015) Differential Globalization of Industry and Non-Industry-Sponsored Clinical Trials. *PLoS One*, 10(12)

Again, this is an important finding, since trials that are run for marketing authorization rely on research conducted in more than one country. Having consulted the EudraCT clinical trial register, the data that was available was found in EudraCT database reports which are compilations of statistics derived from EudraCT registered trials. The statistics are compiled on a monthly basis, but as of the writing of this chapter, the most recent are those from May 2017. I have taken the reports from May of each year (the earliest available report being from 2011) and listed them for illustration in the graph below. What we can see is a consistent ratio of commercial and non-commercial sponsorship at 79% and 20-21% respectively. The EudraCT contains clinical trials run both within the EU and the EEA, as well as some trials conducted outside of these areas.[24]

Date of Report	Total number of trials registered in EudraCT database	Sponsor type: Commercial (%)	Sponsor type: Non-commercial (%)	Other sponsorship (%)
May 2017	50723	79(%)	21(%)	1%
May 2016	47529	79(%)	20(%)	1%
May 2015	43595	79(%)	20(%)	1%
May 2014	40403	79(%)	20(%)	1%
May 2013	36981	79(%)	20(%)	1%
May 2012	33451	79(%)	21(%)	1%
May 2011	29424	79(%)	20(%)	1%

Data taken from European Medicines Agency EudraCT Public Web Reports (May) from 2011 to 2017. Available at: https://eudract.ema.europa.eu/statistics.html

The effects of progress in medicine, an upsurge in quality and stringency regulations and guidelines for medical research, as well as implementing that research into the stream of medical practice, draws with it exceeding costs, and much of the progress in medicine can only be executed by relying on the financial buttress that the pharmaceutical industry provides. Pharmaceutical industry sponsorship is everywhere in medical research, and while industry funding rises, government spending decreases. Handing over the research and development costs to industry, and decreasing spending on medical research in the academic sector, is as much a trend globally (Bodenheimer, 2000; Chopra, 2003; Ehrhardt et al., 2015; Atal et al., 2015) as was identified during fieldwork in both Hungary and the Netherlands. The extended influence of industry in medical knowledge production is not restricted to the academic-industry partnership of preclinical research, but is present in the drug development stages. I have discussed

[24]Trials outside of the EU and EEA are included if they form part of a paediatric investigation plan (PIP), or they are sponsored by a marketing authorization holder, and involve the use of a medicine in the paediatric population as part of an EU marketing authorization

how the economic incentive is being introduced in academic medicine and basal research – the "R" in drug R&D. In the following I will assess the role and consequences of industry in medical knowledge production in the stage of the product lifecycle when a product has been approved to be tested in humans. These are the clinical trial Phases I, II, and III.

6.4. CONSEQUENCES OF INDUSTRY-FUNDED CLINICAL TRIALS

"*So there is going to be a clinical trial by a big pharmaceutical company international, which is completely sponsored by the company. We will see what the results are. Probably it's going to show positive results*." [NLDR04].

Industry-sponsored clinical trials are more likely to produce results that are favourable to the company drug compared to publicly funded research (Lexchin et al., 2003; Lewis et al., 2001; Kjaergard & Als-Nielsen, 2002; Lundh et al., 2012; Stamatakis et al., 2013). These findings make emergent the question, as to whether we can trust the data from medical research that is funded by drug companies. This is a catch-22: meeting clinical standards increases the costs of drug development which then relies on industry funding. The industry has become the dominant financier in drug development, but money comes with strings attached, and these strings take the form of a desire to produce trial results that ensure market authorization of a product. While there is much research that both challenges, as well as warns doctors that results should be approached with scrutiny, there is still a tendency to overlook such dangers of biased research. I was curious to know why industry-sponsored clinical trials were not subject to critical assessment by medical professionals and found that scrutiny is highly dependent on the interpretation of fraud and bias in clinical trial data. Fraud is seen as criminal and a direct violation of scientific standards, while bias is interpreted as a natural part of the scientific process. In addition, the interpretation of validity of scientific knowledge is located in the surety of technicalities of clinical trial design and execution, basing ethical compliance not on research questions, but on meeting the technical requirements of research design.

6.4.1. PROBLEMATIZING FRAUD AND BIAS IN CLINICAL TRIAL DATA

Manipulation of clinical trial data is predominantly taken to mean data fabrication and falsification. Fabrication is the production of results without actually having conducted any research, while falsification happens when research has been conducted, but the end results are then doctored, re-written, removed, or complemented. Respondents considered this type of manipulation to be more of an urban legend, something which may have happened in the past, but which had almost no chance of happening today. Reasons for the low probability of falsification or fabrication were found to be the combined product of increased regulatory stringency – a product of the ICH GCP guidelines and subsequent adherence stipulated in the EU Clinical trials Directive – as well as the belief in convergence of the goals of industry and medicine to the greatest

extent in the stage of medical research. The 3 phase system of clinical trials, the modernization of clinical trial data collection and documentation, and the strict adherences to the technical requirements of running clinical trials are considered to create a certified system in which direct manipulation of raw clinical trial data is eliminated.

"*Since there are many levels at which the results of clinical trials are inspected, even under time pressures you cannot falsify the data. Since the source document and the parallel real time data (is) collected online, these make post-bookkeeping (post-data entry) or the falsification of data almost impossible*." [HUDR20].

In addition to safety guaranteed by following technical methodologies, the majority of respondents found even the idea of data fabrication/falsification to be completely obtuse, in that it serves the interests of none of the parties concerned. The interests of industry and medicine were commonly interpreted to be in complete concordance, at least regarding clinical trials.

"*I think (the pharmaceutical companies) do not want to influence the clinical research process. The interest of the pharmaceutical companies is that their medication be as safe as possible, that it has little side-effects, and that it be effective*." [HUDR04].

The strong association of manipulation of clinical trial data in the actions of fabrication and falsification, however, results in not much attention being paid to the phenomenon of bias in medical research. As the above quote shows, while the interests of industry and medicine may rightly coincide, the method by which this goal is achieved differs. Bias in clinical trials can be introduced in a variety of ways which has nothing to do with the manipulation of the raw data, but it is the art of designing a clinical trial and presenting the findings in a way that supports a desired outcome. Bias is taken to mean a partiality which reduces objectivity, or in the case of statistical analysis, the deviation of an estimate from a true value (Jadad & Enkin, 2008). Contrary to scientific fraud, the definition of what constitutes acceptable bias is open to negotiation, and during field research, this type of negotiation in the meaning of bias was what downplayed its effects, or diverted attention from it completely. Bias may be introduced in a variety of ways (Lexchin, 2012), and some manifestations of bias I found during fieldwork.

Bias can be introduced in the very beginning of clinical research in the way in which the study is designed (Lexchin, 2012; Lexchin et al., 2003; Goldacre, 2012). Taking an example from the field of cardiology, a respondent explained that selection of research participants is already extremely important as to what result you want to produce, and as such selection criteria revolve around the basic question of which patient population will show that your drug works. In testing statins for example, all those included will have high levels of cholesterol so as to produce results that have a higher chance of showing efficacy i.e. lowering of cholesterol levels.

"*The chance of showing that lowering very low to even lower is of course much smaller than showing (the effects) in somebody with very high levels of cholesterol. And so, all*

the trials, the initial trials in cholesterol lowering (medication) are in people with very high baseline LDL cholesterols. Now that is, if you look at it, is a bias, because it doesn't study the entire population, it only studies those who have high cholesterol. Now you can call that bias (…), it will make the drug look better if your hypothesis is right. But on the other hand, you can call it bias, but you can also call it scientific selection." [NLDR12].

It seems to be exonerative if bias proves a hypothesis that is right in the first place. No harm no foul, the bias may be there but without the bias we would have seen the same result anyway, if perhaps less statistical significance, right? The question becomes slightly more complicated if trials are designed around a particular outcome. A respondent endocrinologist [HUDR04] described how she had seen trial protocols designed in a manner in which the outcome was already known. Calling it comparing "*apples to oranges*" the respondent described a clinical trial setting to test the efficacy of diabetes medication. While one group receives the traditional drug "A" and a statin (high cholesterol is common in diabetes patients), another receives drug "A" as well as insulin therapy. According to the respondent, those given the insulin therapy will show better results if the end point of the study looks at blood sugar levels. This type of end point restriction rings with familiarity as in the case of Vioxx, the painkiller that turned out to increase chances of cardiac complications four-fold. Merck, the manufacturer, stated that the point of trials was to test for gastrointestinal tolerance of the medication, and as such, the drug's effects on the heart were not part of the assessment, and not included in the study publication (Hill, 2008). Although Vioxx is perhaps more an illustration of rationalizations as to why data was overlooked, while the example of comparing apples to oranges shows bias in hard-end point selection, the two examples show there are more nuanced ways in which efficacy and safety of medication may be emphasized through the way a research question is posed, as well as how the trial is designed, and what end-points (outcomes) are selected. However, bias also comes without manipulating the trial design, as another respondent from vascular medicine concisely expressed.

"*They don't lie about their results; they just sort of highlight other things. So the only thing is that a lot of initiated studies by those pharmaceutical industries, and I just think a lot of the times you can do a lot with statistics, like being a researcher myself I know that you can kind of move the data the way it looks good, and then you present it.*" [NLDR06].

What this respondent describes is the difference between direct manipulation (fabrication or falsification) of clinical trial results, and placing more emphasis on the results that make a product look better. The former is considered direct deception, while the latter is considered bias. This type of bias is also known as "selective reporting" – failure to report negative findings, or "selective publication" – publishing positive findings numerous times (Melander et al., 2003). One of the reasons that drug companies can do so is that there is no obligation on companies to make raw clinical

trial data available to the public, citing endangering company trade secrets behind this rationale. In fact the EMA has in the past been sued by pharmaceutical companies Abbvie and InterMune for jeopardizing company trade secrets when it tried to make already market-approved medicine's clinical trial data available to the public (EMA vs Abbvie and InterMune, 2013).

Bias can also be introduced by choosing what to compare medicines with. In clinical research Randomized Control Trials are the best way in which to test the effects of a drug in that the trial will compare drug safety and efficacy in the comparison of two groups (see Chapter 5 evidence hierarchy). The use of a placebo in an RCT is important in that it enables researchers to assess whether the drug in question is actually having an effect over the "placebo effect" of getting better just because a patient is receiving care (Misra, 2012). In testing a novel medicine for which there exists no treatment, the placebo-controlled trial is vital. However, concerns are raised when there exists a treatment on the market already, but there is limited support for comparing a new drug to existing medication. The paradoxical consequence of the use of placebos to minimize the unconscious placebo-effect is that it creates another bias: a decreased applicability in medical practice where the consequences are ultimately felt. As a urologist from Hungary described:

"*In simple terms, there are efficacy and safety studies for drug A, B, C, D, E, and F. Each is compared to a placebo. But there are no studies comparing these to one another. Two companies have never joined arms to investigate that. It's a nightmare. It does not help medicine if I cannot tell whether to use A instead of B, because those have not been compared*" [HUDR10].

Biases, it was claimed during fieldwork, are unavoidable attributes of medical research, which are corrected during the clinical trial process, for example by including higher numbers of patients in trials, or by relying on statistical evaluation of significance of findings, introducing randomization, and blinding; I found that trust was deeply rooted in the consistency of the technical aspects of clinical research. In short, if a trial follows the protocols and contains all the elements of the blinded RCT, then the evidence it produced should be accepted. More simply put: the focus of trust is rooted in *how a trial is conducted*, and not necessarily *what* the trial is researching. This is what Abraham calls the solely instrumentalist view of clinical trials (1994). So strong is the belief in the statistical method of evaluation as providing reliable scientific truth that questions of ethicality are completely dismissed. One respondent argued that evidentiary levels for example had no place for discussions of ethicality. "*So what if a study does not meet the evidentiary criteria? That's not a question of ethics.*" [HUDR20]. This retort was a response to the ethicality of using different research methodologies, such as RCTs versus open labelled clinical trials (un-blinded) which the respondent saw as a question of science and veracity of evidence, an issue completely devoid of questions of ethics. If a trial was conducted under strict contracts, was granted authorization by an ethics committee, if the data was compiled in a

systematic fashion, and the protocols were strictly adhered to, then the question of ethicality was seen to be solved. I was even explicitly told not to go into the ethics of trial protocol or evidence levels in my research, since the two concepts could not be coincided, and I would be assessing irrelevance [HUDR20].

Ethicality however does arise, contrary to what was claimed or warned of during fieldwork, and here we must consider the terms of internal and external validity of clinical trials. Internal validity is the ability of research to show that changes in a dependent variable can be attributed to changes in an independent variable. In short, that X action causes Y result. External validity, however, is the ability to generalize the applicability of clinical trial results i.e. directly transfer results to clinical practice. While internal validity is constricted to the technical plane of research, its consequent effects on medical practice do evoke the question of ethicality since they impact the decisions that are being made in medical practice. The examples above illustrate potential methods of biasing clinical trials, as well as the consequences for medical practice, but as all researchers in any field know, bias may not always be intentional. In addition to illustrating bias in the above examples, analysis went beyond examples of root causes. In the case of medical research, bias may be unavoidable; however, there lies a question of whether the bias is a product of scientific uncertainty or exploited and abused by economic incentives. From the perspective of institutional corruption theory, it is not the existence of bias per say that must be criticized, but whether the bias is a product of scientific medical decision-making, or the product of an external third party interest. In my own argument I see the existence of bias in and of itself as not the most worrying issue, since systematic peer review and re-evaluation should allow for biases to be corrected. However, in a setting where industry is in control of not only trial design, but also how the results are reported, and what data is available, the absence of independent review, and the equation of GCP with good research, endangers the independence, integrity and reliability of medical knowledge production. A more tangible example is presented in the following sections, which describes industry-enforced bias through the lens of industry outsourcing of clinical trials.

6.5. FOLLOWING THE SCENT OF BIAS: THE ECONOMIC PRESSURES IN CLINICAL TRIALS

To understand the process of clinical trials, the respondent sampling process led me to speak to people who worked for Clinical Research Organizations (CROs). Despite the fact that the pharmaceutical industry sponsors the majority of clinical trials across the globe, pharmaceutical company respondents rarely engaged in discussion about clinical trials outside of what is already embossed on company pamphlets, generally limited to the contribution that industry makes to society, or being the only entity capable of funding such expensive trials. The entire subject of clinical trials is the most important trade secret of the pharmaceutical industry, and so attempts at discussing trials with pharmaceutical industry respondents were superficial, in that respondents

did not divulge detailed accounts, but stayed within the realms of general descriptions, and what they are contractually allowed so say. One industry compliance officer (who constantly reminded me throughout the interview of her legal obligations as to how much she could disclose) upon discussing corruption in the pharmaceutical industry made note that the "*risk*" was with contracted third parties [NLPH04]. Elaboration did not follow, as the respondent was generally on edge about talking to me at all. CRO respondents, however, were more willing to discuss how clinical trials work, as well as the economic aspects of drug development, because CRO employees see themselves and the company as providing an impartial service to industry.

6.5.1. CROS IN R&D

At first I saw CRO respondents as just access points to pharmaceutical company respondents and doctors, but as the interviews progressed I came to learn that much of what I thought clinical research looked like was a very out-dated version. Most innovative pharmaceutical companies today outsource the running of clinical trials to reduce costs as well as expedite the process (Carroll, 2005). The innovation crisis and the patent cliff are partly a source of this development. In 2010, a third of all pharmaceutical R&D expenditure went to outsourced clinical trials (Goldacre, 2012). Today over half of clinical trials are outsourced to CROs, and make up for 70% of total pharmaceutical R&D spending (van Huijstee & Schipper, 2011). The global CRO market rose from $20 billion to $27 billion in 2014, and is estimated to be around $32 billion in 2017 (Rani, 2015). CROs have evolved to become enormous conglomerates that provide services at each and every single stage of the pharmaceutical product lifecycle, however for this thesis I shall concentrate on the services of CROs in clinical trial execution. CROs are the middlemen between pharmaceutical companies and physician investigators and clinical trial sites (hospitals). Instead of hiring experts to search for potential sites, it is more cost efficient for pharmaceutical companies to employ the services of CROs whose business it is to establish relationships and create networks of major trial sites, and these networks are then capitalized upon and sold to the pharmaceutical companies as clinical trial execution services. In addition to providing the social and intellectual capital, CROs execute the clinical trials according to the research protocol designed by the sponsor, monitoring adherence to the trial protocol, collecting trial data, and sending the data to the sponsor upon completion. CROs work closely with medical institutions, hospitals, and academic medical centres, given that these provide for large potential patient populations across many disease areas [HUPH11], [HUPH08].

Speaking to respondents from the largest and most profitable CRO in the world, I was given a description of how CROs not only improved clinical trial execution, but since they do not hold an interest in the outcome of the product being tested, CROs may be seen as maintaining impartiality. However, when conversations entered the area of industry-CRO collaborations, it was revealed that in fact the business of providing clinical trial services creates market pressures exerted onto the research sites. A

pharmaceutical company could easily decide to drop a CRO and work with another if a company was "*unimpressed*" with a CRO said a respondent [HUPH07]. Asking why a company would be unimpressed, certain "*sub-optimal situations*" were cited, which could range from bad communication between the CRO and the trial site to problems such as the inability of the CRO to provide the desired patient numbers, if the data was not "*clean*" enough, or if the physician investigators were unhappy with the CRO and this somehow got "*back into the ear*" of the sponsoring company [HUPH07]. I was not given further details as to the meaning of unimpressive situations, or whether CROs were pressured to control participants or data, but physician investigators were only too happy to elaborate.

"*(I have) only one sentence. So, the clinical research organisations have been created for good reasons and that is to control the original data. So, a clinical research organisation will go to the institute of the investigator and check what it is on the case record form, and the original data, these forms contain the information the patient going through into trial… Fantastic idea, because you have a quality control, and a signature on what comes out of the patient documents as well as what goes in. But the CROs are listed on the stock market and have an incentive to make money. And they make loads of money. And their model to make money is contradictory to the process of research. They get paid by different elements that they create out of the database (paid to produce certain data). They have to deliver to the owners. They have no interest in medicine. They don't give a shit about medicine. They only want to make money.*" [NLDR13].

Although there is no conclusive proof of whether or not CROs would directly manipulate the data as [NLDR13] claimed they not only did (create elements), but were paid to do by their employing pharmaceutical companies, the fact that doctors have limited say in the clinical trial execution, or how the data is interpreted, was described by a respondent from a smaller CRO company. As the respondent explained: all that a participating doctor must do is follow the prescribed format of clinical trial execution. Taking the example of Adverse Drug Reaction (ADR) reporting the respondent described how:

"*The doctor does not have to decide anything. (The physician) is asked his opinion on this page (of the protocol) which he has to fill out whether (the ADR) is linked to the medication or not. But this is just his opinion, and this does not mean that it is (related). And this is not even relevant in the later stages, because it's the statistics that will determine the correlation (between drug and reaction).*" [HUPH01].

The data is controlled by the sponsoring company and the interpretation of the data through the use of statistical methods is no guarantee for impartial results. The motivation for doing so is once again presented as the result of an economic pressure to provide desired results in a timely manner. The monetary reward system that typically characterizes the pharmaceutical industry is then translated by physicians

partaking in clinical research into personal rewards for the physical and mental effort they put into the trial.

"*You want to have positive results. If you have done a lot of effort to look for something new, you want to have positive results. No negative results. So there is always a force to make it look better than (it is)*." [NLDR13].

Clinical practices are at risk of being structured and executed along economic rather than scientific considerations. Using the words of another respondent, "*CROs are beholden to industry to provide good results*" [NLDR17]. These economic considerations were most apparent in description of how clinical trial sites were chosen. Asking a respondent from a smaller CRO, the fact that a hospital or medical institution had access to a sufficient number of patients, as well as the right disease area, comes second to trial execution efficiency: the ability to complete a designated task in time, and in the "*right*" fashion [HUPH07].

"*And so the local group (local CRO company) will choose to include (Hospital A), and (name of city) and the… well not (hospital B) because the last time we went there they didn't do the work, we had to keep nagging them to do something. So we know who, to contact in the same research area, and we know that we will never sign a contract with them, because (he/she) is an impossible character, (he/she) won't do the work, and we just have problems with (him/her). We have to squeeze everything out of them*." [HUPH01].

This is a vital piece of information because the decision to include or exclude certain hospitals as sites for clinical trials is heavily dependent on whether or not the physicians incorporated in the study execute the trials according to CRO expectations of expediency. Clinical trials are important for medical institutions. Firstly, they provide an additional source of income for both doctors who participate, and for the hospitals where the trials are conducted. Clinical trials also provide the opportunity for doctors to participate in research, which is a fundamental criterion for career progress. Trials also expose patients to the possibility of receiving experimental treatment which is, for some diseases, a last option. "*It's good for the hospitals, good for the patients, and good for the doctors, where they are paid good money for each enrolled patient*" [HUDR16].

By being able to promote certain research sites over others, CROs are in the position to hold hostage clinical research sites in the same way in which industry holds hostage funding of basal and clinical research. In basal research the infusion of economic incentive structures is done through the reinterpretation of the duty of medical research, concealing economic interests under a rhetoric that translates duty to society (social contract) as being crystallized in product delivery and marketability. In terms of clinical research, CROs are the extended arm of pharmaceutical companies, capitalizing on their established relationships and clinical trial site networks. The power of the CRO to make decisions on which sites to include or exclude brings with

it the added pressure for investigator physicians to deliver desired results. While economic pressures alone do not translate directly into scientific misconduct or bias, they certainly increase the incentive structures for doing so. Economic pressures to produce desired results have the potential to "trickle down" (Vaughan, 1997) into the sites and personnel. By normalizing a system of clinical trials as services provided to industry, the expectations of expediency and favourable trial data creates an incentive structure where economic pressures rationalize and normalize the use of techniques and methods that reproduce the aforementioned biases in clinical trials. The solely instrumentalist view of clinical trials (Abraham, 1994) and the methodologies applied prevents questions of ethicality from entering the conversation, making ethics a simple question of following the protocol rules. In addition, the instrumentalist viewpoint is also enabled by spatial and temporal distance between drug development and clinical applicability. Those who execute the trials may never fully realise the effects of low external validity or biases, being that they are far removed from the practical medical setting. Thus micro-level implications are very much absent in the protocol adherence based interpretation of ethically sound research because it takes science out of the social context within which it ends up being applied. Being that the medical profession is divided along the lines of medical science and medical practice, this division of tasks and knowledge creates a divide between task and subsequent consequence. In a situation in which the effects of bias in clinical trials are overlooked, the immediate pressures of industry-sponsored clinical trials (expediency and favourable results) have greater relevance than the societal consequences which come only much later.

6.6. CONCLUSION

The devil is in the details, and as I have described, it is in the very complexities of medical research and how it is conducted that industry influence and manipulation ensue. What is usually described as one stage of medical knowledge production (Busfield, 2006) is in fact two, at least with regards to the modus operandi of economic incentives affecting the independence of macro-level medical autonomy. Research (both basal and preclinical) is swayed by an incentive structure that places pressure to conduct research with high probability of attracting private investors, and the TTO which was aimed at protecting scientific claims to data and research, also ensures university profits, being now a stakeholder in research marketability. Even if a biotech company is formed independent of an academic parent institute, medical researchers are offered hefty rewards which could "*set them up for life*" [NLDR18], thereby further incentivising profitable research areas to be pursued, potentially removing more needed, riskier, and less profitable research from the investigator physician's consideration. In the preclinical phases, the very regulation that protects patients via stringency and efficacy requirements has also driven up clinical trial costs, which necessitate industry funding. Strings attached to funding once again determine not only what is to be researched and reinforce the belief that technical procedures can ensure reliability, but also diminish critical assessment of research question or trial data surety and clinical applicability. Researchers far removed from the clinical applicability of

research may not even fathom the consequences, since task division and an instrumentalist view of clinical trials alleviates consideration of such matters, and with that the necessity to exert professional control over the determination of medical research, thus leading to the weakening of independence, and the institutional corruption of macro level medical autonomy in knowledge production.

CHAPTER 7: BETWEEN KNOWLEDGE PRODUCTION AND KNOWLEDGE INTERPRETATION

In the following section I would like to discuss and analyse where the two levels of medical autonomy, macro level autonomy (medical knowledge production) and meso level autonomy (medical knowledge interpretation) overlap each other, as we proceed through the analysis of the institutional corruption of medical autonomy. Although Chapter 7 deals with the specificities of knowledge interpretation in medicine, these categories, as I have stated in Chapter 2, cannot be so sharply cordoned off from each other, and this chapter is a testament to that fact. We come to the stage of the pharmaceutical product delivery chain that concerns medical research after a drug has been approved for the market. Post-approval clinical trials as well as the regulatory approval of pharmaceutical products fulfil dual roles of medical knowledge production and interpretation simultaneously, and thus I have chosen to devote this chapter to the analysis of Phase IV clinical research and the assessment of the approach of regulators to the role of the pharmaceutical industry in medicine because they present the intermediary phase where macro level autonomy phases into meso level autonomy and embody both. Although chronology would dictate an assessment of medicines regulatory authorities first, and post-approval trials second, logical flow leads me to do otherwise, beginning rather with post-marketing trials because their problematic nature can only be fully appreciated if contrasted immediately with pre-authorization trials, whereas their proliferation is then subsequently explained by medicines authorization policy.

7.1. SCIENCE OR SEEDING?

Somewhere between where scientific information ends and where marketing and promotional information begins is a no-man's land in which the differences between marketing and science become unclear. We come now to the assessment of Phase IV clinical trials, which are conducted once a pharmaceutical product has been approved for the market but enjoy relatively less regulatory oversight regarding their technical execution, because the trials involve drugs that have been approved for the market and thus can be used in normal clinical practice. Phase IV clinical trials are conducted to study the effects of drugs in real-life settings. These trials are not mandatory, but can be required by a regulatory agency, or can be initiated by a company for numerous reasons such as post-marketing surveillance of the drug, uncovering new markets (new indications/uses) of a product, or for regulatory purposes such as monitoring ADRs that might require changing warnings on package inserts (Suvarna, 2010). Phase IV can also be physician or medical association initiated independent from a company, or with industry funding. In general, Phase IV trials can provide valuable information that complements safety and efficacy studies of drugs that have been tested in

controlled environments. In pre-approval clinical trials it is the professional consensus that double-blind RCTs produce the highest level of evidentiary validity. However, as I have discussed, while internal validity is ensured, the controlled setting of clinical trials may hamper external validity of clinical trial results, especially regarding results based on strict inclusion and exclusion criteria of trial patients, comorbidities, and combination medication use. This is where post-marketing surveillance studies play a vital role in the pharmaceutical product lifecycle since monitoring the product in real-life settings will complement the knowledge of the product and provide for generalizability of research results which inform clinical practice.

Phase IV trials have become the target of much scrutiny, in that they may be abused by pharmaceutical companies to hide marketing schemes under a medical, scientific wrapping. The practice of embellishing trials with marketing purposes was unveiled thanks to the Vioxx® analgesic scandal in 2004 (Law, 2006, pp. 87-103) – a marketing practice that up until then was something physicians had suspected, but for which hard evidence was lacking (Sox & Rennie, 2008). Withdrawn from the market in 2004 after having been linked to approximately 60,000 deaths by the FDA (Herper, 2005), internal documents from Merck were made public as a result of the lawsuits filed against the company. The charges against Merck were based on the accusation that the company had intentionally downplayed and concealed evidence of the deadly side-effects (cardiac arrest and stroke) of Vioxx from the FDA. Internal documents produced evidence of Merck using trials for marketing purposes – collectively called seeding trials. "It may be a seeding study, but let's not call it that in our internal documents" (Internal email communications "ADVANTAGE[25] ideas" email thread, 1999).

'Seeding' is a marketing strategy that is based on the medical theory of contagion related to the germ theory, according to which diseases can be passed from person to person though exposure to the infected individual. In marketing, the theory of contagion relates to how specific information is planted among a small seed population which will then, via social interaction and word-of-mouth strategies, be conveyed to the larger target audience (Watts & Peretti, 2007). The intent (and name) of a seeding trial follows this marketing logic and aims to increase the prescription and use of a product among prescribers. By influencing the prescribing practices of a select group of doctors, the seeding trial relies on the so-called Hawthorne-effect (Jaffee, 2001, pp. 25-26) where individual behaviour is influenced by the observation of the practices colleagues. Seeding trials are not illegal, but raise questions of research ethicality, since it is not the patients that are the trial subjects, but the participating investigator physicians themselves. This means that patients are given a certain product and exposed to drug side-effects with arguable necessity. In short, patients are just the collateral for marketing to physicians under the guise of medical science and thus should warrant more scrutiny than currently given.

[25] ADVANTAGE trials: Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness

Phase IV falls into the crevice between legitimate science and pharmaceutical marketing. When describing the lifecycle of a pharmaceutical product, the regulatory consensus defines phase IV clinical research as post-authorization drug research conducted after a medication has been authorized to be put on the market. Looking into the specification and nuance in definition, Phase IV clinical trials are labelled as such not according to chronological timing, but according to what the research question is. "Not all phase IV studies are post-marketing surveillance (PMS) studies but every PMS study is a Phase IV study" (Suvarna, 2010, p. 57). Some call seeding (marketing) trials phase V studies – "*The non-existent trials. The money makers*" [HUPH13]. Others have used the moneymaking characterization also describing phase IV trials as "*not really clinical trials but paid trials*" [NLREG02]. Although the term phase V trials is not used at all by the FDA or the EMA, and is not recognized as an official term, it may be used informally to differentiate between legitimate Phase IV, and studies with marketing intentions (Blaskó, 2011). The confusing definition of what a Phase IV trial is, and where it is placed in the pharmaceutical product lifecycle, will have implications for the extent to which a seeding incentive can be determined and, as such, makes regulatory professional oversight incredibly difficult, sowing seeds of mistrust among those in the medical community.

7.2. AWARENESS, ATTITUDE, AND ACTION

Regarding awareness or professional discourse concerning seeding trials, fieldwork revealed that in the Netherlands there was greater awareness of the *defined* phenomenon of phase IV clinical trials. What I mean by this is that when discussing clinical trials as marketing tactics, Dutch respondents used the term "Phase IV" consequently, and identified seeding trials as trials conducted to test pharmaceutical product explicitly *after* a licence had been provided by the National Medicines Regulatory Authority. This can be linked to the active role of the Dutch Healthcare Inspectorate (IGZ) in providing a definition, and a prospective checklist criteria for physicians, which promotes and enables critical assessment of marketing incentives hidden in clinical trials (Inspectie voor de Gezondheidzorg Rapport, 2009, pp. 27-33).

The IGZ defines Phase IV trials as research that takes place after a drug has received market authorization, and is permitted to be used in daily practice. "Phase IV research can be used to gather data about quality, safety, and efficacy of a drug" (IGZ Report, 2009, p. 5).[26] The report asserts that not all Phase IV research must be interpreted as a marketing scheme, but stresses that there are many elements or "red-flags", which in combination could signify that a trial may have more marketing than scientific rationale. Summed up, the most obvious qualities as compiled by the report are:

1. Unusually high compensation rates for physicians, or compensation in kind given after patient enrolment quotas or number of prescriptions filled.

[26] Fase IV-onderzoek is onderzoek dat plaatsvindt nadat een geneesmiddel is geregistreerd en wanneer het wordt gebruikt in de dagelijkse praktijk. Fase IV-onderzoek kan worden gebruikt om gegevens te verzamelen over de kwaliteit, veiligheid en werkzaamheid van een geneesmiddel.

2. Non-specific research goals or very simple research questions for which data is collected in a simple fashion such as "ticking boxes" on a survey. Usually the data collection itself does not require too much time (e.g. 2 minutes to complete a form).
3. No clear indication is made as to how the data will be published or made available to the investigating physicians themselves or to the wider medical community.
4. The marketing department of the sponsoring company is involved in the trial execution, and the budget may be provided by the marketing department itself.
5. There are no clearly defined trial protocols, and the number of patients incorporated in the study is not pre-defined, the number of patients included will be unusually high.

In Hungary, during my research I did not find any national authority or medical association research or report that discussed the seeding potential of trials apart from a definition of Phase IV trials provided by the Hungarian Regulatory Authority (OGYÉI). Phase IV studies are "examinations with medicinal products owning a marketing authorisation which have already had authorised therapeutic indications, dose range and approved Summary of Product Characteristics (SOP) with the aim to collect further information concerning the risk-benefit rate, to adjust dosing and recognize the side effects occurring rarely" (OGYÉE website[27]). There is no further elaboration or formal acknowledgement of the possible marketing incentive hidden in Phase IV such as with the Dutch IGZ report. Numerous Hungarian physicians, however, used the exact English term "bullshit study", which they did not explicitly link to specific clinical trial phases but denoted in general clinical studies described as being useless, lacking a research question that would add to existing medical knowledge or inform clinical practice [HUDR10], [HUPH13], [HUDR02], [HUREG02]. These studies were described as simplistic in terms of execution, this level of simplicity allowing doctors to pass off their clinical trials tasks to medical assistants.

"*There are these patient observational studies, they (company) asked for these information-sheets, which were completely laughable and the assistants filled them out. The company then collected them, and gave the doctors various allowances (money) in the form of legitimate contracts. From here on out these various observational studies, so how should I put this? When form is given to promotion.*" [HUDR10].

Speaking to a respondent with a background in ethical approval of clinical trials about his experience in reviewing phase IV studies in Hungary, his suspicions that a trial may be orientated towards marketing incentives relied on gut feelings and suspicions rather than any sure qualities that would unequivocally define a seeding trial as such. The respondent stated that critical assessment should be afforded to Phase IV non-

[27] https://www.ogyei.gov.hu/clinical_trials/

interventional, observational, and/or compliance studies which require administering a product in accordance with SOP, noting adverse reactions, and monitoring patient adherence to the product regime [HUREG02]. His specification had less to do with the amount of payment doctors received, or patient numbers, but focused on the research question and the study design (such as in points 2, 3, and 5 in the IGZ report).

An identification of a problem begins with awareness of it. Knowledge pertaining to the existence of seeding trials among respondents I interviewed could be characterized by asymmetric dispersion, and definitional inconsistencies along the lines of investigator physician and clinician. Investigator physicians who routinely partake in the pre-authorization clinical trial process are well aware of the potential seeding nature of post-marketing studies. Clinicians, those who are the actual target participants in these studies are not aware of, unable to distinguish, or ambivalent about the existence of seeding trials. Discussing Phase IV clinical trials during fieldwork was difficult due to factors such as willingness to engage in discussion at all, possession of comprehensive knowledge of the clinical trial process, and was limited to those who claimed non-exposure, such as the account of a Dutch investigator physician.

"*What really irritates me is phase IV. It's when the drug is on the market, and is owned by the marketing department. The scientific, research and development part of the industry is usually out of sight. It's the marketing that takes over. And I sincerely believe that the collaboration between academia and pharmaceutical industry all the way up to phase 3 is perfect*." [NLDR13].

This type of aversion to studies post-authorization was reiterated many times by investigator physicians, phase IV trials being perceived as the first and most apparent emergence of industry influence in medical research. Again the division between pre- and post-market authorization stages and the restriction of industry influence to post-authorization interactions between industry and medicine is reflected. Being able to take refuge in the belief of independence afforded by scientific protocol adherence that characterises pre-approval medical research, the quoted respondent openly expressed a generalized disdain for phase IV clinical trials. Although not all Phase IV are marketing in disguise, the generalization stemmed, I felt, from the respondent's anger that it was at all possible to capture, to any degree, the process of scientific inquiry. In addition, his opinions on Phase IV stemmed from having had experience of being threatened personally by a pharmaceutical company when a Phase IV study conducted by the respondent produced unfavourable results. Stating that this happened "recently", he told me of the unfavourable data conducted in the Phase IV, and how "*a guy (from the company) invited me for dinner, no details, (and) he said: "I can break your career. I will break your career*." [NLDR13]. This was one example, of which type the respondent claimed to have many, characterizing phase IV and industry pressures for favourable results as the "*the military-industrial complex*".

"*We were, and I understand to some extent we were killing one of their leading drugs, not killing, we were having negative findings of their, of a drug which was on the market and which (…) families depend on. And they would try to defend their interest and negative publications would not help them. It's understandable, but that's phase IV*". [NLDR13]

Ethicality provided by an adherence to instrumentalism emerges again as a tool (mechanism) to divide ethical from unethical medical science. However, the ability to rationalize and equate impartiality with clinical trial protocol adherence disappears in phase IV clinical trials, finally allowing critical assessment to emerge. So deeply ingrained in the medical mind is the notion that the difference between ethical and unethical behaviour runs along the artificially constructed division between protocol-adhering science and post-authorization marketing, that safety from conflict of interest is ensured when a physician contains his/her activities behind the line of regulatory approval [NLDR12].

As I have illustrated in the previous sections, this perception – that there is a line drawn between where undue pharmaceutical influence and conflict of interests manifest and where they do not – limits a much needed scrutiny over the pre-approval stages. However, contrary to raised awareness and criticism, Phase IV clinical trials have not been subjected to any major opposition by either regulators, or the wider physician community. The IGZ report (2009) was not met by the regulatory or self-regulatory reform that it called for in its opening statement to the then Minister of Health, Welfare, and Sport (to whom the report was addressed). In Hungary, the answer to my question of what processes there were for stopping a seeding trial if there was enough reason to believe one had been identified, was met by the answer "*Quote this exactly. There are none.*" [HUREG02].

Seeding trials or "bullshit studies" are still conducted in hospitals, academic hospitals, and recruit GPs and specialists both in public and private practice. Those aware and critical of Phase IV explained a paradoxical situation, torn between an opinion that dismissed Phase IV studies altogether, and that of a responsibility to keep the execution of phase IV trials in academic institutions.

"*I think academia should in principle stay away from the phase IV, unless it is very well organised which means that it really has made clear what is going to be investigated, what is going to happen to the results. (…) I would say, try to stay out of phase IV studies. The problem is who is going to do the phase IV studies if academia stays out? Then the phase IV studies are done in other hospitals.*" [NLDR13].

These other hospitals, the respondent categorized as "*vulnerable*" [NLDR13] sites, and according to him, these physicians are incapable of assessing the scientific validity of Phase IV trials. In addition, the lack of concise understanding and experience of the clinical trial process allows for "*implicit knowledge*" [NLREG01] or stereotypical assumptions limiting critical review of whether or not to engage in clinical trials. An implicit assumption is, in this example, the idea that participating in a clinical trial

denotes high professional status, and which warrants a high financial reward for important work. Thus clinicians incorporated in marketing studies refrain from critical assessment due to inability to do so (lack of experience) and are further prompted to refrain from doing so by implicit assumptions of due financial reward for expert clinical, scientific work. Testing this assertion, and speaking to physicians from these so-called non-academic, "vulnerable" clinics, we spoke of their participation in clinical trials. Taking the IGZ report, and the characteristics described by doctors seasoned in clinical trial execution, I have applied the "red-flag" assessment to 2 accounts – one from the Netherlands (Cardiologist), and one from Hungary (General Practitioner) respectively. I have also, in a second column, highlighted the rationalizations used by respondents to explain qualities of Phase IV research that present either a motivation for participation, or ethical validation in terms of the scientific instrumentalism I described in Chapter 5 & 6.

7.2.1. NETHERLANDS: CARDIOLOGIST CASE ANALYSIS [NLDR06]

Respondent Description	Red Flags	Rationalizations
"They had all these papers, and you fill them in and if there is a serious adverse event you reported it immediately, called them up or emailed depending on the urgency of the situation.	The task is simple, and requires no more than noting ADRs	
It was quite interesting, (…) depending on what type of supervisor I had back in the day, of course more patients in studies meant more money for them as well as more status	Fee per patient inclusion and the monetary incentive for inclusion. No pre-defined number of enrolled patients	Status achieved by performance determinants of being able to provide many patients and not linked to scientific quality standards
Sometimes, you think, personally, what if somebody doesn't want to (participate)? Sometimes you feel it's not good for them. Of course it's good from a research perspective, that you (include) all patients in your study and not only a selection, but sometimes you think, well I'm not sure (…) You don't feel it's good for the patient to participate or try another blood thinner because he is already prone to bleeding, but that (quality) is not in the exclusion criteria	There are no clearly defined exclusion criteria of patients, no clearly identified trial protocols, or non-specific research goals	The doctor engages in rationalizing the necessity of including a patient for whom the drug might not be beneficial by evoking the scientific necessity of Phase IV marketing studies and generalizability of research. Ethicality is questioned but dismissed in the face of adhering to loosely defined protocols
I sometimes feel, of course if you start making your own selection, it's not completely representative and not a fair outcome. On the other hand as a doctor you want patient safety first. So sometimes it was very conflicting for me.		Rationalizing personal ethical concerns, validating a potentially non-beneficial (patient) outcome with the reasoning of contributing to medical science.

Upon asking this doctor whether these concerns could be raised or discussed with colleagues, especially with regard to including patients in a study that was not necessarily helpful to the patient, the physician told me that in this instance there was another colleague which was also "prone to the same feeling" and so these concerns could be raised. However, at the same time the position of researcher was "abused" in the sense that "nagging" too much would come off as not appreciating the position or the opportunity to participate in a trial. I also asked whether the respondent thought that she had been made to do something that she would not have done, had she been in a leading position. The answer was an uncertain "Yes, I think so", but then reaffirmed that from an ethical standpoint, nothing wrong had been done. As a conclusion to this account, the respondent saw her personal aversion to "selling" as the root cause of this internal conflict – the respondent preferred to practice medicine within the process of being approached by patients for help, and not dictating where and what a patient should take part in.

7.2.3. HUNGARY: GENERAL PRACTITIONER CASE ANALYSIS [HUDR25]

Respondent Description	Red Flags	Rationalizations
(The company) contacts you and says: if you have 15 patient to whom I prescribe a drug, then we (basically) follow up (on them)	Observational study	
so they (companies) don't necessarily expect the patients stay on that medication, so as I say, only those for which the medication is necessary… but if I prescribe that drug, and we create a job out of it.	Simplicity of task and unclear research question	
There are patients whom we follow (monitor) for 3 or 4 months. For that we get money.	Compensation fee per patient, no pre-defined number of enrolled patients	
So actually there was one trial that I would have liked to participate in, which would have been a trial to test an analgesic patch, which I don't think is worth anything, but the patients like it		Evoking patient preference despite not believing in the medication itself, alleviating the need to ethically appraise the efficacy of this product
We would have had to see if it caused photosensitivity. For some reason the regulatory authority made it a prescription-only medication, maybe because there was some (evidence of) photosensitivity. In my 25 years I have never seen that side-effect in my group (of patients), so there were probably not many cases of that (happening) but someone probably made a big deal over that. And if they make a drug available with prescription only, then the turnover decreases immediately because up until then the patient could just buy it, now they have to see a doctor to get a prescription	A clear marketing incentive of the clinical trial	As opposed the recognition of a marketing incentive behind this particular clinical trial as unethical, the physician presents a form of sympathetic understanding.

In this case there are a lot of revealing statements, such as "*creating a job*" out of a follow up, or the fact that tying a drug to a prescription decreases its sales. However, there is an inability or an unwillingness to connect these glaring circumstances to the possible marketing motive of the trial. In addition, I asked as to how this doctor was chosen specifically to participate, to which the answer was that she had successfully completed trials in the past, earning a place in a research database from which previously expedient doctors can be randomly picked to participate in future trials [HUDR25]. The reasons for which participation is sought out has less to do with the results, a good publication, successfully answering a research question, or furthering medical knowledge. Success here is simply the ability to execute a task in an efficient manner, success in completion.

It is important to make note here that neither respondents are harming patients, and cannot be accused of intentionally doing anything wrong. Medicines in Phase IV can rightly be prescribed to patients, albeit one may wonder as to their necessity. It is evident that the desire to contribute to medical knowledge, as well as the status that comes with participation of research, drives both respondents. I dismiss financial compensation as a driver, but rather as an ancillary reward for additional time and effort rendered outside of daily practice. In contrast to a complete lack of awareness of marketing incentives as claimed by the academic physician previously [NLDR13] – since both accounts mentioned market factors (selling, and drop in return in sales) within their descriptions of these trials –it is inability, or unwillingness, to assess the wider implications of seeding trials as regards the intrusion of marketing into medical research.

While "*vulnerable*" [NLDR13] clinicians may not be able or willing to differentiate between valid science and seeding tactics, it is wishful thinking that those in academia, who have no need for status verification due to an already established professional prowess, who are well paid, and who are able to identify pseudoscience, will refrain from advancing the scientific-promotional goals of the pharmaceutical industry, as is illustrated by the head of department in an Dutch academic hospital.

"*The company supported us very well for a very easy introduction. There is always a lot of company driven force for the implementation. If the company doesn't organize it very well, your product will (fail). So you need good products. You need good marketing. And good training of the doctors. But the same is true for a bad product. If you have a bad product but good marketing and good training, you will be very successful. So it's not the product itself; it's how you put it in the market and how you train the doctors. So who is capable of having a real, objective judgement of the product itself? Not the doctor. And the doctor is relying on FDA, or the (EMA) or whatever. But maybe that's not enough. And (…) it's not so difficult to get FDA approval. But that's what we have to rely on.*" [NLDR18].

Despite the fact that one is completely aware of the intention of easy introduction, which is a purely market driven incentive, the question of ethicality is downplayed,

and even dismissed by the very fact that regulatory approval is relied on. If it's *safe* and *efficacious* as the regulator has deemed it to be, then the responsibility of the physician in ascertaining ethicality is solved, by way of shifting the responsibility onto the regulators who approved the drug in the first place (trust in the regulatory authorities will be the punch line, and hence the logical order of describing Phase IV first). In addition, the concept of easy introduction is important to emphasize. There are many medications on the market already, and the use of one depends greatly on raising awareness among consumers. Promotion via the use of pharmaceutical sales representatives is the most common form of promotion by pharmaceutical companies and the most visible. The sales representative is easily identified as a marketing tool, and recent additional regulation and stringency regarding direct-to-physician advertising (DTPA) has implicated the effectiveness of sales representative advertising (described in Chapter 9). Thereby Phase IV clinical trials present an increasingly attractive mode by which to achieve awareness of an approved product among doctors, simultaneously capitalizing on the trust that physicians place in regulatory approval of safety and efficacy, quench the desire of physicians to help patients by furthering medical science, and endow doctors with prowess gained by clinical trial experience. As a respondent from a CRO company said, it is a "*beatific*" thing for physicians to participate in clinical trials, since it makes the physician feel as though he/she is "*contributing to the wellbeing of mankind*" [HUPH08].

7.3. HAS MARKETING INFECTED PRECLINICAL TRIALS?

Despite physician respondents condemning seeding trials, comfort was found in the fact that seeding trials are restricted to post-approval stages and thus any trial before drug approval is safe from marketing schemes. Reading the critical literature on the Vioxx case, however, (Hill et al., 2008) another study was accused of being a seeding trial: the ENHANCE[28] study. The ENHANCE study started June 2002 and ended in April 2006, and was sponsored by Merck and Schering-Plough[29]. The particularity is that the ENHANCE study was a Phase III trial (pre-approval phase) to test the effects of a combinatory treatment of two already approved drugs: Simvastatin (statin) and Ezemitimibe (cholesterol absorption inhibitor). However, Greenland and Lloyd-Jones (2008a) challenged the scientific validity of ENHANCE on a number of technical points: the end-point chosen to evaluate the efficacy of the combination therapy was not the most powerful, nor the commonly accepted end-point by which the FDA will evaluate the beneficial effects of a drug on coronary heart disease. Using novel methods for testing the weak end-points was another criticism given by the authors in that researchers used an uncertain method to further test for an uncertain end-point, thereby not only slowing data accumulation, but risking the clarity of the data so gathered. Another criticism was that the results of the study itself answered clinical

[28] ENHANCE trial: Effect of Ezetimibe Plus Simvastatin Versus Simvastatin Alone on Atherosclerosis in the Carotid Artery

[29] Now Merck and Co. since the Merck and Schering Plough merger in 2009, but known as Merck Sharp & Dhome or MSD outside of USA and Canada

questions of safety and efficacy which were already known by the FDA from the data that was submitted when the two products (Simvastatin and Ezetimibe) were approved individually. Thus the end results, about whether the combinatory treatment of the two drugs was safe or efficacious, was irrelevant because both drugs had been approved by the FDA already. The outcome would only have affected marketability, and Greenland and Lloyd-Jones (2008a) agree that the fact that the results of the ENHANCE trial were postponed to two years after conclusion, only supports their claim of its seeding nature.

A lengthy dispute followed the publication of this criticism, entailing the ENHANCE investigator's reply (Akdim et al., 2008), and further criticism by Greenland and Lloyd-Jones (2008b). But what is concerning is that this dispute regarded a Phase III trial, which leads us to question whether marketing is contained to Phase IV alone.

One such questionable example arose during during fieldwork when interviewing a Dutch physician describing his participation in Phase III clinical trials for Nivolumab, a cancer drug which was licenced for use in the treatment of metastatic melanoma in December 2014 FDA[30] and then licenced for treatment of non-small cell lung cancer by the EMA in July 2015, and subsequently the FDA on October 9 2015.[31] Reviewing the interview I noticed some qualities of this trial which, based on the IGZ report, raised some "red flags". According to this physician, he and his colleagues (at a non-academic hospital ziekenhuis) were contacted by a pharmaceutical company to participate in this trial.

[NLDR09]: "*They ask how many patients we can offer in a period of time, 3 months. And then we do it with our whole group, with 8 lung physicians and we try to participate with 10 patients each, and we do it on our own outpatients, and we follow the protocol they give, and that's it*."

Anna: "*Do you get paid for each patient that you recruit?"*

[NLDR09]: *"Yes. That depends how much work it is. If it is a one stop visit, then it will be €50 (per patient), but if it's complicated like in lung cancer than it can be €1500*".

The red flags pertain particularly to the high compensation rates for physicians directly, and that the physicians tried to get 10 patients in the trial each, meaning there was no pre-defined number of patients in the initial trial protocol. As to the publication of the clinical trial results, I searched both the Dutch Clinical trial database, and the ClinicalTrials.gov database. The Dutch database does not allow for multiple search items at a time, and is quite rudimentary, but a search for "Nivolumab" resulted in 1 search result, which concerns the use of Nivolumab, but the start date is January 1st of 2017, and does not include the hospital where the respondent works as a trial site. The clinicaltrials.gov database allows for multiple search items, and using the keywords

[30] https://www.drugs.com/history/opdivo.html
[31] https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm466413.htm

"Nivolumab", "Lung Cancer" and "Netherlands" without allocating the trial phase. Of the 11 clinical trials produced by the search, only 1 trial included among the trial sites the hospital where this respondent worked, but this trial was a Phase II study of Nivolumab for the treatment of refractory multiple myeloma, and will only be recruiting patients in September of 2017[32]. I contacted the respondent again but he had since left the hospital and directed me to another colleague who he said would provide the answers. The colleague referred me to the same websites where I executed the unfruitful research. My own assumptions of this trial being a Phase III seeding trial are inconclusive, and I can only rely on the red flag criteria as my guide. The fact that I could not find any clinical trial that resembled to any degree the trial that the respondent spoke of, may be either because the respondent may have provided the wrong information, or that the trial was not registered in any database, nor were its findings published. If the latter is the case, then my suspicions that this trial could have been a seeding trial are all the more established and warrant scrutiny. Although inconclusive, the Simvastatin example provides precedent for advertising to infiltrate Phase III, which for lack of time and word count, I cannot myself further pursue, however the suggestions make this subject particularly pertinent for future research and must be mentioned.

7.3.1. SEEDING TRIALS AND THE EROSION OF PROFESSIONAL TRUST

Seeding trials endanger medical autonomy over knowledge production as well as interpretation in that the knowledge that phase IV trials produce is whether the data from controlled clinical trial setting can be generalized to medical practice. However, seeding trials do not produce knowledge, since the very aim of the trial, and thus the research question, are not designed to achieve this goal. Knowledge interpretation is void as well, because the absence of a significant research question eliminates any valid knowledge that would add to the interpretation of controlled trial data. Additionally, seeding trials damage another incremental feature of the medical profession, which is the trust that is afforded to other colleagues in the field. In the Simvastatin example, medical doctors debating the validity of a clinical trial, reviewing the research question, and challenging the necessity of conducting a trial, is a good example of the necessity of peer review – a vital component in the autonomous self-monitoring structure of the profession of medicine – but let us approach it from another angle, which pertains to the trustworthiness within and among the medical community. Like all scientists, physicians are unavoidably destined to make mistakes in research, the correction or re-evaluation of which is maintained through the peer-review process. However, in this case the core challenge has less to do with scientific veracity (although criticism is based on the whether the trial was scientifically necessary or not) than it has to do with the integrity of the physicians involved in the clinical trial, thus a loss of trust among medical professionals themselves irrefutably damages medical autonomy. It is one thing to challenge a colleague regarding the

[32] ClinicalTrials.gov number: NCT03184194

results of a clinical trial, which may be due to error of method or analysis, but quite another to challenge the integrity of a medical professional. Connecting seeding trials to the previous analysis of medical knowledge production, I mentioned that industry financing stifles innovation by concentrating research funding in areas of medicine where the chances of success in producing a product are higher. This is illustrated in the phenomenon of "me-too" medication; the production of similar drugs of little or no therapeutic superiority. In a saturated market where there are numerous variations of a drug for the same therapeutic class, the competition is higher and "*easy introduction*"/marketing [NLDR18] becomes vital. Seeding trials may proliferate if there is no incentive structure to promote the reasearch of truly novel medication as opposed to researching simply different versions of already marketed drugs. This responsibility should lie with regulators, who approve medications. Now we get to the punch line: assessing the approach of regulators to the involvement of the pharmaceutical industry in medical research.

7.4. ATTITUDES OF REGULATORS AND "TONE AT THE TOP"

The division of medical knowledge into pre- and post-market authorization is bridged in the stage of drug authorization. Medicines Regulatory Authorities (MRAs) are government institutions, but as regards their function in the profession of medicine, these institutions are the final frontier, and the last stage of independent assessment of the statistical data that will determine whether a drug can be sold on the market. Simultaneously, they are the first stage of medical knowledge interpretation. The 3 levels of medical autonomy (knowledge production, interpretation and implementation) as I have stated in Chapter 3, can be categorized as specific stages that follow each other. However, in real life settings, these stages are not cordoned off, with one process starting once the previous one has been completed. Instead, many of the stages, given that they are determinants of each other, may overlap. This is the case of knowledge production and interpretation crystallized in the role of the medicines approval process. The approval process is very much linked to technical aspects of clinical trials i.e. meeting technical requirements of RCTs, and adherence to trial protocol provides the standard of evidence to evaluate safety and efficacy. However, when providing approval for a drug, the regulatory agency places on it a stamp of approval which already implies an interpretation: the drug is deemed by physicians as being safe and effective, and can be used in medical practice.

I was referred to Medicines Regulatory Authorities (MRAs), but what interested me was how they described their perceptions of the pharmaceutical industry, being that these bodies are the final barrier of critical assessment before a drug is approved and used in medical practice. Their fundamental duty with regards to the autonomous practice of medicine is the "seal of approval" that doctors, untrained or inexperienced in the technical mazes of medical research, rely on when deciding to use a pharmaceutical product. "Regulatory science", the analysis of regulatory evolution (Lewis & Abraham, 1998) is a discipline of itself, and many of its considerations

informed my own research. However, as a bottleneck of the influences in medical knowledge production prior to market authorization of pharmaceutical drugs, the attitudes of Regulatory Authorities is paramount, which I aimed to assess by speaking about the official position of MRAs with senior representatives. I propose that the lax interpretation of bias, and the inability to incorporate critical ethical scrutiny of industry-sponsored clinical trials is very much defined by the tone set by the agents that execute regulatory oversight. In organizational criminology, the "moral tone" (Coleman, 1995, p. 368) of an organization depicts the attitudes of top management towards illegality. This is represented in arguments that locate corporate culpability in the directing "mind of the manager" (Punch, 2000, p. 253; Colvin, 1995), stating that it is the managers who define the culture of an organization, which is adopted and followed by the employees within it. The "tone at the top" (Weber, 2010) argues these points asserting that it is the moral integrity of CEOs that will determine the corporate culture and thus acceptance/unacceptability of criminality and corruption among employees (Lambsdorff, 2015). Although not charged with governing the practice of medicine, the tone set by regulatory authorities, their explanations as to the role of industry in medicine, as well as the regulatory interpretation of industry-run trial results and medicines, will be incorporated into the evaluation of and trust in the safety and efficacy of a medication, and thus the interpretation of medical science into practice.

In Hungary there is one central MRA, the National Institute of Pharmacy and Nutrition (OGYÉI), which is responsible for authorization of clinical trials, the provision of market authorization for medicines, and implementation of the Hungarian Medicines Legislation. In the Netherlands the Dutch Medicines Evaluation Board (MEB) is in charge of data evaluation and provision of market authorization. My experience with the Hungarian MRA respondent was slightly reserved. In discussions relating to ethical medical practice, responses were very much orientated around prescription practices of physicians. The respondent and I had started discussing general monitoring of medical practice, and the responsible authorities, such as monitoring prescription practices of doctors, or the evaluation of standards of physical infrastructure of medical institutions. In a moment of reflection of medical malfeasance directed more to self than to me, the respondent brought up industry influence over prescribing activities of doctors which could sometimes warrant a criminal investigation, since it "*grazes the borders of corruption if (a doctor) represents the interests of a pharmaceutical company*" [HUREG01]. Taking advantage of the fact that the respondent had mentioned corruption, I proceeded to ask what the respondent defined as corrupt practices.

"*Well, what is meant by corruption? It's quite difficult to define. But let us say, if the decision (of anyone), the objective decision, if I define it, even within regulatory framework, is if an objective decision is changed in exchange for financial benefit. For instance if a patient needs a medication and the doctor makes a decision that is*

different from what is rational in that situation for financial gain. That's what I would define as corruption." [HUREG01].

I proceeded to ask the respondent whether corruption is a question of personal evil or a product of coercion, to which there was an almost immediate shut down reaction, where the respondent started firing back questions to me, asking what the purpose of my research was, which university was supervising me, and whom I had spoken to prior to this interview. After evading these question by describing that it was not quantity of respondents but quality of interviews that mattered, from that point on the answers to further questions became shorter and more abstract, where the respondent took refuge in the legal duties of the MRA in monitoring unethical marketing practices (i.e. professional scripts). We had to conclude the interview quickly both because time was running out, and because another meeting was scheduled in for the respondent, when we were interrupted by a secretary, who said someone from the pharmaceutical company Boehringer Ingelheim had arrived, and had asked to speak to the respondent specifically. Although I had asked if I could be referred to others within the institution, the respondent declined, did not consent to providing further referrals, and asked me again whether the interview would really remain anonymous, and that she would like a copy of the transcript once I had completed it. The interview was steered away from any comments or descriptions as to the how the regulatory authority viewed the role of industry in medicine.

Contradicting my expectations, the regulatory authority was the most difficult to gain access to, so I tried getting assistance from government officials in Hungary to help me gain access to the OGYÉI and to provide me with contacts that could explain the regulatory processes. After sending the names of my supervisors, my PhD proposal, and a "few words about myself" upon request, I received the following answer:

"*I read the summary of your research subject. I did not find any person that I could suggest contacting in pursuance of this subject. Good luck with your research*." [Email excerpt: 25/01/2016].

Albeit this time around I had been completely honest with my stance as a criminologist which may have added to the refusal to help, however according to physician respondents the Hungarian Government, and thus the Hungarian MRA, has no interest in addressing any financial aspects of the healthcare system especially any financial income, legal or illegal, of healthcare professionals. Among physicians, the dismissal of the subject of industry in medicine by the government and MRA was described to me as being intentional. The salaries of all healthcare service providers in Hungary are among the lowest among OECD countries (F11-071 EN, 2011, OECD, 2014). The legal system of informal payments in Hungary was argued to be kept alive intentionally so that the government did not have to increase healthcare spending [HUDR10], [HUDR01]. Similarly these respondents stated that engaging in contractual agreements with industry is also part of this construct. Regarding clinical trials in Hungary, respondents explained that participation in, and compensation for,

medical research was a vital element in salary compensation, and important for keeping doctors from leaving Hungary and finding work in higher income European countries [HUDR14], [HUDR25].

In the Netherlands, I was more successful in discussing the role of industry in medicine with regulatory bodies. I required a strong referral to gain access, one which I managed via personal networks, since none of the cold calls resulted in any responses. I was nevertheless welcomed by those I was referred to, and my questions regarding industry influence were not treated as taboos such as they were in Hungary, but as important issues that one should not shy away from. Interviewing at the MEB, I dived head first into what the opinion of the respondent was concerning the pharmaceutical industry.

"*I think that, as an authority I should be very critical towards the industry because it's our role, also to be very critical on the dossiers, on their behaviour, on their claims etc. So our authority attitude is: "okay, show me the data, show me the evidence and behave yourself". On the other hand, as a citizen, I think as far as I know, we really need (the) pharmaceutical industry to do R&D, and to make products, and I think that in general we don't recognize that role as a society. We always believe that these are the money makers so they only have one interest*." [NLREG01].

Highlighting the role of industry in medical research, the respondent confirmed what was described in Chapter 6, that most of the "R" in R&D comes from the academic sector, but that academia does not have the financial capacities to execute medicines Development. As such the industry is vital [NLREG01]. However, when it comes to the ethical responsibilities and the direction of medical knowledge production, keeping the industry in check was seen more as something that should be done by regulators, as well as by society and by NGOs. As to what the MEB can do in this sense, it is restricted to giving industry leaders advice, because the legal duties of the MEB extend to authorization of medicinal products and pharmacovigilance, thus the impact that the regulator can make on business decisions of the pharmaceutical industry is limited to advice. Using the example of psychiatric medication, the respondent described how there have been no significant advancements in the past 10 years, due to economic reasons as opposed to social need:

"*(…) and not because there is no medical need, but for tons of reasons pharma is not interested. Or maybe they are but they don't invest in it. And I understand the reasons. The science is weak. Patient organizations are not easy to approach. Clinical trials are hard work. So that the whole complex, it's much easier… Easier is not the right wording, but it's strategically more attractive to go to oncology, or neurology, or multiple sclerosis, or diseases like that*." [NLREG01].

This type of sympathetic understanding of what drives business was also described in the respondent's approach to the phenomenon of "me-too" medication, which I have described as being problematic as it does not add medication of significant therapeutic value to the market (Angell, 2004; Gagnon, 2013). At the MEB, me-too drugs and the

ethics of flooding the market with multiple similar drugs was reasoned to be something that was "not essentially a bad thing." Describing it as the "*formal position of the MEB*" [NLREG01] medicines cannot follow a one size fits all model, and patients may react to one drug differently than to another. Thus it is the official regulatory view to support me-too drugs.

"*Ever-greening, or squeezing the lemon, I think it's part of the business model, and of course we can like it and dislike it, but I think it's part of it (…) at the end of the day this development ends up as a product where you could say how different it is compared to what is already there, (and) that's a fair question*." [NLREG01].

Ever-greening is a term used to describe the industry's patent extension tactics using me-too medication as was the case with Prilosec® and Nexium® (see Chapter 6). While it may be argued that me-too medication is good for patient variability, and consumer choice, in Chapter 6 I described how flooding the market with me-too drugs, and using ever-greening tactics are detrimental to medical practice. Reiterating a Hungarian respondent, these is a general lack of clinical trials (and thus information) which compare similar drugs already on the market [HUDR10]. A respondent from a Dutch healthcare NGO illustrated how this problem is reproduced by MRAs by way of the protocol-based scientific evaluation system, and the absence of medicines superiority requirements in the medicines authorization process. The fact that only safety and efficacy are the required standards for approval means that no one is examining the actual necessity of the product itself for patients.

"*In a registration process like the EMA or in Holland, the MEB, you don't look at the value of information, you just look at whether; 1) is it better than a placebo and 2) that you don't die from it immediately. These are the two things they look at. Not whether it's an improvement over the standard therapy we already use. You know one thing for sure, that the new therapy will be more far more expensive than the old therapy. That's the only thing you know for sure*." [NLOO02]

In further contrast to the MEB's position regarding me-too medicines, a Dutch physician then stated outright, that doctors are not interested in drugs that have no superiority to the already available treatment [NLDR13], illustrating the enormous discrepancy in what clinicians see as useful for medical practice, and what the MEB endorses. Industry in medicine as viewed by the MEB is something to be embraced, and "*not a conspiracy against society*." [NLREG01]

Regulatory authorities, as it turns out, are financed predominantly by the pharmaceutical industry, and I believe that this defines the level of scrutiny afforded to the role of industry in medicine, being that the regulatory institutions rely on industry financing. For every drug application, authorization, as well as any scientific advice regarding application and licencing procedures, pharmaceutical companies need to pay the MRAs. Both the MEB and the OGYÉI website make available the list of tariffs payable to MRAs for application, authorization, or scientific advice services.

This is common practice regarding EU members states, as well as for the EMA, "For 2017, the total budget of the European Medicines Agency amounts to €322.1 million. Around 89% of the Agency's budget derives from fees and charges, 5% from the European Union (EU) contribution for public-health issues and 7% from other sources"[33]. The fees from pharmaceutical companies as well as the annual fee paid for each medication authorized on the Dutch market form "the basis of the MEB's income"[34]. The fees for each regulatory service are determined by the Dutch Ministry of Health, Welfare and Sport. The Hungarian OGYÉI is no different, apart from the fact that the tariffs payable are not listed on the OGYÉI website, but in Appendix 1 of the Act XCV of 2005 (GyTV). Responding to ethicalities of being financed predominantly by industry, reasoning was limited to the fact that this practice is no different than that of the EMA [NLREG01]. It seems harmonization is not limited to regulatory, quality, and safety standardization, but also a normative interpretation of which financial relationships between industry and MRAs are proper.

The advisory role of regulators is particularly interesting and presents another conundrum, the dual role of regulatory stringency and critical assessment coupled with a less adversarial advisory role. The MEB respondent described this as regulators having to "*wear all the hats*". Having more than one role to fulfil is the basis of conflict of interest, however the conflict of interest manifests when two opposing interests clash, dissolution found in partiality towards one interest over the other. Wearing the hat of regulator we see me-too medication as fulfilling a patient interest of product variability and safety and efficacy, but when we come to changing the hat to that of an advisor, the rationale is to stop companies from "*doing research that is useless, not give answers to relevant questions."* [NLREG01]. The line between the benefits of medication variability and putting yet another pharmaceutical product on the market that adds no added value to what is already available is open to interpretation depending on the hat on the head.

7.5. CONCLUSION

Low risk diseases are more commonly funded research areas, resulting in market saturation of pharmaceutical products in single therapeutic classes. The competition increases as drugs of similar therapeutic value are fighting for a piece of the specific disease market. Easy introduction and uptake are achieved via the use of commercially motivated research posing as scientific knowledge production: the phenomenon of Phase IV seeding trials. The abuse of Phase IV trials which are a vital part of controlled clinical trial knowledge production generalizability – and thus contributing to the interpretations of pre-approval knowledge production – destroys the integrity of medical science. Physicians are unable to distinguish between marketing trials and

[33]EMA Website:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000130.jsp&mid=WC0b01ac0580029336
[34] MEB website: https://english.cbg-meb.nl/about-meb/contents/governance/funding

scientific trials due to lack of awareness, but those that may possess the knowledge to do so have their conscience cleared by the fact that the drug in question has been approved as safe and effective, thus alleviating their own responsibilities to drug regulators. The coveted role and ethical requirement of contributing to medical science further incentivises participation and may even dismiss consideration of the "red flags" (IGZ report, 2009) that may signify an anterior motive than that of advancing medical knowledge.

Regulatory authorities charged with monitoring safety and efficacy of pharmaceutical products reproduce the problem of market saturation and stifling of medical innovation, in that there are no requirements that have to be met regarding innovative quality of a drug seeking approval. As long as the clinical trials adhere to the technical standards, drugs are approved. The question of whether the next drug under regulatory scrutiny produces therapeutic advantage is simply overlooked, and the practice endorsed. This endorsement has purely economic incentive-based reasoning (the variability of products) which is in stark contrast to medical professional opinion. What doctors describe as useless, the regulatory authority sees as necessary and beneficial. The regulatory authority relationships, in that they are funded by industry, and that safety and efficacy trump necessity in pharmaceutical product approval, filters back to the unquestioning acceptance of industry determination of medical knowledge production. The institutional corruption of medical knowledge production is apparent in the inability of medicine to dictate the progress and direction of its own knowledge development. The reinterpretation of ethical research into marketable product is not the cause of loss of macro level medical autonomy, but a product of it, where market driven medical science is rationalized as bettering society under the rhetoric of ensuring availability on the market. The dependency on industry funding has not only allowed industry to control what knowledge is produced, but also resulted in medicine being pressured to produce marketable knowledge in an expedited manner, and in a flurry to meet deadlines, one only has the time to ensure that the protocols have been followed, and not whether the subject matter of research is that which will benefit patients in the long run. This question is even more belittled, because those operating in the pre-approval stages are far removed from the consequences of performing research that is orientated to producing drugs that lack innovative qualities, or are merely reproductions of already available medication. Although physicians and regulators may feel that there are more products available, the detrimental effects manifest in the later stages of clinical application, thus their removal from actual clinical practice denies them the ability to perceive the wider implications of economically-driven research.

CHAPTER 8: INTERPRETING SCIENCE INTO PRACTICE: INSTITUTIONAL CORRUPTION OF MEDICAL KNOWLEDGE INTERPRETATION

> "The doctor's professionalism means that he must act in an evidence-based way to the greatest extent possible according to the most up-to-date scientific insights".
> – KNMG, Medical Professionalism, 2007

The science and practice of medicine, although divided in professional activity, competency, and separated in the pharmaceutical product supply chain stages of pre- and post- medicine approval and regulation, are nevertheless highly connected – each stage is built upon the other. The notion of translational medicine discussed in Chapter 6 embodies this endeavour, orientated towards developing theory into a practically applicable clinical artefact or action. It also embodies the rationality behind evidence-based medicine (Pearson et al., 2012). Up until now I have described how, in medical knowledge production, scientific inquiry is subject to directional changes in research subject along the promise of return on investment and marketability. I also offered hints already about how the effects of investment return-driven research impacts clinical practice: the doctor who exclaimed that the practice of testing drugs against placebos gives no information as to superiority of multiple treatments available for the same disease [HUDR10]. The story, however, does not end here, because knowledge production is only one stage which concerns what information is produced and made available to begin with. Even if some questions remain unanswered or available information/data is multiple, the stage of medical knowledge interpretation should account for these informational absences or incongruences, because knowledge interpretation is the act of assessing all available information, and coming to a medically-informed conclusion as to how the available data should be interpreted and applied in clinical practice.

8.1. EVIDENCE-BASED MEDICINE

Evidence-based medicine (EBM) is the process of "evaluating and incorporating research evidence into medical decision making" (Timmermans, 2010, p. 309). Also known as evidence-based healthcare, EBM relies on combining individual clinical expertise with scientifically-validated research (Pearson et al., 2012; Sackett et al., 1996; Timmermans & Oh, 2010). Imagine a conveyor belt on which medical knowledge production is the raw material that must go through the processes of conversion into practical knowledge. EBM itself is an umbrella term which incorporates a wide variety of actions, closely linked to the Evidence Hierarchy described in Chapter 5. The Evidence Hierarchy triangle ranks scientific data according to evidentiary power i.e. what type of evidence can be trusted the most, provides strongest validity, and is least tainted by possible biases. However, the

scientific data derived from each mode of scientific inquiry is still "unfiltered" (Lambert, 2009) meaning that the data derived from various medical research is raw, primary, devoid of context. The information has to be filtered: interpreted, and conveyed into the context of application. If knowledge production is on one end of the conveyor belt, and practice on the other, then the intermediary process of translation or filtering primary data is the phase of medical knowledge interpretation, expressed in the practice of meso level medical autonomy – the ability to independently select, assess, interpret, and translate raw medical science into clinical practice. The image below complements the hierarchy of the evidence triangle, with an additional triangle of filtered information, placing systematic reviews of scientific data at the pinnacle, followed by the practice of developing medical guidelines for clinical practice, and then by the critically appraised individual medical literature.

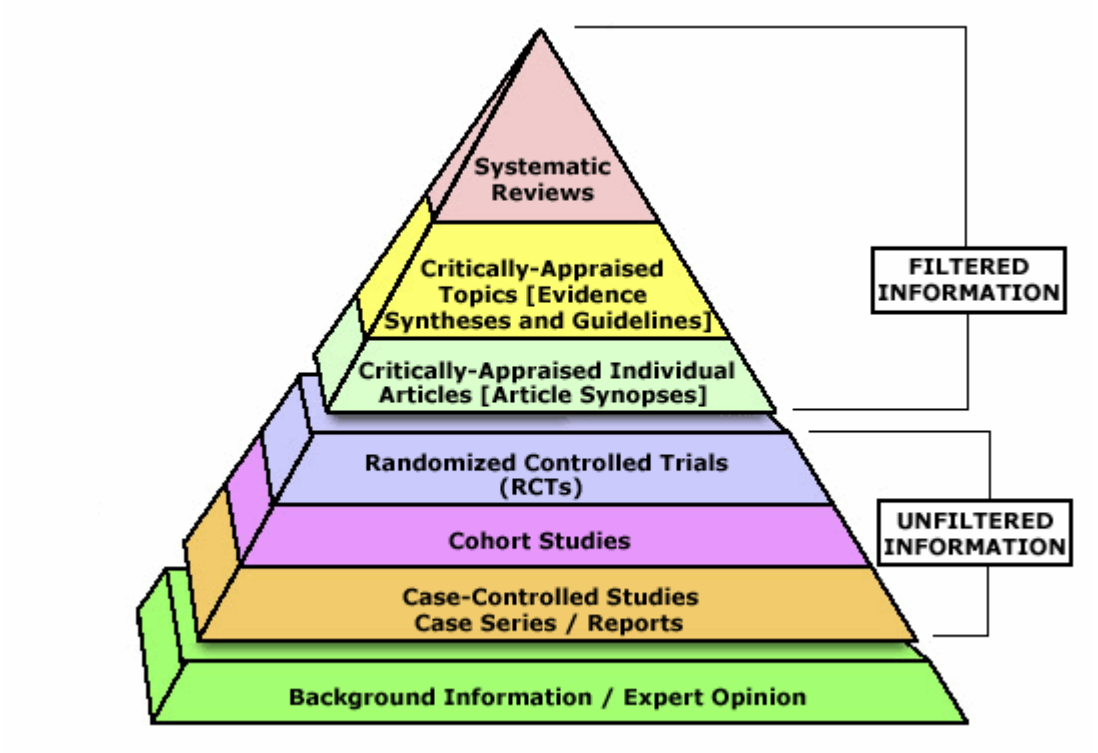


Image source: Lambert, H. (2009). Evidentiary truths? The evidence of anthropology through the anthropology of medical evidence. *Anthropology Today*, 25(1), p. 19

As a consequence of division of labour and fragmentation of competencies through knowledge specification and specialization, clinicians are not always equipped (nor can it be expected of them) to fully comprehend the technicalities of the clinical trial process itself, or to disseminate statistical significances derived from raw data [NLOO02]. To this point, the profession of medicine as a professional knowledge-based organization has its own processes of ensuring that the scientific basis of medical knowledge production is efficiently translated into practical guidelines which inform clinical practice as well as define requirements to ensure that the rapidly expanding knowledge base is kept up to date. Following the conveyor belt analogy, these tools of translations I call vehicles, and fieldwork led me to identify 3 vehicles of knowledge interpretation which mediates between science and practice. These are the

implementation of (1) medical guidelines to inform clinical decision-making, (2) the reliance on medical expert assessment, and (3) the formal requirement of participating in Continuing Medical Education (CME) throughout the medical career. Again, let me reiterate that these 3 vehicles of knowledge translation are all manifestations of the general concept of EBM; they are the execution of EBM itself, not to be seen as phases in a chronological order of interpretation but as tools which are part of the translation process (EBM in action).

The subject of EBM is highly polarized (Knaapen, 2014) and has been since its inception in the 1980s. On the one hand EBM is considered the pinnacle of medical practice, and provides a firm foundation based on the rigour of the scientific method, agreed to be a vital component in the trust awarded to the profession of medicine as well as increased certainty, and quality afforded by calculated standardization (Sackett, 1997). As I described in Chapter 5, EBM was introduced as an operative intention to stabilize uncertainties and reduce variation in medical practice (Sackett et al., 1996; Sackett, 1997; Lambert, 2009; Timmermans, 2010), and establish the autonomy of the professional collective (Knaapen, 2014; Mykhalovskiy & Weir, 2004). On the other hand, critics see EBM as the fortification of scientific positivism, professional bureaucracy, and the industrialization of medicine (Rees, 2008; Rastegar, 2004; Karreman et al., 2002; Abraham 1997). These arguments claim that standardization damages the humanist qualities of medical care, where patients are depersonalized, their illnesses cut away from the person (Wade and Halligan, 2004), and medical practice becoming so-called "cookbook medicine" (Knaapen, 2014), industrializing the "art" of medicine (Karanth 2010, p. 673).

EBM and the vehicles of knowledge interpretation have raised the issue of medical autonomy, in that they are tools used by third parties to inject and solidify other ancillary interests, which consequently decrease the autonomy of medical practice. The most debated aspects are the cost containment measures imposed on healthcare professionals in their own practice and concern healthcare insurance mechanisms. Whether insurance is provided by the state, such as in Hungary, or provided by private insurance companies as in the Netherlands, cost containment measures "tie the hands of doctors" in that physicians are obligated to take into consideration which medications are covered by state or private insurance, described as evidence-based medicine's "*Trojan horse*" [NLEX02].

It is important, however, to address another risk to medical autonomy which assesses the way in which the pharmaceutical industry has also taken to decrease the autonomy of the medical profession, but in a more invisible, subtle manner, embedded in the very tools used to execute EBM. Discussed in the previous chapter was how industry funding of clinical trials biases the evidence provided by RCTs, and thus the knowledge produced about a pharmaceutical product before its authorization for the market. The previous analysis, however, mainly concerns bias in knowledge production. When it comes to medical knowledge interpretation I argue that indirect influence is exerted as a concomitant process of knowledge production executed in a

consequential manner different from the visceral dependency of holding finances hostage.

The arena of interpreting science into practice is executed and organized by the medical profession. It is an activity which is not regulated by any external body, in contrast to conducting clinical trials, or regulation regarding medicines promotion. This level of autonomy, its execution, is constructed and carried out by the medical profession itself, and relies on the professional hierarchy – positioning of individuals based on expertize – and the knowledge-based organization of the medical profession. This level of autonomy becomes slightly transitionary regarding regulatory oversight. We leave both the international arena of harmonized clinical trial guidelines, protocols, and medical research ethics, and enter into a section of medical activity that is governed by Guidelines and Codes of Professional Conduct compiled and issued by National Medical Associations and partially by the pharmaceutical industry self-regulatory codes of ethics concerning promotion to physicians.

This level of autonomy requires a type of work that can only be executed by medical experts. Within medical knowledge production, the role of industry is necessitated by its ability to provide the financial backing needed to conduct clinical trials and cover the costs of the drug application process. Its ability to influence rests on the monopoly over the tools (money) needed to execute a task, and thus exercises discretion in its decision to finance certain research as opposed to others. The same (will become) apparent for advertising to physicians in Chapter 9, where the industry is in possession of information on particular products. These are both very concrete things, which manifest in objects, money, facilities, trial data, visual aids, pamphlets. In contrast, knowledge interpretation is a knowledge- and experience-based endeavour, which requires possession of abstract qualities that cannot be touched or held. This is the very knowledge that medical professionals acquire and possess through years of medical practice and experience. The first aspect of EBM to be assessed is the translation of raw data from medical knowledge production into written guidelines that inform doctors and which they apply to their practice. These documents are known as Medical Guidelines and are the most common and visible expressions of EBM. A medical guideline is a technical description tailored to a disease area which provides physicians with a guide to diagnostic methods and criteria for disease identification, as well as treatment regimens and disease management procedures. Guidelines form the basis of standardization and quality assurance in medical service delivery. Guidelines follow international medical developments although they are assessed (or translated) and approved by National Medical Organizations/Associations. This is why, although medical knowledge could be described as universalistic, in that scientific evidence knows no boundaries of the nation state, there are variations in the application of evidence regarding the first line treatment, which depend on qualities of the national healthcare system, budget, healthcare infrastructure, the organization of medical professionals, and national medical practice traditions and laws (Knaapen, 2014).

The website of the Hungarian Association of Medical Societies currently lists 128 separate Societies. Hungary has an additional layer regarding the professional organization of medicine, which is the employment of Medical Specialist Colleges which comprises 61 Colleges along 44 disease areas. These colleges are not specific organizations with a registered address, but are made up of members with medical association affiliations and convene at least twice a year to issue opinions on healthcare policy issues, CMEs, and the introduction and application of medical guidelines as mandated by Ministerial Decree (Edict 12/2011 (III. 30) of the National Ministry of Human Capacities. Medical guidelines can be accessed via a centralized online database of Hungarian medical guidelines which at the time of writing comprised of 506 medical guidelines.[35]

In the Netherlands there are 3 Medical Professional Colleges, the Federation of Medical Specialists (FMS), and 2 organizations for General Practitioners, the National Family Practice Association (LHV) and the Dutch College of General Practitioners (NHG). The LHV works to further the professional interests of Dutch GPs while the NHG maintains and issues medical guidelines for GPs. Guidelines can be found on the NGH website and I found 64 available GP treatment guidelines[36].The FMS works closely with 32 specialist medical associations, and the Richtlijnen database[37] maintained by the Kennisinstituut (Knowledge Institute) holds the guidelines for medical specialists which currently contains 231 medical guidelines. Medical science progresses at incredible speeds, both due to fast-paced evolution of knowledge, as well as a result of increased internationalization of research and medical expertise. Thus guidelines may change or new ones may be issued on a yearly basis. The use of guidelines is standard practice in medicine today, and in both Hungary and the Netherlands are integral tools for informing individual clinical decision-making. Again I must stress that medical guidelines are not the same the world over, although the increasing dominance of international medical associations forecasts medical guideline universalization, or at least the intention to discourage great discrepancies regarding the application of science into practice. In contrast to the uniform standards in clinical trial execution necessitated by international pharmaceutical markets, medical service delivery is highly embedded in the socio-economic and legal traditions of a country. In this analysis, these national disparities will also be taken into consideration when evaluating EBM in practice.

8.2. EVALUATING EBM IN THE FIELD

The first and foremost expression of EBM is the adoption of medical guidelines in clinical practice, and I wanted to assess what doctors thought of guidelines in general, aiding or hindering their work. Illustrating the approach towards guidelines as

[35] Hungarian Database of Medical Guidelines: https://kollegium.aeek.hu/Iranyelvek
[36] Dutch Medical Guidelines for General Practitioners database: https://www.nhg.org/thema/nhg-behandelrichtlijnen
[37]Dutch Medical Guideline database: https://richtlijnendatabase.nl/?query=&specialism=&sort=0

expressed by physicians in the clinic is important, because it provides for reflection on perceptions of sacrificing individual autonomy for that of the professional collective. Opinions were found to reflected the polarization described in the EBM literature.

In both countries under study, those physicians that were completing or had recently completed residency, saw medical guidelines as not only a helpful tool in practice, but also as the only possible means by which to ensure that patients were treated according the best scientific evidence. A resident doctor in Hungary, fresh from medical school, described the value of medical guidelines as a guarantee for treatment quality, scientific proof, and a way in which to eliminate inaccuracies of intuitive medicine, an element he associated as being reminiscent of an underdeveloped form of medicine which has no place in the scientifically-based practice of today.

"*I want to bring the two together (science and medicine). Medicine itself is developing very fast. We can treat many more (diseases) and the guidelines are there to determine what we can do (regarding treatment) … I think those so-called doctors who put their hands on a patient and then claim that they know what the problem is… that time is over. The technical advancements of today make this type of intuitive medicine a thing of the past*." [HUDR06].

More experienced physicians were well aware of the benefits of having a guideline to return to, but were quite vocal about the individuality of patients and disease, and saw guidelines as exactly that: guides and advice, not rules or laws of mandatory dictation. Guidelines were also described as training wheels [HUDR07], [HUDR03], there for safety and certainty but less important when one had acquired a "basic feel" for the practice of medicine over time; a Dutch physician exclaimed that practicing physicians use guidelines less and less, because the practices of others (observing colleagues) constantly informs one's own decisions [NLDR07]. More experienced doctors were also much quicker to point to standardization of medical treatment as a restriction on medical autonomy, a vehicle on which other interests could break into the sphere of medicine, such as the aforementioned cost reduction interests by the state and/or medical insurance companies, or a convenient foothold for aiding a growing trend of holding physicians legally accountable to dissatisfied patients.

I asked physicians to talk of the state of medicine or how they saw the healthcare system and medical practice in their own countries, as well as their own perceptions of their profession. It was in the general question of describing the national healthcare system, that a Dutch physician expressed his personal opinion on the protocolization of medicine.

"*In general, Dutch Healthcare is very well organised. Here and there I feel that (there are) too many rules, and it is getting more and more difficult to follow, or to react spontaneously because too much is protocolized. But on the other hand, I don't say that is wrong, because here and there we need guidelines of course but it shouldn't frustrate innovation, that's my only concern*." [NLDR16].

As mentioned before (Chapter 5), standardization was introduced to reinforce the autonomy of the collective profession of medicine as a whole, with the curtailment of spontaneity – the source of variations among medical practice. This quote however reveals the deeper consequences of limiting individual discretion in that innovation in medicine stems also from clinical experience. Innovation, despite being commonly interpreted as something restricted to the scientific sphere and confined to the laboratory, also manifests itself in clinical practice. While intuitive medicine in the sense of Reiki-like practice is dismissed in the face of scientifically-grounded medical diagnosis and treatment, intuition is also understood as the implicit knowledge that comes with experience alone. Innovation in individual practice would be an important component of the ideal of EBM – integrating clinical practice with scientific evidence. Medical guidelines, as this respondent saw it, were both a realization of quality maintenance, but also produced an internal conflict regarding practice based on experience, and practice based on scientific evidence; the two do not always coincide. Striving for quality assurance produces a conflict between the standardized procedures outlined in a guideline, and the professional experience-based conviction of the individual. This respondent further described this conflict as "*when you are convinced of something that needs to be explored and the rules are saying "well, we have our doubts" and then maybe you can find a way but I think guidelines make it more difficult*." [NLDR16].

On a similar note, Hungarian physicians described how the nature of a guideline is precisely that: "*so the English word guideline expresses this accurately. It's not the law*" [HUDR16]. A medical professional may deviate from a treatment guideline when having a valid reason for doing so. This respondent explained how guidelines are combined with individual discretion, using an example of individual competency complemented medical guideline use. A study may produce a result that states, out of 20,000 patients, 18,000 reacted to a treatment positively, and as such, this treatment may be suggested as the first line treatment (first option) for a disease. The guideline may state this, but it is only through the exercise of individual discretion that a doctor is able to assess whether a patient would fall into the "*majority*" category, or not, and thus adjust treatment accordingly, which would warrant guideline deviation [HUDR16]. His account described the helpfulness of medical guidelines, in that treatment decisions could be formulated with scientific evidence, and further stressed that this provides for equality of clinical practice among physicians in general, because guidelines enable evidence to take priority.

Minimising variation is not, however, just about creating systematic order in practice. Standardization, although technical in nature, also affects the individual's autonomy on the level of willingness to voice a concern. A Dutch resident for example, expressed a concern about greater chaos created by the continued updating of guidelines, sometimes even on a yearly basis, which causes more uncertainty in practice than stability, citing the confusion it causes patients when treatment regimens were changed regularly [NLDR06]. This concern reiterates the previous quote, which again states

that the abundance of guidelines makes medical practice difficult to follow, even for doctors.

These examples reflect what the majority of interviewed respondents said with regards to the standardization of medical practice via the use of evidence-based medical guidelines in both Hungary and the Netherlands, which pertain to a constant evaluation of generalized medical consensus versus the decision of the individual. Following a guideline ensures that decisions are based on evidence that fortifies decision validity irrespective of personal persuasion and experience i.e. impartiality in practice. Guidelines provide a safety net which, in the case of non-response to treatment or patient deterioration of health, cannot be held against the physician in question. However, simultaneously, collective autonomy incapacitates individual clinical persuasion, up to the point where it may silence critical opinion – an important sentiment to consider regarding physician willingness to challenge potential pharmaceutical industry influence in medical guideline development.

8.3. INDUSTRY INFLUENCE IN MEDICAL GUIDELINES

A Hungarian cardiologist [HUDR03] assessed the question of medical guidelines being a vehicle of knowledge interpretation that may possibly be influenced by pharmaceutical companies. He began by stressing that in an "*ideal scenario*" a physician would be required to trust the complete impartiality of a medical guideline, but then added that simultaneously one cannot dismiss the "*lobbying power*" of pharmaceutical companies. Whether or not this lobbying power extended to the issuing of medical guidelines themselves, and whether they were manipulated by pharmaceutical companies, was not something that the "*periphery*" (the line of clinicians that physically execute healthcare delivery directly to the patient), himself included, would generally be able to evaluate, because the activity of drafting a guidelines was done by the "*higher ups*", experts in medicine. As such, he could not provide evidence, or claim that he had witnessed manipulation in action. His opinion was one that saw industry influence as being a very real possibility, which he described using an example from his own clinical experience. Discussing the general direction of current medical treatment, this respondent felt that there is an over-emphasis on using pharmaceutical products. His reflection connects the consequences of pharmaceutical product-orientated medical research in clinical practice.

"*Today's medicine tends to go in the direction of deciding to treat with or without pharmaceutical intervention, not with prevention. There is much less word given to what kind of lifestyle someone lives, despite being an equally important component of treatment. Since 25% of the "health space/arena" is life expectancy, quality of life, genetics, what we inherit, 20% is our environment, how we live and what we do, 25% are lifestyle choices such as whether or not you smoke, and 10% is drug intervention. I wrote an article about how regular exercise has benefits for cardio-metabolic functions. Just think how many medications we could stop taking (…) if we simply engaged in regular exercise as we become older*." [HUDR03].

This respondent touches upon what is known in medical sociology as the medicalization process wherein "non-medical problems become defined and treated as medical problems, usually in terms of illness and disorders" (Gabe et al., 2004, p. 59). Illustrative examples of medicalization can be found in the field of psychiatry and the treatment of psychiatric illnesses. Post-traumatic stress disorder, depression, and attention deficit hyperactivity disorder developed from being social stigmas to becoming medically recognized illnesses in need of treatment (Wade & Halligan, 2004). Medicalization claims to be a product of the development of medical science and increased disease understanding, but medicalization is criticized for laying the basis of another phenomenon, known as the process of pharmaceuticalization (Abraham, 2010), the increased consumption of pharmaceuticals in society and the trend in medicine that supports pharmaceutical product-based treatment. Similarly to medicalization, pharmaceuticalization is also explained as the product of increased disease understanding and the rapid development of medical science. Linking the two processes together, Abraham calls this the "medicalization-pharmaceuticalization complex" (2010, p. 608), and sees commercial interests of the pharmaceutical industry rather than increased medical understanding as its source. Chapter 6 discussed pharmaceutical industry influence in manipulating medical research, where scientific inquiry is directed towards producing treatment solutions entrenched in the pharmaceutical interpretation of medical care. Thus instead of aligning research with the question of "what treatment works", it is reformulated to ask "what pharmaceutical treatment works", and this forms the basis for the 'pharmaceuticalization of EBM' argument.

In the previous account the physician [HUDR03] advocates that the scope of illness should evaluate qualities of a patient's life(style), and not just the pathology writhing within the body itself. However, his description illustrates a pattern of medicalization over-arching medical pathology; medical intervention extends to the medicalization of lifestyle choices which are remedied not by changing lifestyle, but by providing lifestyle questions with pharmaceutical answers – the medicalization and pharmaceuticalization of e.g. diet, exercise, or nicotine addiction. Cardiology specifically is especially interesting for the study of the pharmaceuticalization-medicalization complex with an eye to a very recent position of the American College of Cardiology (Tuhoy & Dodson, 2015), and endorsed by the US Preventative Service Task Force (2016) to implement in medical guidelines the prescription of statins to adults between 40 and 75, as a preventative measure against heart disease irrespective of prior cardiovascular problems.

Other examples of treating lifestyle changes with prescription medication can be found such as the use of antidepressants to ease the pains of smoking cessation. The way in which I was made aware of this was during the conclusion of an interview with a Dutch respondent when we informally discussed the difficulties of stopping smoking. He suggested that I try antidepressants, as he himself was using, because after getting used to the "*dry mouth*" side effect, it actually "*works pretty well*" [NLOO01]. This information was not actually meant as part of the interview, but I decided to assess it

nevertheless. Searching for clinical trials on this subject, I found a systematic review (highest level of filtered evidence) presented by the Cochrane Collaboration which provides data that validates the use of antidepressants as a treatment for smoking cessation side-effects (Hughes et al., 2014), and is also a recommended second-line treatment (following nicotine replacement therapies, such as a nicotine patch) by the Dutch GP Medical Guidelines (Chavannes et al., 2007), with the use of Nortriptyline (not licenced for smoking cessation) or Bupropion (licenced for smoking cessation). In contrast, Bupropion is not licenced in Hungary for the treatment of smoking cessation, yet it appears in the medical guidelines, and can, if approved by a psychiatrist, be prescribed to patients suffering from depression, and who would like to quit smoking (Egészségügyi Közlöny, 2014). The Cochrane Collaboration meta-analysis examined 90 clinical trials evaluating the efficacy of antidepressants in smoking cessation, 66 of the 90 trials investigated the use of Bupropion in smoking cessation, and almost half (44) studied Bupropion against a placebo. 40 of these trials were funded either partially (26) or fully (14) by GlaxoSmithKline, the company that holds the patents for Bupropion (Brand name Wellbutrin/Zyban).

These examples support the claims of the medicalization-pharmaceuticalization complex (Abraham, 2010). Medical research focusing on pharmaceutical products effectively defines the approach to treatment in the clinic, again being orientated toward drug intervention. A Hungarian Nephrologist redefined this as "*medicine-based evidence*", [HUDR09] highlighting that the evidence available is already such that pharmaceutical product-based intervention is overrepresented. However, these cases are inextricably linked to what is considered a medical pathology, and what is not. The pharmaceuticalization process is also visible in examples where the question of whether a pathology should belong to the discretion of medicine or not is undisputed. Using the example of prostate cancer a Hungarian Urologist described how the decision between 2 medically approved interventions both included in a medical guideline, tends to favour that of the pharmaceutical drug, a practice that this respondent felt was the result of pharmaceutical industry influence.

"*Let's say that for a specific disease there are the alternatives of treating with surgical intervention or with medication. As I said, very often there are many alternatives in the treatment options for an illness within a guideline, and the pharmaceutical industry is capable of turning this (treatment choice) into one that will benefit them, that is: influencing the physician to prefer treatment with medication, which is of course impermissible, but those are the facts. More specifically this means, in the case of diagnosis of prostate cancer we know that with early diagnosis and surgery, we can cure the patient without resorting to any additional treatment. But no one apart from me is interested in that. Not the director of the hospital, because surgeries and all the tools we use are expensive. Not the patient, because he does not know that he needs to be operated on, (only that) there is a drug available. The specialist is absolutely not interested because if he sends the patient to the inpatient institution, to the hospital director, he will miss the opportunity to benefit off of informal payments. While, if he*

regularly calls the patient back, on a monthly or tri-monthly basis to administer an injection, he stands to gain a little profit from that, not to mention benefits from pharmaceutical product promotion. For example in the Czech Republic they don't allow the pharmaceutical industry to promote to doctors. They didn't create a situation in which the medical professionals would compromise their professional medical decisions. So in the Czech Republic interestingly enough, alongside similar population numbers, they still execute two thousand more early stage prostate cancer surgeries than in Hungary. There is absolutely no other explanation than industry influence." [HUDR10].

I especially prize this example, because it illustrates a much more nuanced form of how pharmaceutical treatment emerges as preferential, based on a sequence of decisions made with varying institutional and personal interests, evoking the argument of embeddedness, namely "that the behaviour and institutions to be analysed are so constrained by on-going social relations that to construe them as independent is a grievous misunderstanding" (Granovetter, 1985, pp. 481-482). As I said before, Medical Guidelines are both based on scientific evidence, but also align treatment options with the economic, social, and cultural determinants of a national healthcare system. In this example the respondent eloquently puts all these factors into context and explains the diverging interests at each level of decision-making, from the hospital director who aims to decrease costs, all the way to the clinician with whom the treatment decision lies. What is interesting is that industry influence regarding treatment options in a medical guideline is exercised indirectly, presenting a potentially financially rewarding scenario attached to the decision to opt for pharmaceutical intervention. In the grand scheme of things, both result in a patient receiving treatment, and both are sanctioned by a medical guideline, but the decision to go with the pharmaceutical intervention as opposed to the surgical intervention in this illustration is more closely tied to financial gain than a medical rationale.

In contrast to direct exertion of pressure, as is the case of industry funding of clinical trials by exploiting monopoly (possession) of a means (financial capital) to achieve a goal (knowledge production), this example shows how persuasion towards pharmaceutical product use manifests as a choice embedded within the healthcare delivery system. This physician described the Hungarian system of informal payments as contributing to pharmaceutical treatment preference by physicians. This 'tradition' is a dark stain on the Hungarian healthcare system, and has a long history of being debated as to whether or not informal payments constitute bribery, as defined by Hungarian criminal law (2012. Law C., §291). The system of informal payments for all its controversy is still prevalent and doctors in Hungary explained this tradition as born of necessity to compensate for the low wages of Hungarian doctors.[38] As a

[38] "Physicians in Hungary can earn 10 times less than doctors in other OECD countries. It is common for well-trained physicians to receive only 270,000 HUF or $1,000 per month in Hungary. Other medical jobs in Hungary also have a relatively low salary including nurses and health administrators. Health workers can earn as little as 141,000 HUF or $520 per month".

consequence, the system of informal payments contributes to a normalization of accepting or actively seeking out additional sources of income, one of which is by aligning treatment decisions that favour pharmaceutical product-based intervention if there is a chance of receiving industry rewards, in cash or in kind.

In Hungary, accounts from physicians as to pharmaceutical industry intervention in medical guidelines themselves was expressed in the processes of medicalization and pharmaceuticalization of clinical care and the practice of medicine in general. As an explanation towards the motives of physicians for preferring pharmaceutical products in treatment decisions, the tradition of complementing low salaries with additional sources of income lays ground for the embeddedness of the hope of financial compensation in medical decision-making. In Hungary, physicians saw undue industry influence in medical guidelines and medical practice as a process closely linked to the medicalization-pharmaceuticalization process, industry influence as dynamic and procedural rather than located in one particular action. In stark contrast, however, in the Netherlands my discussions regarding industry influence in medical guidelines was described as being a question of whether the guideline author him/herself was influenced by the pharmaceutical industry. In contrast to Hungary, where industry influence was described as manifesting the pharmaceuticalization of medical treatment, Dutch physicians interpreted influence to occur in the confines of individual financial relationships with guideline authors.

In the Netherlands, although doctors agreed that it was definitely in the interests of pharmaceutical companies to have their products listed as treatments in medical guidelines, industry influence over the content of the guidelines was, in reality, improbable. This conviction was based on the fact that the KNMG has in place written recommendations for the management of conflict of interest specifically for guideline authors (The Code for the Prevention of Improper Influence due to Conflict of Interest: KNMG COI Code, 2012), which a Dutch gynaecologist described as "*strict rules*" that prohibit any conflict of interest, and stated that the medical associations monitored any type of financial relationship between a guideline author and pharmaceutical companies [NLDR18].

Reading this code is interesting in itself, because the opening paragraph emphasizes how "scientists and the business community are increasingly working together" (KNMG COI Code, 2012, p. 3), and further states that "business relationships" do not necessarily imply undue influence. However the KNMG COI Code lists relationships that may pose "obstacles" to impartiality. These obstacles are listed as: personal financial interests, personal relationships, receiving external funding for research, and an interest invested in a valorised product (KNMG COI Code, 2012, pp. 4-5). The solution to minimizing undue influence is seen in the enforcement of transparency where all guideline authors are made to disclose relationships of the above nature.

https://forum.facmedicine.com/threads/lowest-paid-doctors-in-the-world.26771/ Data Source: (F11-071 EN 2011)

Discussions in the Netherlands with physicians about medical guidelines and industry influence, if not asked specifically, never came up, and I would assume that this is due to the inconceivability of pharmaceutical companies manipulating an activity which belongs decisively to doctors alone. Most of the interviews where I did bring up the subject concluded with a dismissal of medical guideline manipulation entirely. It was with Dutch pulmonologists that I was able to further disseminate the specific reasons for considering guideline manipulation improbable. The first account stressed impartiality of the medical associations that issue medical guidelines [NLDR09]. The second interview placed trust in medical experts as a firewall against undue influence.

"*Because when you write a guideline (…) you're not asked to write a guideline very easily, you have to be an expert and it would make you very vulnerable to influence (if a doctor received payments from a company). And there are checks and controls on that*." [NLDR15].

Talking then to a pharmaceutical company general manager, it was using an example of an asthma medication that we entered into the subject of the independence of medical guidelines wherein it was stated that companies do not take part in writing guidelines, but that they did inform physicians about their drug to ensure that the drug was prescribed to the right people and that doctors were able to diagnose whether a patient fell into the right asthmatic phenotype [NLPH06].

These accounts illustrate a perception of industry being far removed from clinical guideline influence. However, during analysis of these interviews I found a unique opportunity to assess the veracity of guideline author independence. As I said, there are a total of 231 medical guidelines[39] in the Dutch medical guideline database for medical specialists. These interviews taken together provided information on a medical specialism, a disease area, and a specific drug. Being in possession of these three criteria, I was able to search the Dutch medical guideline database using the search terms: pulmonology, asthma, and the name of the medicine. Placing these terms into the Dutch medical guideline database search engine, the result produced the medical guideline for Severe Asthma. Using then the Dutch CGR transparency database for disclosures of financial relationships between physicians, healthcare organizations and pharmaceutical companies[40], I searched for possible financial relationships between companies and guideline authors that may constitute a conflict of interest, ensuing in the following case analysis.

[39] https://www.kennisinstituut.nl/kennisgebieden/richtlijnen/richtlijnendatabase
[40] http://www.transparantieregister.nl/nl-NL/Home

8.3.1. A DUTCH CASE STUDY OF INDUSTRY INFLUENCE IN MEDICAL GUIDELINES

The guideline for Severe Asthma[41] (Annex 3) was initiated by the Dutch Association of Physicians for Lung Diseases and Tuberculosis (NVALT website) According to CGR Transparency register data, the NVALT has been receiving a constant flow of payments from pharmaceutical companies for the past 3 years[42], the majority of which are for sponsoring meetings, and projects. A detailed table of these funds can be found in Annex 4 to this thesis. For each year consecutively, the NVALT received:

2014: €207,972 (23 separate payments from 9 pharmaceutical companies)

2015: €278,617 (29 separate payments from 12 pharmaceutical companies)

2016: €332,049 (24 separate payments from 11 pharmaceutical companies)

These companies are AstraZeneca, Boehringer Ingelheim, Chiesi Pharmaceuticals, Eli Lilly and Co., GlaxoSmithKline, Mundipharma Pharmaceuticals, Novartis, Roche Nederland, Takeda Nederland, Bristol-Myers-Squibb, Gilead Sciences, Pfizer, and Sandoz. In the graph below, which ranks the top respiratory medication brands, and the manufacturing companies, taken from market research website statista.com, we can see that it is these companies that dominate the respiratory diseases market in the United Stated (Asthma, COPD, and Cystic Fybrosis), thus there can be no misinterpretation that the companies involved in these disease areas are the ones that regularly sponsor the Dutch Medical Organization which is the authority and provider of expertise on Respiratory diseases.

[41] https://richtlijnendatabase.nl/richtlijn/ernstig_astma/ernstig_astma_-_startpagina.html#verantwoording

[42] Data is kept for only 3 years. During the writing of this thesis the data for 2014, 2015, and 2016 was available. 2017 data will be available form 2018, and 2014 data will be deleted.

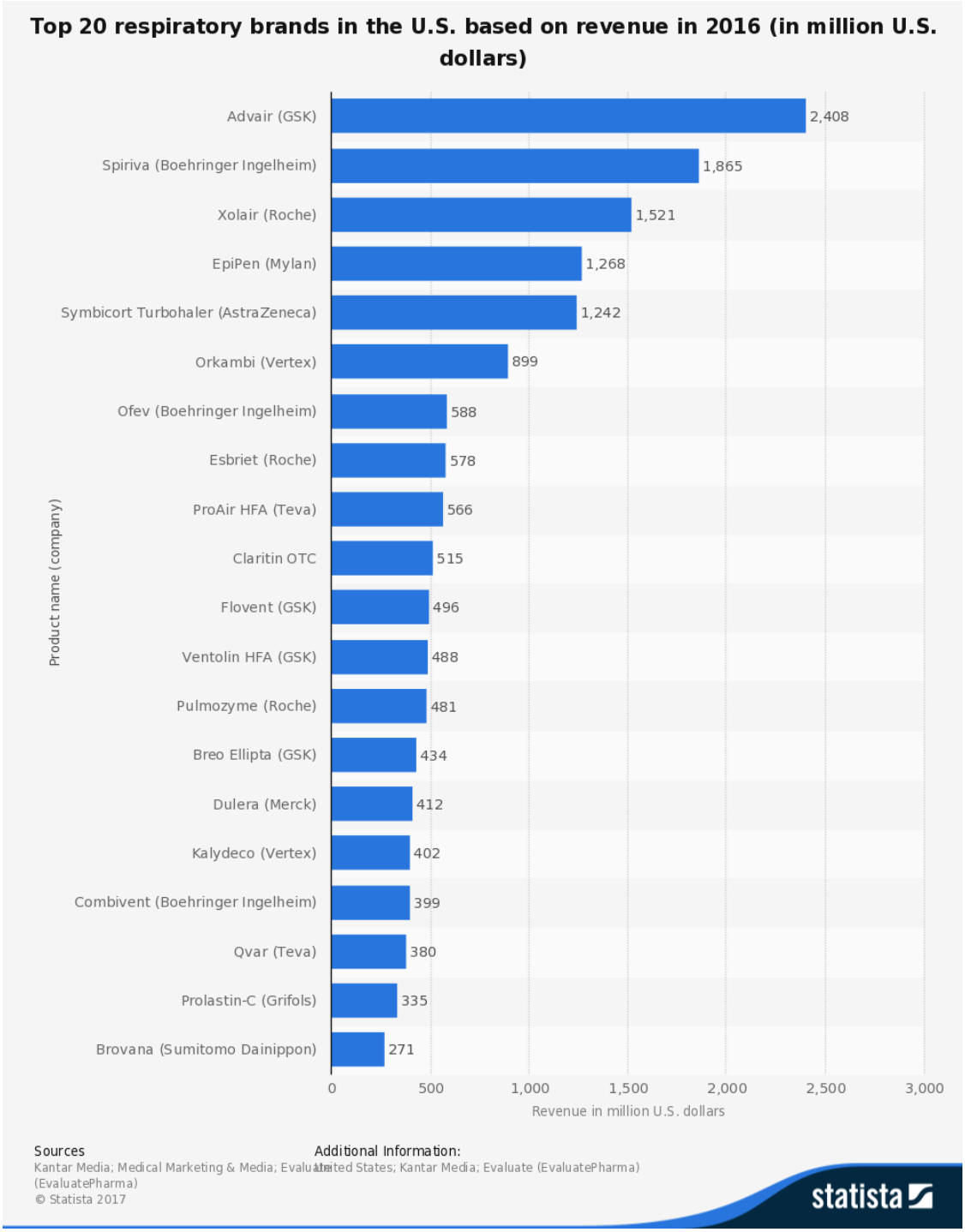


Image source: statista.com
https://www.statista.com/statistics/318251/revenue-of-top-20-respiratory-products-in-the-us/

Although destructive of the image of independence, the question still remains as to medical guideline influence, since we can see that companies themselves are financing the Association heavily, but does this in any way mean that the guidelines themselves are affected? Taking the Medical Guideline for Severe Asthma (14-05-2014), I found that of the 6 authors, all of them received varying amounts of pharmaceutical company sponsorship throughout the years 2014 – 2016.

Author 1: Pulmonologist, Academic Medical Centre, Amsterdam

Year	Total	Sponsoring companies	Services rendered
2015	€5.022	Boehringer Ingelheim Novartis Teva Nederland Vertex	Advisory Consultancy Speaking fees Service related expenses
2016	€6.267	Boehringer Ingelheim Chiesi Pharmaceuticals GlaxoSmithKline Teva Nederland	Advisory Service related expenses Speaking fees Other services

Author 2: Pulmonologist, Academic Medical Centre, Amsterdam

Year	Total	Sponsoring companies	Services rendered
2015	€1.050	GlaxoSmithKline	Advisory

Author 3: Pulmonologist, St. Franciscus Gasthuis, Rotterdam

Year	Total amount	Sponsoring companies	Services rendered
2014	€ 4.415	Boehringer Ingelheim Novartis Astra-Zeneca ALK Abello	Advisory Speaking fees Other services
2015	€12.025	Boehringer Ingelheim Novartis GlaxoSmithKline Takeda ALK Abello	Advisory Other Services Hospitality costs Consultancy Speaking fees Service related expenses
2016	€ 5158	Novartis Chiesi Pharmaceuticals GlaxoSmithKline ALK Abello	Speaker fees Service related expenses Hospitality costs Advisory

Author 4: Pulmonologist, Medical Centre, Leeuwarden

Year	Total amount	Sponsoring companies	Services rendered
2014	€1.260	Novartis	Advisory
2015	€1.146	Novartis GlaxoSmithKline	Advisory Hospitality costs
2016	€979	Teva Nederland	Hospitality costs

Author 5: Pulmonologist, Dutch Asthma Centre Davos, Switzerland

Year	Total	Sponsoring companies	Services rendered
2014	€1.083	Teva Nederland	Hospitality costs

Author 6: Pulmonologist, HAGA Hospital, The Hague

Year	Total	Sponsoring companies	Services rendered
2014	€3.605	Boehringer Ingelheim Bayer	Advisory Speaking fees
2016	€3.325	Boehringer Ingelheim Chiesi Pharmaceuticals	Speaking fees Service related expenses

The guideline itself was last reviewed in 2014, and so an assumption of direct conflict of interest might be argued to apply to only three of the two guideline authors who received payments from pharmaceutical companies in the years of the guideline review. None of the payments for 2014 can be found in the conflict of interest disclosure sheet that accompanies the guideline itself (Annex 5). This is in contradiction to the KNMG COI Code, which states explicitly that "the most obvious cause of a potential conflict of interest" are personal financial interests which include being a member of an advisory committee of a company which is involved in the "sector" of disease for which a guidelines is written, or rendering services to a company such as being a consultant. (KNMG COI Code, 2012, p. 4). Perhaps the payments are not included precisely because these are disclosed in the transparency register; but I have no evidence to support this hypothesis, as well as having no evidence of these payments being assessed or taken into account by NVALT or the KNMG.

Despite only three authors receiving payment in the year of the guideline review itself, conflict of interest still applies to all six authors because they are mandated to monitor the guideline for five years after the date of implementation, considering if any revisions should be made, and evaluating the necessity of a complete revision after the five year assessment, meaning that payments after 2014 will continue to pose a conflict of interest.[43] Nevertheless, as the KNMG COI Code (2012) states, payments in and of

[43] "De werkgroep heeft het mandaat van haar opdrachtgever (de NVALT) om gedurende een periode van 5 jaar jaarlijks te bezien of er wijzigingen in de richtlijn moeten worden doorgevoerd. Indien

themselves do not necessarily mean that there is a conflict of interest. Conducting an in-depth analysis, I took to looking at whether the specific companies from which payments originated have an interest in the treatment guidelines for Severe Asthma, and thus I translated and assessed the medical guideline itself with the use of a guideline flowchart (Annex 3). Although guidelines suggest first, second (etc.) line treatments, they do not contain the brand names of pharmaceutical products, only the name of the active ingredients of a medication, so first a search must be performed to find the active ingredient, and then find the generic and/or original brand, followed by a search of which companies manufacture that drug.

For asthma the "cornerstone of treatment" (Severe Asthma Guideline, 2014, p. 18) includes Inhaled Corticosteroid (ICS) and respiratory medication, such as bronchodilators (long-acting β2 adrenergic receptor agonists: LABA). The following companies manufacture first line asthma treatment. AstraZeneca: Symbicort® (ICS and LABA), Takeda: Alvesco® (ICS acquired by AstraZeneca In: Bradshaw, 2015) GlaxoSmithKline: Flovent® (ICS), Advair®, (ICS and LABA), VentolinHFA® (bronchodilator), Teva Pharmaceuticals: Qvar® (ICS), and ProAirHFA® (ICS and LABA), Chiesi Pharmaceuticals: Foster® (ICS and LABA), Atimos® (LABA), Clenil® (ICS)

The Richlijn database flowchart details the first line medications to be administered once the diagnosis of Severe Asthma has been identified in addition to those above, which are: administering a trial treatment of Leukotriene Receptor Antagonists (non-steroidal anti-inflammatory bronchoconstriction prevention medication: LRTAs). Brand names include Merck: Singular®, but now produced in generic form by numerous companies, among them Teva Pharmaceuticals. Brand name LRTAs also include AstraZeneca: Accolate®, and Chiesi Pharmaceuticals: Zyflo CR®. Theophylline, Long acting muscarinic antagonist LAMA, Boeringher Ingelheim: Spiriva® (tiotropuim bromide: anticholinergic bronchodilator short acting bronchodilator LAMA) Following administration of first line treatment, if a patient does not react to any of the above (Insufficient improvement, analysis of exacerbations based on the Asthma Control Questionnaire, lung function examination), then doctors are advised to seek advice from a specialist centre. If the asthma can be tied to an allergic reaction, then the use of an anti-IgE antibody is advised. The current competitors on the anti-IgE market are Novartis XOLAIR® developed by Novartis and Genetech (Genetech is a subsidiary of Roche In: Pollack, 2009), but is in high competition with the very recently authorized GlaxoSmithKline drug Nucala®

nodig zal de richtlijn (in modulaire vorm; uitgangsvragen) worden aangepast. Na 5 jaar zal bezien worden of de richtlijn in zijn geheel gereviseerd moet worden."
https://richtlijnendatabase.nl/richtlijn/ernstig_astma/ernstig_astma_-_startpagina.html#verantwoording
(https://richtlijnendatabase.nl/richtlijn/ernstig_astma/organisatie_van_zorg_bij_ernstig_astma.html#verantwoording

(authorized in 2015 in Europe), and the very recently approved CINQUAIR® from Teva Pharmaceuticals (approved in 2016 in Europe).[44]

The very same companies that produce the highest grossing asthma medications are the same companies with which these medical guideline authors foster financial relationships, which is by both my own analysis, as well as the KNMG COI Code (2012) a very strong conflict of interest. What is revealed goes beyond the Severe Asthma Guideline itself, which is how industry influence in guideline development is hidden from practitioners themselves due to the distance between the dots that connect financial payments to guideline authors and pharmaceutical company interests. The independence of the guideline drafting process is a perception that is supported by trust among colleagues and the image of professional autonomy. Influence is hidden by design, in the complex system of conflict of interest management, ironically within the disclosure structure itself. Be the fact that these payments were not disclosed in the declaration of interests accompanying the Medical Guidelines itself for reasons such as unintentional oversight, intentional concealment, or non-requirement due to disclosure in the CGR database, these reasons do not change the fact that the systems in place for disclosing financial interests are such that it is incredibly difficult for anyone, even doctors, to track down this information – this analytical excursion taking roughly two weeks to compile.

As I mentioned at the beginning of this section, opinions as to how pharmaceutical companies influence medical guidelines differ in Hungary and the Netherlands. Two modes of industry influence are revealed. The first mode of influence is the pharmaceuticalization of medical guidelines, a mode of influence that is a result of medical knowledge production (i.e. the Evidence, in EBM) being pharmaceutical product orientated. Thus, "*medicine-based evidence*" [HUDR09] will result in a pharmaceutical-based approach to medical treatment. Secondly, industry also influences medical guidelines in a more direct manner, which is by fostering financial ties with medical guideline authors. Given that Hungarian physicians emphasized pharmaceuticalization, and that Dutch physicians emphasized financial relationships with guideline authors, this might suggest a conclusion that established different methods of industry influence in medical guidelines in Hungary and the Netherlands. However, I was privy to one account in Hungary that exposed the same kind of direct financial influence in medical guidelines in Hungary as in the Netherlands. This respondent, a Hungarian Nephrologist, turned out to be a medical guideline author himself and, as such, is contacted by pharmaceutical companies "*every day*". I asked him with whom he meets and what they discuss, and he provided me with the following account.

[44] The flowchart (annex 3) also advises the use of antimicrobial medication if the exacerbation in non-related to an allergy, but rather to a viral or bacterial infection. However, antimicrobials reduce infection, but do not have an effect on lung functioning. Also two additional treatments are mentioned in the flowchart, but there exists no, or inconclusive trial data to support their use. The first is the suggestion that breathing air at high altitudes may be helpful, and the second is the use of a minimal invasive procedure using a bronchoscope to deliver thermal energy into the lungs.

"*(I meet) key opinion leaders and sales representatives. But routinely (I meet) the medical director, commercial director, sometimes even with the head of the company, routinely with the higher levels. We (co-authors) also participate in the international (rib-cage i.e. structure) of these companies as consultants. This is always a two-sided thing. In reality, from time to time they listen to what our opinions are, but obviously they also tell us what their expectations are*." [HUDR09].

An execution of a similar guideline author analysis could not be done for Hungarian guidelines since payments to doctors, although also newly transparent, are collected in a manner that makes such an analysis impossible. I will, however, later discuss financial ties between industry and the medical associations/societies/colleges that approve guidelines. For now my analysis will limit itself to a conclusion that challenges the belief that medical guidelines are isolated from industry influence. Not only is the very evidence (clinical trials) used to fashion guidelines already subject to industry influence, but financial and friendly ties and meetings behind closed doors between authors and industry are not conspiracy theory urban legends, but a very real phenomenon. Doctors' belief in impartiality of authors, as well as the pharmaceutical industry's activities of informing doctors about their drugs provides a veil of credence to a deplorable backdoor to guideline influence.

These accounts also reveal a singularly important point and the subject of the ensuing section. Reiterating what the Dutch pulmonologist [NLDR15] said, guideline authors are experts in their field. These experts are also known as Key Opinion Leaders, and their role in informing medical practice is not only apparent in guideline authorship, but also another tool for pharmaceutical industry influence in medical knowledge interpretation.

8.4. KEY OPINION LEADERS

The higher up physicians are in the medical hierarchy, a head of a department – a hospital manager, a principal investigator – the more they are targeted by pharmaceutical companies [HUDR09]. Within medicine, the status of expert is particularly coveted, and it is these experts who take the lead in medical opinion and practice formulation. They are most certainly those called upon to partake in the assessment of evidence and its translation into medical guidelines [NLDR15], [NLMJ01]. Industry exploits the hierarchical structure of the profession of medicine, reflected in the knowledge interpretation triangle, which places much emphasis on individual appraisal of medical research by experts. Contrary to the low evidentiary power of expert opinion in medical knowledge *production*, the *interpretation* of medical knowledge values individual expertise. Experts in medicine have their own special terminology – the Key Opinion Leaders (KOLs) – and are incredibly vital vehicles of knowledge interpretation.

Corollary to the use of medical guidelines, medical professions continue to use as important sources of information the experiences and testimonies of peers and

superiors. Practicing physicians maintain their own networks of specialists from various fields of medicine to inform their own practice. This tendency was explained by respondents as a combination of factors: each patient is individual, and while guidelines serve as crutches, medicine is not a 'one size fits all' activity [NLDR07], [NLDR12] [HUDR18]. The respect for peers is also part of the Hippocratic tradition itself, where it is explicitly stated that a doctor must recognize the limits of their professional competencies (Nederlandse Artseneed versie 2003, In: KNMG Nederlandse Artseneed, 2010) which mandates the consideration of the opinions of colleagues in diagnostic and treatment decisions across specialities (MOK Etikai Kódexe, 2012, p. 17; Gedragsregels voor Artsen, 2013, p. 3).

The term Key Opinion Leader is an intriguing one, although I could not pinpoint its origin. I had collected a fair number of interviews, some of them from respondents who identified themselves as such. The first time I had come across a similar term was while reading Robert Whitaker's book: Mad in America (2010) which gives an elaboration of the abuse of clinical research by the pharmaceutical industry in the field of psychiatry. Whitaker describes medical experts, leaders in the field as "Thought Leaders", academics that held much disdain for pharmaceutical companies interfering in clinical trials, right up until the 1980s (Whitaker, 2010, p. 262) – about the same time that EBM was implemented in medical practice, and clinical trials became increasingly funded by industry via the introduction of the Bayh-Dole Act. The term itself is now used as typical jargon by physicians whether in the academic research setting or the confines of a hospital or clinic, as well as by pharmaceutical company employees and regulators, and even in Hungary where my interviews were conducted in Hungarian, the term itself was used in English. A Dutch physician [NLDR16] described how KOL does not have an exact definition, and so reflected rather on his status as a KOL; being a "*pioneer*" in a certain treatment, knowing all the risks and benefits involved, as well as having an overarching knowledge of the disease area and being able to identify what questions are still unanswered regarding medical research. A Hungarian physician reflected on his 20 years of experience in the field, as providing him his KOL status [HUDR09]. KOLs like these respondents are regularly contacted to review journal publications [NLDR16], partake in guideline committees [NLDR15], and to present at conferences and medical education events [HUDR10]. In conclusion, physicians described the term KOL as not something that an individual would use to formally describe his status, but an implicit denotation of medical experts that are active in forming medical opinions; a small group of individuals well-known for their accomplishments by others in the field.

8.4.1. KOL STATUS IN INDUSTRY ENDORSEMENT

When does someone become a KOL? Taking all the interviews from physicians in both countries, the elemental features cited by doctors, KOLs themselves, are (1) *Experience*: a lengthy career track and years of working within a specific disease area, (2) *Exposure*: the requirement of participating in and/or providing a continuous stream

of publications in highly regarded medical journals, and (3) *Esteem*: afforded respect, trust, and professional recognition from colleagues within the field. The term KOL is even more than simply expert, because it adds to being perceived just as a good and competent doctor, to a good and competent doctor that also has the ability to shape the opinions and professional practice of peers.

The KOL is essential to pharmaceutical companies. Speaking to legal counsel for one of the world's biggest pharmaceutical companies in Hungary, a description was given of how it is common industry practice to foster good relationships with KOLs. "*Every pharmaceutical company needs doctors, and there are these opinion formulating KOLs on the market who are very knowledgeable on specific diseases, and provide important input for companies*" [HUPH12]. Being "*on the market*" as a KOL is an interesting way of putting it, because the industry rhetoric describes an image of a KOL as someone companies turn to for help and advice. Being "on the market" did not make too much sense until an account from a Dutch virologist described how the ability to give scientific advice is capitalized upon by doctors themselves. "*(…) we can show a paper in Science, a paper in Nature, good journals. "Hey guys (he says to a company) we are the top of the world, if you want to do that and go to the FDA, we can give you scientific advice", and for (a company) that is value, and we (physicians) capitalize on that*." [NLPH03]. The transition from medical expert to KOL is thus presented as a status that is achieved not solely from recognition and allocation by peers in medicine, but as a status that is solidified by working with pharmaceutical companies. "*Imagine (companies) would have a proper sort of drug against Alzheimer's. That might be then, only in that case it might be worth it, making me a KOL, a Key Opinion Leader*." [NLDR07] said a Dutch geriatrician, which shows the contrast between himself as a potential KOL, but one who has not been approached by a pharmaceutical company yet.

These accounts lead me to consider the KOL title as a function which the pharmaceutical industry has effectively captured and rebranded as professional status. Today, these KOLs are a distant cry from Whitaker's (2010) description of thought leaders in opposition to the pharmaceutical industry. KOL identification has become a business in itself, and a simple Google search for "KOL identification" reveals a plethora of companies which market various strategies called KOL management or influence mapping. The evolution of KOL targeting strategies (Dutta, 2015) advertise efficient forms of KOL identification via the use of social network analysis, the study of relationship structures, which analyses the flow of knowledge and information among actors within a social network. Network science is a creation of the 21st century (Barabási, 2016), but traces its history to Bourdieu's theory of social capital: the possession of personal networks and institutionalized relationships which solidify a person's membership in a group. "The volume of the social capital possessed by a given agent thus depends on the size of the network of connections he can effectively mobilize and on the volume of the capital (economic, cultural or symbolic) possessed in his own right by each of those to whom he is connected" (Bourdieu, 1968, p. 51).

Studies using sociometric methods have found correlations between an individual's centrality in a network (opinion leader), and expediency in his/her adoption of a new technology in healthcare, as well as the importance of friendships and peer advice for network periphery members in innovation adoption (Coleman et al., 1957; Becker, 1970). In fact this remains the case today, as physicians explained that innovation in medical guidelines themselves may happen routinely, but it is the expert endorsement and use of a specific medication in the field that will ultimately drive widespread implementation among clinicians. A Hungarian gynaecologist used the example of how uptake in use of the novel hormone intrauterine device was largely due to senior physicians adopting its use despite many doctors being sceptical when it was first introduced [HUDR19].

"*It's important for the pharmaceutical companies that with relevant clinical information, or money, they win over prominent physicians. And then they can say that all senior (physicians) in the female clinic use this product. And then they spread the word at congresses, half drunk in the sauna, that this is a really good product, and that they have had good experiences with it. And if he/she says this honestly, then the rest (of the physicians) will follow suit and start using it.*" [HUDR19]

The KOL is incredibly vital for a medicine's use and preference by other physicians. Companies know this and exploit the professional hierarchies that medicine itself has developed.

8.4.2. INFLUENCE BY PROXY

Traditional methods of KOL identification – observation of experts (experience), survey methods of expert identification (esteem), literature/publication searches (exposure) – are placed aside in favour of sociometric analysis that identifies KOLs (nodes) based on the number of formal and informal ties within a network (Dutta, 2015). The influential power of KOLs is a tool for industry to transform the social capital of one medical professional into economic capital at a later stage when KOLs are able to form medical practice and prescription behaviour of other colleagues. I do not suggest that the baseline characteristics of experience, exposure and esteem are null and void, but rather that the KOL status is only truly validated by being a valued target for industry which is closely linked to how many professionals a KOL can be said to have in his/her network of influence. KOL influence extends beyond strong dyadic ties, and the "weak ties" among group members form the basis of individual actions as being adopted by the larger organization (Granovetter, 1973, p. 1360). As such, it is for this quality that KOLs are sought out, and paid for various services rendered to pharmaceutical companies. A Dutch gynaecologist spoke of KOLs being bought to advertise a product despite their own lack of commitment to it.

"*For Dutch people as we see how they work. So companies buy the opinion leaders. If they have a new product what they do, if it's meant for a gynaecologist, you go to the opinion leaders and you pay them money: "Do you want to become a consultant for*

me this year"? You pay them a couple of dollars, they do a small trial, they give a nice presentation, and everybody is happy. This opinion leader doesn't use it anymore, but he told (everyone), that it's a very good product." [NLDR18].

Specification as to what services are most often rendered by physicians to pharmaceutical companies in actuality was described in interviews with pharmaceutical company respondents. According to their accounts KOLS advise companies, are paid to be speakers on behalf of pharmaceutical companies, and "*share their experiences (with a certain product), being the most common activity*" said pharmaceutical company respondent [HUPH12] in Hungary. Similarly in the Netherlands, another top pharmaceutical company general manager cited advisory board participation as the most common "*service provided*" by KOLs [NLPH06]. Services provided *for* companies is slightly euphemistic, producing an image that doctors fulfil a task that the company is not capable of doing alone, like answering a difficult business question, or telling companies what should be researched, a knowledgeable agent for the principal. In Hungary, the discussion with pharmaceutical company legal counsel described the role of the KOL in medical guideline advisory activities as helping the company itself decide where and how to position a drug company product in a treatment protocol/medical guideline, whether the drug should be promoted as a first, second, or third line treatment, as well as requiring their professional support when drug companies apply for the product to be placed on the insurance reimbursement list [HUPH12].

Physicians asserted that those high in status or professorial positions were paid more by pharmaceutical companies. "*We're all different (in status) and there are those who routinely hold presentations, and there are those, who because of their positions, we call them "opinionistas" (megmondóember), professors etc. They surely get much more from the pharmaceutical companies*." [HUDR12]. Another physician described the emptiness of the KOL status in his comments about KOL professors being hired to deliver a presentation, regardless of whether he/she was an authority on the subject or not, reflecting on how status is abused by the industry, and was of the opinion that KOLs actually derogate the quality of medical conferences [HUDR10]. Others stated that experts are paid by industry to write academic articles which promote a company drug [HUREG02], [HUPH01], [HUDR13]. Interestingly, Dutch respondents easily talked of, and even pointed out KOLs, while Hungarian respondents acknowledged their influence, but lacked the ability to specifically point them out. This I feel is largely due to the fact that in contrast to the Netherlands, the transparency of financial payments to physicians from pharmaceutical companies until 1st of July 2016 did not exist. Fieldwork in Hungary concluded before these disclosure reports were made public, although I did discuss the transparency initiative with physicians, which I shall detail in the forthcoming sections. However, lacking such transparency, the relationships between KOL and the pharmaceutical industry have yet to be made visible by transparency data, but accounts from pharmaceutical company respondents confirmed the regular practice of employing KOLs in Hungary. Transparency reveals

these connections, and in the Netherlands where there is a longer tradition of disclosing these financial relationships to the public, the KOL status is much more definite, thus the identification of a KOL is more probable if one simply "*follows the money*" [NLDR18].

To further support my assertion, that KOL status is inextricably solidified by having financial relationships to pharmaceutical companies, are the explicit accounts of Dutch physicians, who declared that if a pharmaceutical company would hire you, or pay you for various services, that is a sure sign that you are an expert in your field [NLDR13]. Reflecting on the American Physician Sunshine Act, another physician in the Netherlands stated that American patients are now using the data on payment disclosures to seed out which doctor is paid the most by companies, because high payments are a sign of high status [NLDR05]. Both respondents were self-identified KOLs. A description by a Dutch medical journal editor, in response to my question of the acceptability of KOLs receiving payments for services by the pharmaceutical industry, stated that apart from the additional money gained by such work, the main driver is the status that accompanies the role. "*When the industry has an interest in you, it shows that you are important, that you are perhaps very intelligent, and that you are a very good researcher or a very good doctor*." [NLMJ01].

When discussing pharmaceutical industry corruption of medical knowledge production in the previous chapter, I already touched upon the ideally self-contained reward system of medical science (Merton, 1957), perpetuated by recognition from peers providing professional prominence, respect, and trust. This maintains that members of the scientific community work towards the goals of the profession itself, and not assume an ancillary reward/compensation based system which may influence their decisions, acting in alignment with the hopes of receiving financial rewards. It bears resemblance to the spin placed on medical success in clinical research and the ethics of research i.e. an emphasis on the duty to produce a marketable product, and success redefined in terms of producing a return on investment for academic institutions. Similarly, financial relationships between industry and medical professionals in the Netherlands are not a sign of possible treachery, but a confirmation of the status and prominence of the KOL. Speaking to key opinion leaders in the Netherlands, there were hints as to the identification of professional worth expressed in the amount that one can put their services on the market for – a monetarization of status.

A KOL in oncology asserted that pharmaceutical companies will call him and ask that he present on a specific subject but that he does not do that very often because a fee of €500 for a presentation would not be worth his while, resulting in a proclivity to choose "*a little bit of consulting instead*" [NLDR14]. The Dutch Medicines Act (GnW: Chapter 9 Art. 94), the GnW Policy Rules (Beleidsregels gunstbetoon Geneesmiddelenwet, section 2/A) and the Pharmaceutical industry self-regulatory Code of Pharmaceutical Advertising (§6.3) proclaim that fees for services rendered by

physician should stay within "reasonable" levels, proportionate to the hours required to execute a task. According to the respondent from the Dutch Healthcare Inspectorate (IGZ), this would be €100 per hour for a General Practitioner and €140 per hour for a specialist, which remains under the limit that the law defines as an amount that would breach the proportionality of "*normal economic business*" [NLREG02] and quantitatively constitute a conflict of interest. In contrast, however, another KOL in the field of internal and vascular medicine described it as "*crazy*" that his hourly rate should be defined by regulatory bodies. Calling on the example of the right of lawyers to determine their own hourly compensation, he described unfairness as being manifest by paying "*second division*" rates to people who are in the "*champion's league*" [NLDR13]. The argument may well be legitimate in the capitalist view of the value of a service. To become a KOL one must go through the motions of a lengthy education, followed by years of work, specialization, accumulation of knowledge, and professional activity. It takes a lot of hard work, and thus today, should be reflected in the level of financial compensation. However, this same respondent only moments later stated that you "*have to be a good speaker; otherwise you won't be invited again*" [NLDR13]. Unless pharmaceutical companies have started providing KOLs with Toastmasters courses, the "*good speaker*" can hardly be interpreted as anything other than "providing information on the medicinal products marketed by the authorization holder" in a manner "performed at the instruction of the relevant authorization holder" (CGR Code of Conduct for Pharmaceutical Advertising, 2015: §5.9 section 5.9.2.).

The central problem is that while physicians do have a right to be paid a fair market value, their market value is not a manifestation of the knowledge of the KOL, but the influence that comes with status which is used to cushion the advertising incentives of the pharmaceutical industry on a professional pillow. The following quote shows how KOLs influence prescription uptake of a novel medication, similarly to the illustrations from gynaecology in the above, but then describes the process of how a new drug is first introduced in the market, how KOLs form the basis of early adopters which increases awareness and use of the drug in the clinic, after which widespread use then in turn is implemented into medical guidelines once the use of the product had proliferated among physicians.

"*There's a new medicine on the market, recently launched, to treat fibroids. And what they often do if they have a new medicine, you organize a group of consultants who advise you what to do, and who will be the early adopters to use it in the clinic, so they ask me, for this medicine, to listen to them, to use it, to give my opinion, to advise them how to bring it in the market, and what studies we need to do before we can change our guidelines so we can use it*." [NLDR18].

A pharmaceutical company general manager described pharmaceutical industry's aim to inform treatment decisions, his response negating a role in the writing of medical guidelines and once again supporting the findings that it is not in direct influence, but indirect influence via the use of KOLs "*(…) making sure they understand what tests*

they have to do to diagnose a patient." [NLPH06] and thus informing physicians as to who to treat, and with what specifically. The rationale behind this is that since the company developed the product, they are in possession of all information pertaining to its use, and as such, are the obvious sources of accurate information about that product. Companies' input is deemed vital if their drugs are considered as becoming part of medical practice. Informing and educating physicians is where the pharmaceutical industry, and the relationships it fosters with KOLs, are explained. KOLs regularly publish in medical journals, and present on behalf of companies at various medical conferences and educational events. They are "*pioneers*" in their fields, and their verbal endorsements, as well as physical use of a product in clinical practice, are observed by other physicians. Despite testimonies of how KOLs shape pharmaceutical company policy, it is the other way around: "*If you were a pharmaceutical (company) (…) do you (hire) a speaker who is not enthusiastic about your drug? Of course not!*" [NLDR17].

This brings me to the final vehicle of medical knowledge interpretation, the forums of continuing medical education. I have already discussed in the previous section the effects of pharmaceuticalization and medicalization from accounts of physicians as a description of how industry influence manifests in medical guidelines, however medical educational events introduce the gradation of meso and micro level medical autonomy, in that not only is the organization and content of medical education under scrutiny, but the "periphery" clinicians also rely on industry funding for conference attendance. In this final section the KOL phenomenon should also be kept in mind.

8.5. EDUCATING THE MEDICAL PROFESSION

> "I would be much more impressed if they were getting out of medical education altogether" Dr Adriane Fugh-Berman, cited in:
> *The Financial Times* (Ward, 2016)

Filtered scientific research is conveyed to the wider physician population in the form of continuing medical educational (CME) events which physicians are mandated to attend; a compulsory requirement of the professional medical career. In both Hungary and the Netherlands doctors must collect a certain number of CME credits every year to retain their medical licence. In the Netherlands, a physician has to work a minimum 16 hours a week, and collect 40 credits every year, totalling 200 credits over 5 years, when a re-evaluation of licence maintenance is conducted (KNMG website[45]). In Hungary, doctors are required to collect 150 credits a year, which is an accumulation of credits derived from medical practice points, attendance at compulsory professional (specialist) training, and additional credits obtained from further training acquired from educational events of a physician's choosing (Hungarian National Healthcare

[45] https://www.knmg.nl/opleiding-herregistratie-carriere/medische-vervolgopleidingen/vervolgopleidingen.htm

Service website)[46]. As described in Chapter 5, I asked respondents to describe the role of industry in medicine, which was generalized to be the role of innovation in medicine and the education of physicians. Respondents from industry specifically, would verbalize these as two vital functions, being the basis of legitimization for a company to finance and personally interact with doctors. A respondent from the Hungarian Association of Pharmaceutical Manufacturers (MAGYOSZ) described their innovation and educational roles in medicine as an industry responsibility to society.

"*We have to educate (doctors), so that they are able to tackle the most difficult questions of the profession, and thereby reach the pinnacle of professional expertise. To possess this knowledge, they have to take part in the kind of events, and learn from the kind of people that provide (this knowledge). This costs money. And when I say education, I mean continuing medical education and conferences, and the sponsoring of symposia*." [HUPA02].

A Dutch pharmaceutical company respondent not only confirmed the important role of pharmaceutical companies contributing to the education of the medical profession, but explained that pharmaceutical companies must continue to inform physicians on how a company product is to be used, what side-effects it may have, how to diagnose the patient, and whether their drug would present the right treatment option and to "*help them make the right choices*" in their practice [NLPH06]. It is this type of information that pharmaceutical companies seek to educate physicians on within the framework of medical educational events. Sponsoring major congresses presents a forum where doctors can come together with industry and discuss the "*future of medicine*" [NLPH06], thereby educational events present an opportunity to inform many physicians simultaneously.

All respondents used the term CME to describe any kind of event for which credits can be awarded. Asking doctors whether there are differences between a medical CME, and a conference or symposium, answers describe these as "*sliding into each other*" [NLDR07]. Officially there are slight definitional differences provided in both the Dutch and Hungarian pharmaceutical industry self-regulatory codes of ethical medicines promotion, which categorize these events as "meetings" and "manifestations" (CGR Code), and "independent events" and "company events" (GyKEK Code). A "meeting" is an event described as being educational and scientific, organized, and the contents sanctioned, by an independent professional (medical) association. The CGR code goes on to stipulate that "Not the organizer, but the content will after all determine the scientific nature of a meeting" (CGR Code, 2015: section 6.2.5. §1), which is important to note, because the categorizations of meetings/independent events, and manifestations/company events seems to be differentiated only by sponsor type, and does not denote that these events would differ in their content quality or accreditation (the ability to award CME credits). The

[46] http://www.enkk.hu/index.php/hun/szakkepzes-tamogatasi-foosztaly/szakkepzohelyi-akkreditacio/akkreditalt-szakkepzo-helyek

GyKEK Code does not specifically identify what an independent event is, although one would assume that these events are independent from any and all pharmaceutical industry funding or organization. The GyKEK Code only extends to detailing the requirements of events sponsored by industry, which then lists "events held for healthcare professionals" – promotional events, advanced trainings, conferences, symposia, congresses – which leads to the interpretation that the industry may fund any medical educational event (GyKEK Code, section 9.7).

Regarding these medical educational events, pharmaceutical companies may contribute to the organization and/or sponsoring of the event itself and/or they are allowed to support individual doctors with hospitality costs covering registration fees, and travel and accommodation costs. I would like to explain the role of the pharmaceutical industry in medical event financing and/or organizing, which pertains to the meso level of medical autonomy.

The umbrella term of CMEs and the multifaceted means by which to attain CME credits renders this arena slightly confounding. The wording of regulatory text differentiates between 2 concepts of CME (independent event) and Medical Conference (sponsored event). Under the term CME, I will be referring to the medical training which is organized and sanctioned by national professional medical associations, usually held in the national language (although CMEs are also becoming international). CMEs are usually held at medical research or academic medical centres. The training courses, the contents, and the speakers are usually pre-defined by the organizing medical association, and physicians are invited, as one would sign up and participate in a university lecture. CMEs are considered scientific, wholly educational, independent and unbiased regarding content. Medical Conference, on the other hand, denotes events which by content should also fall into the category of scientific information. Conferences can be national or international, the subject of which usually deals with specific disease areas. Conferences can be sponsored and/organized by both medical associations and private companies. As with all conferences, some speakers will be explicitly invited to attend and present, but conferences are open to all physicians to submit abstracts, posters etc. Although self-regulation has undoubtedly constrained the nature of pharmaceutical promotional activities at conferences, promotion and advertising is still more openly permitted and accepted at these medical conferences, if in line with the pharmaceutical industry codes of conduct.

8.5.1. KOLS IN CME

Medical educational events, be they CMEs or Medical Conferences, are something in which the pharmaceutical industry is naturally interested in, both from the educational and the promotional aspect. These medical events bring together large groups of physicians, either from the local or the international physician community, and thus present an opportunity to convey information on their products to many doctors at once. Although medical conferences are known to be the arenas when science and

promotion may meet, CMEs themselves should ideally be completely independent of any third party interests – purely academic, scientific, and wholly educational. The impartiality of CME is challenged on two main grounds; the first is the use of the above described phenomenon of influence by proxy by KOLs. A journal editor from the Netherlands described the KOL role in CME, and the way in which they are used to promote brand name medications.

"*Well of course the industry sees a target in the medical education. They can promote through medical education, (through) lectures for instance, by letting medical opinion leaders talk about drugs and especially about their drugs, and it's well known that these MOLES: Medical Opinion Leaders, talk about the industry's products, and they don't use the generic name of the drug but they especially use the brand name. And that is one of the ways in which they promote the drugs of the company. Through medical education, they create an atmosphere in which they are credible*." [NLMJ01].

A "*MOLE*" is a much less euphemistic term that a KOL, but it is nevertheless more accurate in description of their precise tasks at educational events, which is to speak for the company that hires them. This is vital, because as I said before, the meso level of medical autonomy, and the interpretation of medical knowledge into practice, is very much in the power of the medical profession – or at least the perception should be kept as such. This is why KOLs are so important, because they are allowed to participate and speak at events, where pharmaceutical companies are not. Respondents from the pharmaceutical industry supported this description, adding to what was mentioned in the above (the importance of KOLs to industry), that KOLs are generally there to educate other physicians. A pharmaceutical company employee specifically denoted the task of the KOL as "*representing the company at various meetings, and speaking on company behalves*" [NLPH06]. Pharmaceutical company employees are well aware of the controversial nature of hiring KOLs to speak on their behalves, but the acquired duty of pharmaceutical companies to educate doctors through other doctors is described as something that is done for the benefit of medicine in general. A compliance officer from another multi-national pharmaceutical company described how the company views KOL in CME.

"*We don't think that paying physicians to educate other physicians is a bad thing to do. They (KOLs) may think this (product) is innovative. It is. But the question is: is this the right thing to do? (Company name) thinks that education is really important for other physicians, and we want to help with that course in an independent... No, not so much an independent, but more of an objective way, so we try to have all these presentations go through an accreditation process, so that the education that they receive is appropriate and it's the right thing to do and that they get their points and they gain knowledge (so that they can) support their patients*." [NLPH04].

The practice of using KOLs is explained as industry altruism, and further justified by the affinity of the KOL in believing that the product they are paid to endorse is truly innovative (thereby the stamp of approval from the expert him/herself), the first step

in an affirmative answer to whether this "*the right thing to do*". Especially notable in this quote is the opposition of the words "*independent*" and "*objective*", which this respondent uses quite consequently, suggesting that independence is not a prerequisite of objectivity. Although not synonymous, I have already discussed the partiality that comes with financial agreements – partiality of KOLs either sought out explicitly (why would a company hire a doctor who is not a believer in the product? [NLDR17]), or partiality created by the desire to secure future collaboration (delivery of a good presentation or risk never being hired again [NLDR13]). The division of independence and objectivity as mutually exclusive is a rationalization through categorization and division of concepts taken out of the context of industry-medicine relationships as a dynamic process or action.

KOLs presenting in CME and educating colleagues is common practice, and although it is scrutinized by the profession, it is accepted as normal. The key to maintaining its acceptability, however, lies in maintaining an open attitude about financial ties to pharmaceutical companies, which is done by disclosing industry sponsorship agreements; acknowledgment of industry sponsorship on the very first slide of a presentation, or disclosure of financial support listed on a journal publication. While the relationship between a KOL and an industry sponsor are more obvious and open, allowing the opportunity for a consideration of how much emphasis should be given to the opinions of these paid experts, there are again less obvious modes of indirect influence in CME which may further implicate the independence of medical education.

8.5.2. PAYING THE PIPER

Critics argue that pharmaceutical companies are increasingly infiltrating the independent arena of CMEs (Davis, 2004; Rodwin, 2012), stating that a large portion of CMEs are now funded by pharmaceutical companies creating a financial dependency wherein the funding of CMEs goes hand in hand with the specific content to be presented and induces a risk of bias towards the commercial interests of the sponsoring company. This, however, is far from secret, and similarly to the above quoted interviews, pharmaceutical companies openly target CMEs. "Your most valuable resource is now continuing education, including continuing medical education and information on nonmedical topics critical to effective practice." states an article titled "The ABCs of CME" in the online pharmaceutical industry magazine: Pharmexec.com[47]. Turning an eye to Europe, the subject CMEs in general will continue to be a priority as regards standardization, and harmonization of the training and knowledge of medical professionals. The European Union of Medical Specialists (UEMS website)[48] in 1999 established the European Accreditation Council for Continuing Medical Education (EACCME website) to address and minimise CME discrepancies internationally. Currently the EACCME is the intermediary body

[47] http://www.pharmexec.com/abcs-cme

[48] The UEMS has 37 National Medical Association Members among which are the Dutch Federation of Medical Specialists (FMS) and the Association of Hungarian Medical Societies (MOTESZ)

between National Accreditation Councils within member states, and seeks to ease the mutual recognition of CME credits between its members, the US, and Canada. Complete harmonization is still a goal for the future, but currently, national bodies are still responsible for monitoring CMEs and providing accreditation. The EACCME published a white paper on CME in Europe to address discrepancies in the accreditation systems of its members, and also debates the increasing role of pharmaceutical industry CME sponsorship. According to white paper estimates, 50% of CMEs are funded by pharmaceutical companies and the authors assert that there is indeed a correlation between funding source and the content of CMEs (Kellner, 2010, pp. 26-28). The exact number of industry-sponsored CMEs and the effects it may have in biasing the content of these educational events must still be researched. However, as to whom should ultimately be responsible for ensuring an unbiased educational content, the white paper states that "as time and experience have demonstrated, it is the course of wisdom to leave this responsibility mainly in the hands of medical associations" (Pardell & Negri, 2010, p. 12).

As to the body of professional medical associations in the countries of this analysis: in the Netherlands, ensuring CME quality belongs to the FMS and the 32 Medical Specialist Associations with which it works in close collaboration. In Hungary, the MOTESZ website lists 128 recognized national medical associations. The large difference in these numbers is because Dutch medical associations group together along a medical specialism, while Hungarian Associations group together along medical specialism as well as disease areas and therapeutic interventions (including complementary medicine). The 61 Specialist Colleges mentioned in Chapter 8 are of particular relevance, because more than one medical association will belong within a particular disease area for which the Specialist College is the authority. This will become clear in the ensuing analysis.

When we assess financial influence of the pharmaceutical industry in medicine, much of it is approached from the analysis of direct funding, such as the direct funding of clinical trials by pharmaceutical companies, or entering into direct financial agreements with key opinion leaders to present at CME or conferences. Of course CMEs are also allowed to receive sponsorship from pharmaceutical companies, but the safeguard in place to minimize bias is the expectation that the organization and content of CME is monitored by the appropriate professional medical association. However, delving once again into the Dutch transparency register, as well as searching through the financial disclosure reports of pharmaceutical companies in Hungary, we come across the fact that these medical associations are in reality being heavily sponsored by pharmaceutical companies.

In the Netherlands, of the 32 Professional Medical Associations, 3 associations were excluded from this analysis given that they do not concern themselves with clinical

disease areas or practical medicine.[49] The remaining 29 medical associations (the same associations that issue medical guidelines) were all sought in the CGR Transparency database. To do this, first each medical association must be sought in the Dutch Chamber of Commerce (Kamer van Koophandel: KvK) database, to find the KvK number of the association, after which the CGR database is searched using the KvK number for the years 2014, 2015, and 2016 separately. Once each report was downloaded, I calculated the total amount paid for each year as well as what amount was spent on sponsoring a meeting. The totals for the year were tallied, and the percentage of funding for meetings as a part of the total amount of funding received was calculated, and an aggregate was given for all three years.

$$\%\ of\ total\ funding\ spent\ on\ Meetings = \frac{\sum Sponsorship\ for\ Meetings\ \ (2014 + 2015 + 2016)}{\sum Funding\ received\ (2014 + 2015 + 2016)}\ x\ 100$$

Of the 29 medical associations, only 3 received no company funding at all over these 3 years. These were: the Dutch Association of Rehabilitation Practitioners[50], the Association for Sport Medicine[51], and the Association of Clinical Genetics[52]. The remaining 26 medical associations all received funding from pharmaceutical companies. The fact that medical associations receive regular financial endowments from pharmaceutical companies reveals more than just a financial relationship. Apart from the 3 associations that received no financial support whatsoever, the areas of geriatric medicine, medical microbiology, neurosurgery, plastic surgery, and the Association for Radiotherapy and Oncology received the least amount of industry funding in total over the 3 years. Neurosurgery received only one payment of €1.200 in 2016.

These areas of medicine (apart from oncology) are ones for which medical intervention does not place an emphasis on the use of pharmaceutical products such as surgery [NLDR05], [HUDR08], or are areas of medicine that are less understood and under-researched, such as medical microbiology (infectious diseases) or geriatric medicine (dementia, Alzheimer's or Parkinson's Disease) [NLDR07]. Thus the numbers reflect respondent accounts that low-risk disease areas are less of a target for pharmaceutical company sponsorship (as in medical research), reflected in the funding of the medical association. For the medical associations that receive a continuous flow of industry sponsorship, it is of course worth noting that the recipients that receive well over the €100,000 mark per year are also areas of medicine that treat predominantly with medication. The top funded disease areas are Cardiology, Pulmonology, Urology,

[49] Klinische Chemie en Laboratoriumgeneeskunde (Clinical Chemistry and Laboratory Medicine (NVKC), Klinische Fysica (Clinical Physics (NVKF), Ziekenhuisapothekers (Hospital pharmacists (NVZA)
https://www.demedischspecialist.nl/federatie/organisatie
[50] Nederlandse Vereniging van Revalidatieartsen (Revalidatiegeneeskunde (VRA)
[51] Vereniging voor Sport Geneeskunde (VSG)
[52] Vereniging van Klinische Genetica Nederland (VKGN)

Internal Medicine, Neurology, Dermatology, Rheumatology, Psychiatry, and Ophthalmology.

I would like to emphasize the nature of this funding, in that the vast majority is spent on sponsoring meetings. The table below shows in euros, the total aggregated amounts of funding received over the years 2014, 2015, and 2016, and the percentage of the total that went towards the organization of a meeting. The raw data, original reports, comprise of roughly 90 pages in PDF format, are available upon request.

Medical Association	Total funding (2014/2015/2016)	Funding for meetings (% of total)
Dutch Association for Allergy (Nederlandse Vereniging voor Allergologie)	71.500	47.000 (65%)
Dutch Association for Anesthesiology (Nederlandse Vereniging voor Anesthesiologie)	72.126	57.101 (79%)
Dutch Association for Cardiology (Nederlandse Vereniging voor Cardiologie)	2.080.503	1.344.552 (64%)
Dutch Society for Dermatology and Venereology (Nederlandse Vereniging voor Dermatologie en Venereologie)	349.829,50	273.079,50 (78%)
Dutch Association for Surgery (Nederlandse Vereniging voor Heelkunde)	13.135	13.135 (100%)
Dutch Internists Association (Nederlandse Internisten Vereniging)	512.689	453.339 (88%)
Dutch Association for Otorhinolaryngology and Surgery of Head and Neck (Nederlandse Vereniging voor Keel-Neus-Oorheelkunde en Heelkunde van het Hoofd-Halsgebied)	68.632	48.667 (71%)
Dutch Society for Pediatrics (Nederlandse Vereniging voor Kindergeneeskunde)	91.925	48.119 (52%)
Dutch Association for Clinical Geriatrics Nederlandse (Vereniging voor Klinische Geriatrie)	18.008	2.833 (16%)
Dutch Association of Physicians for Lung Diseases and Tuberculosis (Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose)	818.503	722.994 (88%)
Dutch Association of Gastrointestinal Medicine (Nederlandse Vereniging van Maag-Darm-Leverartsen)	21.296	16.796 (78%)
Dutch Association for Medical Microbiology (Nederlandse Vereniging voor Medische Microbiologie)	14.435	11933 (83%)
Dutch Association for Neuro-surgery (Nederlandse Vereniging voor Neurochirurgie)	1.200	1.200 (100%)
Dutch Association for Neurology (Nederlandse Vereniging voor Neurologie)	395.786	332.220 (84%)

Dutch Association for Nuclear Medicine (Nederlandse Vereniging voor Nucleaire Geneeskunde)	28.450	28.450 (100%)
Dutch Association for Obstetrics and Gynecology (Nederlandse Vereniging voor Obstetrie en Gynaecologie)	21.100	19.850 (94%)
Dutch Ophthalmic Society (Nederlands Oogheelkundig Gezelschap)	128.665	123.595 (96%)
Dutch Orthopaedic Association (Nederlandse Orthopaedische Vereniging)	19.012	12.512 (65%)
Dutch Society for Pathology (Nederlandse Vereniging voor Pathologie)	55.500	49.000 (88%)
Dutch Association for Plastic Surgery (Nederlandse Vereniging voor Plastische Chirurgie)	6.725	3.335 (50%)
Dutch Association for Psychiatry (Nederlandse Vereniging voor Psychiatrie)	132.450	132.450 (100%)
Dutch Association for Radiology (Nederlandse Vereniging voor Radiologie)	88.656	88.656 (100%)
Dutch Association for Radiotherapy and Oncology (Nederlandse Vereniging voor Radiotherapie en Oncologie)	5.833	5.833 (100%)
Dutch Association for Rheumatology (Nederlandse Vereniging voor Reumatologie)	345.672,25	243.791,20 (71%)
Dutch Association for Thorax Surgery (Nederlandse Vereniging voor Thoraxchirurgie)	10.600	8.900 (84%)
Dutch Association for Urology (Nederlandse Vereniging voor Urologie)	618.169	255.372 (41%)

Data source: Transparantieregister Zorg: http://www.transparantieregister.nl/nl-NL/Home

Industry funding of medical associations goes to either of two things: sponsoring a project, or sponsoring a meeting. What a project is precisely does not enjoy any elaboration, nor does the description of a meeting, but as the numbers show, over half of industry sponsorship to medical associations goes towards meeting organization. Assuming the definition of a meeting in the CGR Code, however, and the professional nature of the association, these meeting are most likely what would be considered

independents events (CMEs) for physicians. No conclusion can be draw as to the ratio between independent and privately-funded CMEs in the Netherlands, although one respondent from the Netherlands with a long history of being involved with CME accreditation stated that about half of CMEs in the Netherlands are industry funded [NLDR17]. Nevertheless this data supports statements of industry funding of CMEs.

A slightly different, more layered analysis, but one which aims to search for a link between the sanctifiers of medical CMEs in Hungary and pharmaceutical industry sponsorship, was also executed with data from Hungary. The complexities of the Hungarian data must first be described.

1. Transparency disclosures in Hungary have only been available since 2016, and so the data only covers the years 2015 and 2016. Disclosure, contrary to the Netherlands, is on a voluntary basis regarding identifiers such as names of individuals or healthcare organizations, meaning that only those that give consent will be listed rendering this analysis limited.
2. The Hungarian Association of Medical Societies (MOTESZ) lists Medical Associations in Hungary, however the list is incomplete or inaccurate because many Medical Associations listed on company disclosure lists are not on the MOTESZ website.
3. Furthermore, as I mentioned before, Hungary has a system of appointing Specialist Colleges (currently 61 colleges across 44 disease areas) who ultimately represent the expertise in certain disease areas, meaning that multiple medical associations may fall under the expertise of one Specialist College, for example: The Hungarian Internal Medicine Association, the Hungarian Diabetes Association, and the Hungarian Endocrinology and Metabolism Association, would fall under the professional competencies of the Specialist College of Internal Medicine, Endocrinology, Diabetes, and Metabolism.
4. According to Edict 12/2011 (III. 30.) of the National Ministry of Human Capacities (12/2011. (III. 30.) NEFMI rendelet 3. Fejezet) Specialist Colleges are charged with presenting opinions as to CMEs in Hungary. Additionally, the Hungarian Medical Universities, which oversee CME Accreditation, delegate members to the 61 Specialist Colleges.

It is armed with this knowledge that an analysis can be executed, and inferences drawn as to pharmaceutical industry influence in CME in Hungary. Thus this analysis first looked at the transparency disclosures and the medical associations listed within them. First, I looked at the total amount that each Medical Association listed (26) received for 2015 and 2016 from pharmaceutical companies, and calculated what ratio of funding was given for medical event sponsorship using the above calculation mode showing how much of industry sponsorship went to funding a medical event. The total received funding is listed in the disclosure report itself, as well as specification of the amount that went towards organization of a medical event. Thus the only thing that

had to be done was to search manually for medical associations by name, add total funding of events for 2015 and 2016, and divide this by the totalled funding received in these two years. The following tables provide for the filtered and aggregated totals expressed in HUF reflected in roughly 960 pages in PDF and JPEG format. Due to volume these are available upon request.

Medical Societies /Associations	**Total funding (2015/2016)**	**Funding for meetings (% of total)**
Hungarian Hypertension Society	100.000	100.000 (100%)
Hungarian Allergology and Clinical Immunology Society	350.000	350.000 (100%)
Hungarian Scientific Society of Andrology	1.250.000	1.250.000 (100%)
Hungarian Anaesthesiology and Intensive Therapy Society	990.000	990.000 (100%)
Hungarian Arterial Stiffness Society	360.000	360.000 (100%)
Hungarian Atherosclerosis Society	200.000	200.000 (100%)
Hungarian Balneology Society	150.000	150.000 (100%)
Hungarian Internal Medicine Society	530.000	530.000 (100%)
Hungarian Dermatology Society	9.104.600	6.820.000 (75%)

Hungarian Diabetes Society	107.246.097	70.752.097 (66%)
Hungarian Endocrinology and Metabolism Society	1.154.720	1.154.720 (100%)
Hungarian Gastroenterology Society	7.474.990	5.407.990 (72%)
Hungarian Paediatric-Oncology Society	300.000	0 (0%)
Hungarian Society of Paediatricians	200.000	0 (0%)
Hungarian Haematology and Transfusion Society	97.350.000	97.350.000 (100%)
Hungarian Infectology and Clinical Microbiology Society	250.000	250.000 (100%)
Hungarian Society of Cardiologists	15.427.900	15.427.900 (100%)
Hungarian Cardiovascular Rehabilitation Society	100.000	100.000 (100%)
Hungarian Society of Clinical Oncologists	20.684.025	20.484025 (99%)
Hungarian Cervical and Colposcopy Society	1.079.500	1.079.500 (100%)
Hungarian Nephrology Society	894.000	894.000 (100%)
Hungarian Neuroimmunology Society	250.000	0 (0%)
Hungarian Neurology Society	1.090.000	1.090.000 (100%)
Hungarian Neuroradiology Society	600.000	0 (0%)

Hungarian Gynaecological Society	86.614	86.614 (100%)
Hungarian Obesity and Movement Therapy Society	200.000	200.000 (100%)
Hungarian Society of Pharmacotherapeutic Oncologists	2.450.000	750.000 (30%)
Hungarian Society of Oncologists	3.130.000	3.130.000 (100%)
Hungarian Orthopaedic Society	660.000	660.000 (100%)
Hungarian Osteoporosis and Osteoarthritis Society	1.850.000	850.000 (46%)
Hungarian Psychiatric Association	11.650.000	8.650.000 (74%)
Hungarian Society of Psychopharmacologists	150.000	150.000 (100%)
Hungarian Rheumatologists Association	5.230.000	5.230.000 (100%)
Hungarian Sclerosis Multiplex Society	500.000	500.000 (100%)
Hungarian Surgical Society	480.000	480.000 (100%)
Hungarian Sexually Transmitted Infection Society	1.566.400	1.66.400 (100%)
Hungarian Stroke Society	1.500.000	1.500.000 (100%)
Hungarian Radiotherapy Society	2.150.800	250.000 (12%)
Hungarian Ophthalmology Society	7.180.000	7.180.000 (100%)

Hungarian Thrombosis and Haemostasis Society	450.000	450.000 (100%)
Hungarian Transplantation Society	5.500.000	0 (0%)
Hungarian Traumatology Society	330.222	33.222 (100%)
Hungarian Pneumatic Society	33.729.500	18.774.900 (56%)
Hungarian Society of Urologists	21.701.020	21.701.020 (100%)
Hungarian Urological Oncology Society	1.500.000	1.500.000 (100%)

Data Source: Official websites of the following pharmaceutical companies:
Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Berlin Chemie, Biogen, Bristol-Meyers Squibb, Boeringer Ingelheim, Celegene, Gilead GlaxoSmithKline, IBSA, IPSEN Janssen, Lilly, Merck-MSD, Novartis, Novo Nordisk, Pfizer Roche, Sanofi, Servier, Takeda, UCB (AIPM member companies subject to EFPIA transparency requirements)

Coinciding with the data from the Netherlands, we can once again see that the vast majority of funding from pharmaceutical companies goes towards sponsoring medical events. As to the top funded areas of medicine in financial order, these are: Diabetes, Haematology, Pulmonology, Urology, Oncology, Cardiology, Psychiatry, Dermatology Gastroenterology, Rheumatology, and Ophthalmology. Coincidently, this list follows an almost identical order to that of the Dutch most highly financed disease areas (see p. 181).

As I mentioned, these disclosure reports are quite incomplete, as many of those organizations unwilling to disclose their identity have the amounts received aggregated into one lump sum at the end of the report, and thus one cannot know which other medical organizations received funding or not. The incomplete nature of these disclosures must be taken into account, yet the data available still shows an overview similar to that of the Dutch data: medical associations predominantly receive funding for meetings and medical events, while funding preference follows a similar pecking order regarding disease areas.

To account for the incomplete nature of the Hungarian MOTESZ list of medical associations, I added another layer of analysis to the Hungarian data which was the cross referencing of these medical associations alongside the Specialist Colleges, the colleges that form opinions on CMEs in Hungary, and among whose members are delegated from medical associations and Hungarian universities tasked with CME

accreditation. These Specialist Colleges should, by any expectation, be independent and impartial especially in consideration to the tasks assigned to them by Ministerial decree. However, taking the time to further assess Specialist College chairing members and their affiliations, I found that the chairing members of the Colleges simultaneously hold board member positions, vice-chairmanship, or chairmanship positions in the same medical associations which received pharmaceutical industry funding. Of the 61 Specialist Colleges each appointing 3 Chairing members, 22 were found to correlate in name or disease area with the medical associations listed in the transparency disclosure reports that received industry funding. This search was conducted by searching the names of the College chairing members among the names of the members of the medical associations. Although this cannot unequivocally reflect undue influence, it does however introduce a kind of ironic twist, in that the heads of Specialist Colleges (those expected to be independent) are in fact simultaneously important position holders in the medical associations that receive industry funding for medical educational events. The tables I have compiled as a result of this search are available in Annex 6, where the complete list of correlating medical association position and College membership are shown for 22 Colleges in a manner exemplified in the table below.

College of Oncology and Radiation Therapy

College Chairmen	**Medical Organization and Position**
Member 1	Hungarian Society of Oncologists: Member of the Board Hungarian Radiotherapy Society: Member
Member 2	Hungarian Society of Oncologists: Member of the Board
Member 3	Hungarian Society of Clinical Oncologists: Honorary Chairman

"Commercial funding may inherently distort education and practice to the detriment of physicians and patients, regardless of the various safeguards to protect the integrity of the enterprise." (Steinbrook, 2008, p. 1060). Additionally to the data that illustrates how much of industry sponsorship to medical organizations goes towards medical education, the additional information that shows Hungarian Specialist College chairing members simultaneously holding leading positions or membership in the medical associations that rely on industry funding. This data adds to Steinbrook's (2008) quote, and reveals not only bias "regardless of safeguards" but rather *in conjunction* with safeguards. It is logical that those selected into these Specialist Colleges be physicians of high esteem, and as such a track record of holding leading positions within medical associations is unsurprising, but the fact that College chairpersons simultaneously hold chairing positions in the medical associations that rely on industry funding for medical education, while concurrently fulfilling the task of forming opinions on CME in Hungary, resembles the same scenario of "*wearing all*

the hats" [NLREG01] described by the respondents from the Dutch MRA, being caught between the incentive to receive funding from pharmaceutical companies to sponsor CMEs, and the duty to formulate unbiased evaluations of CMEs.

Presented in this analysis is an in-depth look at the financial ties between medical associations and the pharmaceutical industry. Accounts of physicians offer testimony of the interests of pharmaceutical companies in extending their influence in medical knowledge interpretation. Through the indirect funding of CMEs through payments made to medical associations, the data shows that the majority of funding goes towards medical educational events. It also shows, despite the incomplete nature of the Hungarian data, that in different countries the areas of medicine that receive greater amounts of industry sponsorship are very similar – consequentially providing evidence that industry exhibits preference in funding CMEs in high prescribing areas of medicine. The ability to downplay the potential of undue industry influence in medical education is astounding, even going so far as to label critics as "extremists" and "witch-hunters" (Maisonneuve, 2010, p. 60). I, however, would challenge such statements, and reflect for a moment on the same dynamic I described in Chapter 6 when discussing industry influence in clinical trials; funding preference given to research that holds higher potential for pharmaceutical product success. This type of preference in funding allocation is also reflected in the variation in amounts provided to each medical association in a specific disease area. Industry sponsorship of medical associations predominantly goes towards funding of meetings and educational events, and I assert that similarly to the KOL phenomenon, where the status of the medical professional is exploited to conceal industry interests under the seal of medical expertise, industry funding of medical education is laundered "ethical" through the associations. The Hungarian analysis then show that the very same people who are charged by Government edict to provide professional opinions on CMEs are heading the medical associations that rely on industry funding to organize and execute CMEs, showing that there is no divide between colleges of professional oversight, and medical associations with pharmaceutical industry financial dependency.

8.6. CONCLUSION

In this chapter I have described the process of medical knowledge interpretation, which manifests the meso level of medical autonomy executed in the translation process of raw data from medical research into knowledge that can then be implemented in medical practice – the basis of EBM. The translation of raw data, the filtering of medical knowledge into practical medicine, manifests in the 3 vehicles of knowledge interpretation identified during fieldwork: medical guidelines to inform clinical decision-making, the reliance on medical experts to interpret and convey medical knowledge, and the mandatory requirement of physician participation in continuing medical education. Each vehicle of medical knowledge interpretation presents an opportunity for pharmaceutical industry influence. Evidence-based medicine relies on grounding itself on high quality evidence, which I have assessed in Chapter 5 and 6 as

being provided by RCTs. These are predominantly funded by pharmaceutical companies and the preceding analysis has discussed how research and medical knowledge production is becoming skewed towards pharmaceutical product production. Accounts from physicians in the field reveal how they perceive medicine to be increasingly pharmaceutical product orientated. This process is illustrated by the medicalization of human conditions that go further than diseases, such as the examples pertaining to medicalization of disease prevention, and pharmaceuticalization of lifestyle choices. The examples from cardiology and the use of antidepressants for smoking cessation support the view that the medicalization-pharmaceuticalization complex is not a product of development of medical knowledge, but development of pharmaceutical industry interests. Pharmaceutical treatment is also preferred over non-pharmaceutical intervention, as the example of surgery versus medication as the preferred treatment for prostate cancer has illustrated.

Treatment decisions are informed by medical guidelines, the implementation of which performs simultaneous roles of providing an evidentiary basis for clinical practice, and enforcing standardization as the antithesis to unreliability produced in clinical treatment variation – sacrificing individual autonomy for the autonomy of the collective. Medical guidelines are perceived to be the product of independent and impartial medical analysis, uninfluenced by the commercial interests of pharmaceutical companies. However, interviews from the field and analysis of financial relationships reveal strong ties between guideline authors and pharmaceutical companies. In Hungary, the relationship was described as guideline authors conducting face-to-face meetings with company representatives, as well as companies employing medical professionals to provide advice on how to introduce a product into a medical guideline. In the Netherlands, the opportunity presented by respondent triangulation allowed a case study of the medical guideline for Severe Asthma, showing that guideline authors foster financial relationships with the companies that produce drugs in the disease area for which the guidelines is devised. Testimonies from the field show that guidelines themselves, however, are only successful to a limited degree in informing clinical decisions, as the medical profession places a high degree of value on the opinions of superiors and experts. Although a guideline may change or incorporate new treatment options, the proliferation of a new guideline or treatment method requires validation by peers and influential physicians known as Key Opinion Leaders. KOLs are targeted by pharmaceutical companies and hired to convey information on a product to the larger physician population. Their ability to influence others is exploited by industry, and capitalized upon by physicians. The solidification of KOL status is actually achieved by maintaining advisory and consultancy contracts with pharmaceutical companies – physicians themselves interpreting these financial ties not as potential conflicts of interests but testaments to professional prowess. The novel methods of KOL identification and engagement through the use of sociometric analysis further proves that KOL status is a question of social rather than intellectual capital.

The main task of a KOL as described by industry respondents is to speak on company behalves about a product. Medical educational events provide the optimal platform, because not only do these events bring together large groups of physicians, but physicians are also mandated to attend as part of the requirement to ensure that their medical knowledge is continuously updated. The role of the pharmaceutical industry in medical education goes beyond employing KOLs to the actual sponsoring of CMEs. CMEs are deemed truly educational and independent if organized and sanctioned by professional organizations such as medical associations. In fact the codes of conduct both in the Netherlands and in Hungary base medical association oversight as the main component of ensuring independence of medical education. However, although the CME may well be organized by a medical association, the funding source is increasingly the pharmaceutical industry. The data analysis provides an overview of the amounts that are paid by industry to medical associations, revealing a preference for funding of certain disease areas over others (similar to the preference in funding clinical research in certain disease areas over others), and also shows that the majority of funding goes specifically towards the organization of meetings and educational events. The Hungarian analysis in particular, despite incongruences and incompleteness of the data in the transparency disclosure reports, shows the extent of indirect financial influence extending beyond medical associations; all the way to Specialist Colleges in that specialist college members simultaneously chair the associations that rely on industry funding of medical educational events.

The institutional corruption of the meso level medical autonomy exercised in the activities of medical knowledge interpretation is perhaps one of the most interesting areas of analysis, because unlike direct correlations between source of funding and clinical trials, analysis requires deeper investigations and making connections between seemingly independent vehicles of medical knowledge interpretation, and behind the scenes financial relationships. I have aimed to not only place the institutional corruption of medical knowledge interpretation on a consequential chain following the medical knowledge production process, but also illustrate indirect modes of industry influence. Pharmaceutical companies do not dictate how EBM should be exercised, but they provide the evidence itself. Industry does not write medical guidelines, but they employ the physicians who do. Industry does not organize CMEs but they finance the medical associations who do. What enables influence is the normalization of financial ties with pharmaceutical companies and the interpretation of those financial ties as professional competence by physicians (KOLs) as well as a complex system of indirect payments which are invisible to many doctors due to the belief in independence of medical associations.

CHAPTER 9: INSTITUTIONAL CORRUPTION OF MEDICAL KNOWLEDGE APPLICATION

In the previous chapters I assessed the role of the pharmaceutical industry in the funding of clinical trials and the biasing of medical knowledge production. I then proceeded to assess the processes of filtering this evidence, how the process of medical knowledge interpretation into practice is influenced directly and indirectly by pharmaceutical companies having strong financial ties with those persons (KOLs) and bodies (medical associations) that are responsible for assessing and interpreting the raw data derived from medical research, and I have analysed this within the framework of meso level medical autonomy, the deterioration of the independence of knowledge interpretation modus operandi. Up until this point I have discussed not only how these levels (macro and meso) of medical autonomy are subject to industry influence, but more importantly, I have aimed to provide an overview of how the distortion of medical autonomy by the pharmaceutical industry is procedural and functional to the roles that the industry plays in the execution of the work of the medical profession. Industry influence is not a force exerted by pharmaceutical companies solely externally and industry-medicine relationships do not form momentarily, suddenly producing a conflict of interest, but rather industry-medicine relationships are foundational for the operation of medical knowledge production and interpretation. Notably macro and meso level autonomy are precursors to defining how medical practice will be executed (creation and interpretation of medical and clinically applicable knowledge), but autonomy in the clinic, individual micro level autonomy, must form the final level analysis as a concomitant sphere of autonomous decision-making.

This follows from the nature of autonomous clinical practice, and the basic idea of evidence-based medicine – the duty of the physician to make decisions informed by evidence (scientific research and standardization of treatment in guidelines) and the simultaneous practice of individual autonomy in clinical practice. Each patient is different, and the doctor is, although part of the wider medical community, still highly individual in the execution of the work in the clinic. We may describe this as a type of ‘communal information’ and ‘individual practice’ in the sense that for all the professional forums and mechanisms of knowledge production and interpretation, the individual physician practices medicine in the clinic individually. Although treatment of some diseases involves a patient being attended to by a “team” of doctors (i.e. cancer teams, which apart from the oncologist physician may include an oncology nurse, palliative care professionals, oncology assistants, a dietician, a radiologist, a pathologist etc.), there is usually one attending physician who maintains most contact with the patient, sees him/her regularly, is most up to date about the individual patient and who ultimately has the final say in treatment decisions. To do this, a physician in any practice must – apart from the standardized and consensual information sources available – select his/her own sources of information to inform individual decision-

making. Reiterating the practice of EBM, it is expressed as the implementation of scientifically validated research *combined with* individual clinical expertise (Sackett et al., 1996; Timmermans, 2010). I have discussed from the perspective of medical knowledge interpretation the vehicles of knowledge translation, in medical guidelines, expert opinions and medical educational events. Knowledge interpretation filters information so that the complex data born of knowledge production can easily be accessed by the practicing physicians, the so-called "*periphery*" [HUDR03]. As with the phenomenon of medical knowledge production merging with knowledge interpretation in Phase IV clinical trials and the medicines approval process of regulatory authorities, knowledge interpretation and application also converge in that while the previous chapter described how those who interpret the knowledge may be influenced (KOLs, guidelines authors, and medical associations), the filtered information is such that it is conveyed to physicians and applied in their practice. Since physicians also possess individual autonomy (agency) within clinical decision-making, doctors remain discretionary in their selection of sources of information to keep their knowledge up to date.

Research which assesses the influence of pharmaceutical companies over the practice of medicine in the clinic, places much emphasis on whether or not the content of information provided to doctors is independent from the pharmaceutical industry. In effect research tends to analyse whether available information reflects scientific truth, or commercially biased advertising. Much research also focuses on drawing correlations between the frequency of exposure to pharmaceutical industry advertising and physicians' prescribing habits (see Chapter 2). These studies, although not inaccurate, focus on influence via general, direct promotion to physicians, or unconscious biases resulting from induced obligations of reciprocity. Although these studies are revealing as to the power of advertising, as well as challenging the ability of medical professionals to remain independent purely by way of professional mandate, these studies lead to regulatory solutions based on simple deductions i.e. promotion and funding influences prescribing habits and thus limiting promotion, general funding, and curtailing financial dependencies via regulation will reduce undue industry influence.

Financial dependencies and advertising tactics have the potential to erode the independence of medical professionals and influence their clinical decisions. Regulations that curtail financial ties and constrain advertising practices are perhaps an important step towards minimizing industry influence and maintaining medical professional independence. However, I feel that this type of approach and studies that draw correlations between advertising exposure and physician behaviour measured in prescribing habits, and then subsequent regulation that curtails specific financial relationships, is presumptuous of individual deficiencies – either assuming that doctors will be influenced by the seductions of financial reward, or reinforcing an image of doctors being too stubborn to admit their own susceptibility to industry influence and promotion. During fieldwork, interviews with practicing physicians led to a more nuanced understanding of reliance on individual financial relationships with

pharmaceutical companies, as well as the reliance of doctors on information provided by these companies. Dependency on industry money and industry-produced information was located as a product of the requirements of the profession itself. We tend to see influence, and thus institutional corruption, to be the product of industry power and the art of clever manipulation, seeking then to curtail the actions of pharmaceutical companies. Industry fulfils many roles in the profession of medicine. Instead of seeing institutional corruption as an external force enveloping medicine, opportunity for influence can also be seen as enabled by the structure of medical knowledge production and interpretation, which aim to increase standardization and quality of medical pratice. While doing so, economic interest infiltration goes unchecked, mainly due to a continued belief that professional status and a commitment to Hippocratic ideals will render doctors impervious to influence.

The following analysis will focus on the micro level of medical autonomy, and industry influence in the individual clinical decision-making of doctors, but by taking to assess how reliance on industry financing and promotional information is produced by the profession itself, thus embedded in the system of knowledge application. Analysis revealed that although the pharmaceutical industry may seek to influence doctors, their ability to remain critical of industry intentions is determined by factors not tied to individual susceptibility but by requirements of the profession of medicine. Medicine is a dynamic and progressive field, knowledge evolving at a very fast pace. Doctors are required to keep their medical knowledge up to date, and as such they are pressured to constantly balance full-time employment with the requirements of continuous education, which costs both money and time. Regulation of individual financial relationships and promotion to physicians has been implemented without taking these professional requirements of education and information into consideration – regulation has restricted the "tools" of goal attainment while still requiring the same goals to be met. There are also divergences between what regulation states in textual form, as well as how regulation is executed in practice, creating definitional inconsistencies and regulatory loopholes which both pharmaceutical companies and doctors can exploit, rendering regulation impotent.

For the analysis of the institutional corruption of micro level medical autonomy, I shall discuss the following:

1) How too much information and the pressure of continuous self-education force doctors to focus on information access (quantity) over information independence (quality).

2) How pressures of constant information access and expectations of physician financial independence push both pharmaceutical companies and physicians to abuse regulatory loopholes to hide financial relationships.

3) Explanations from physicians as to what factors influence their prescribing behaviour.

9.1. TOO MUCH INFORMATION: QUANTITY OVER QUALITY

"*Don't have the illusion that you are able to look at all the information that is out there; to weigh whether it's interesting or valuable to your practice. You are not able to do that. Everyone who thinks he is able to do that is an idiot.*"
[NLOO02]

Medical science and knowledge suffers from an affliction of the knowledge-based professions; information overload, too much information, and the "publish or perish" (Colquhoun, 2011) anomaly (Eppler & Mengis, 2003; Bawden & Robinson, 2008). These phenomena present themselves in all professions that are research based, and are not limited to the medical profession alone. Systems of quality assurance in academia for example, where institutional prowess is measured in amount of publications per year in peer-reviewed journals, is criticized for putting pressure on researchers to focus on quantity of work over quality (van Dalen & Henkens, 2012; Rawat & Meena, 2014). According to authors Björk, Roos, and Lauri (2009), 2006 alone saw the publication of 1.3 million peer-reviewed scientific journal articles from the areas of science, technology, medicine, social science and the humanities. Regarding medicine specifically, some studies assess the harsh reality that it is impossible for doctors to read all the novel literature – Garba et al., (2010) estimate that a new medical journal article is published every 26 seconds. An epidemiologist would have to dedicate 627.5 hours every month to read all newly published articles (Alper et al., 2004); a general practitioner would have to read 17 articles a day (Subramanyam, 2013). The opening quote to this chapter, from a respondent from a Dutch non-profit organization dedicated to providing independent information on drugs to doctors, touched upon not only the inability of doctors to read all available literature, but expressed the necessity of taking advantage of the systems of knowledge interpretation which assist professional decision-making.

"*You need your umbrella organizations. You need standards and guidelines. You need independent magazines*." [NLOO02].

Returning to the conveyor belt analogy, the interpretation process configures the raw scientific data into applicable information: reviewing, condensing, and formatting it. While interpretation rephrases, translates, and condenses the data, the sheer amount of interpreted information remains vast, manifesting in journal articles, medical magazines, and a variety of online medical forums. It is still a burden of too much information that plagues doctors in the clinic despite the accessibility provided by the vehicles of interpretation. A respondent from a CRO, one who is at the forefront of clinical trial execution, expressed the burden of information overload in the clinical decision-making of physicians by reflecting on his time spent as a clinical doctor.

"*Doctors resent that the vast amount of information that comes from clinical trials does not help their practice. How does one orientate him/herself even just in the information regarding his/her own practice, especially if a doctor must also treat*

patients? I try to read into the transplant literature, search for one or two keywords, but there are so many articles I can't even decide which current article to read. It's baffling!" [HUPH11].

Doctors are regularly bombarded with mail, sent journals and emails, and the ancillary of too much information is met with too much complex information – statistical calculations and complicated scientific processes which do more to confuse than to clarify. Thus doctors turn to informational sources that are condensed and simplified. "Often they read this material not in journals but in what are condescendingly known as `throwaways' i.e. newspapers that use journalists to summarize complex material and which are free because they are funded by pharmaceutical advertising" (Smith, 2006, p. 116). Bawden and Robinson (2008) identify "pathologies of information": behavioural coping strategies of people exposed to the anxieties of information overload – choosing to avoid the information altogether, developing strategies such as keeping information sources to a minimum, or "satisficing": the conscious decision to select "just enough information to meet a need (…) also known as bounded rationality" (Bawden & Robinson, 2008, p. 185; Klein & Epley, 2017). This behaviour I linked to one of the questions I posed to individual doctors, asking them what sources of information they specifically used to inform individual clinical decision-making. As regards to medical journals and scientific literature, the answers were diverse. As I have mentioned in the previous sections the division of knowledge and labour in medicine manifests in the diversification of information sources of medical professionals. Physicians more active in academic and research institutions will cite the scientific literature as their main sources of information. Physicians in the clinic, however, are less absorbed in what would be classified as peer-reviewed scientific literature, and their attention to it varied in personal accounts. The pressures and time limitations of full-time employment were often cited as reasons for limiting or bypassing assessment of research publications.

"*I have a colleague who always follows up on the literature. I (follow up) less frequently. I only read the literature if (companies) promote the use of a medication, and it doesn't work out with the patient. That's when I might follow up on the literature, but that's rare because I use (treatment) methods, medication that has been used for a long time. My colleague reads up on everything, the statistics and the significance. I don't have any time for that. I provide treatment. I'm a practicing physician. Reading the literature and verifying what pharmaceutical companies say is something I don't have time for. There are those who are interested in that, and they follow up*" [HUDR19].

The above quote from a Hungarian gynaecologist illustrates not only the immense individual variation in choosing information sources, but that scientific sources (medical journals) are not a necessity to practice, revealing both the importance of translated information and the phenomenon of satisficing. "*One article is not an article*" [NLDR04] said a physician in the Netherlands, reflecting on the paradox of time versus amount of information. A practicing physician may not have time or

energy to read more than one or two articles a day after a full day of work, and realizing the futility of doing so may also render complete avoidance, dissuading individual verification of information in scientific publications from the onset.

Too much information creates not only an impossible situation of not being physically capable of assessing it all, but further complicates the matter by creating uncertainty about which of the many journals or medical publications are of any worth. Even the scientific medical literature is often challenged, and while the most prestigious journals were often cited as "*The Journal of the American Medical Association (JAMA), JAMA Internal Medicine, Annals of Internal Medicine, The Lancet, The British Medical Journal (BMJ), and The New England Journal of Medicine (NEJM)*" [NLMJ01], the list varies depending on specialization [NLDR04], disease area [NLDR05], and individual preference [NLDR12]. While prestige and peer review may provide some reference for medical literature reliability, there is no, nor can there be straightforward consensus as to what should be mandatory literature, and what should not, since medical practice, specialization, and personal preference will inevitably diversify informational needs.

A Dutch GP [NLDR02] cited the Netherlands Journal of Medicine (peer-reviewed and in English), a Journal issued by the Dutch GP Association, as well as journals from other medical associations as literary guides. Journals or rather magazines are issued by the Royal Dutch Medical Association (KNMG): "Medisch Contact", "Huisarts en Wetenschap" issued by the Dutch GP Association, "De Medisch Specialist Magazine" issued by the Dutch Association of Medical Specialists and the Hungarian Chamber of Medicine (MOK): "Orvosok Lapja" issue articles on diseases and medication, but also more general subjects pertaining to healthcare policy, global healthcare, innovation in medicine, and opinion pieces, and include titles like "Mindf*cker Victor Mids: 'suggestion can help the doctor-patient relationship' (Medisch Contact, issue 72, April, 2017), or "National (Health)insurance Again!" (Orvosok Lapja, Issue 4, 2016). These are informative, and discuss pertinent issues in medicine, as well as keep a doctor generally up to date about the world of medicine and healthcare; however, they are not the equivalent of a scientific peer-review publication, classified rather as medical magazines. Regarding even academic peer review, there is little consensus on what is a viable source or not, and what a practicing physician may deem as his/her "go-to" sources, others can dismiss with ease, such as a KOL and internationally-renowned cardiologist in the Netherlands who stated that in his opinion, there is no journal in the Netherlands that is of any relevance. "*I don't read anything that's coming from here. I don't even look at it*." [NLDR12].

Too much information, variations in what physicians may consider viable sources of information, as well as time and energy constraints, may lead to practicing physicians engaging in some of the "pathologies" of too much information such as avoidance (choosing to negate scientific journals) and satisficing (relying on relevant, condensed, and easily accessible sources of information) for *individual* knowledge procurement. As to what the most readily available sources of information for clinical doctors are;

"*Sources could be conferences, CMEs, and sales representatives*" [HUDR22] – physicians placing emphasis on accredited medical educational events, and the ancillary, digested information from sales representatives [NLDR07], [NLDR18], [HUDR25] [HUDR23]. The emphasis concerning knowledge attainment is on accessibility and availability. CMEs and sales representatives are both important sources of information, yet both from a different perspective.

The ensuing analysis will address both informational sources, as well as how each represents a different mode of industry influence. I shall begin with discussing CMEs and then proceed to discussing dependency on information provided by sales representatives. This analysis becomes a little more intricate regarding these two information sources. With regards to CMEs, I shall focus on the mandate of physicians to attend continuous medical educational events as a source of industry-medicine financial relationships. The potential of industry biasing the content of CMEs had been discussed in Chapter 8; influence within the vehicles of medical knowledge translation. This section describes not potential industry-induced bias in the content of CMEs, but individual physicians' dependencies on CME participation and the role of pharmaceutical companies.

9.2. THE STRINGENCY SMOKESCREEN AND FINANCIAL DEPENDENCY ON CME SPONSORSHIP

Drawing upon what was described in Chapter 5, the theoretical and regulatory divide between pre- and post-authorization information about a pharmaceutical product is important. As illustrated, doctors themselves are convinced of the spectrum of independence of medicine to move along this line of pre- and post-authorization: knowledge about pharmaceutical products before authorization being a product of independent and unbiased scientific inquiry, while post-authorization knowledge having a higher probability of being influenced by pharmaceutical companies via explicit promotional activities (Chapter 5 & 6). National medicines law in Hungary and the Netherlands states clearly that advertising is restricted to medications that have acquired a marketing licence (Chapter 5) maintaining the perception that promotion (and thus influence) only happens in the post-approval arena. It is thus no wonder that the majority of regulation is focused on relationships between industry and medicine post authorization, and mainly regulating individual financial relationships. During fieldwork I kept being told by all respondents that regulation regarding financial relationships between pharmaceutical companies and individual physicians is not only highly rigorous, but increasingly so especially in the last few years, and skimming the self-regulatory documents certainly seems to be in line with these statements – the majority of the regulatory codes in Hungary and the Netherlands are preoccupied with individual financial payments, gifts and donations to physicians, sales representative interaction, and promotional material content restrictions. However, taking a closer look at the regulatory text itself shows that sometimes, an abundance of legal vocabulary does more to impress than curtail.

We must revisit the regulatory framework with a keen eye to what individual financial relationships are permitted, and to what extent. When looking at the definition of advertising and promotion itself, we must remember the hierarchical nature of regulation, the Directive 2001/83/EC being at the pinnacle of EU regulation, upon which further national law, followed by pharmaceutical industry self-regulation, are built. Article 86 of Directive 2001/83/EC defines advertising as including "any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products" (Title VIII Advertising, Article 86). Listing these promotional outlets, much of the emphasis is placed on micro level, person-to-person advertising, and predominantly on advertising to physicians specifically (since DTCA is only allowed for OTC medication in the European Union). Regarding medical events, the Directive 2001/83/EC lists sponsorship of events that are attended by those authorized to prescribe medicines as being a form of advertising, but the particular emphasis is still placed on the individual financial relationships pertaining to individual physician sponsorship: "sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products *and in particular payment of their travelling and accommodation expenses in connection therewith."* (Article 86 (1) emphasis added). It is in national pharmaceutical industry self-regulatory documents where further particularities are distinguished.

The role of industry in "*educating the medical profession*" [HUPA02], [NLPH05], [NLPH06] as discussed in Chapter 8, manifests in individual physician sponsorship and funding of their attendance at CMEs or Conferences, thus contributing to their *individual*, *personal* education – a prerequisite for clinical autonomy. Medical education costs money, whether a CME or a Conference, and attendance usually involve registration fees, and travel and accommodation costs. While in the chapter I spoke of Key Opinion Leaders being invited/paid to speak at medical events, individual practicing physicians (non-KOLs) may also seek out companies and apply for sponsorship of costs associated with event attendance: these are hospitality agreements and not consultancy contracts as is the case with KOLs. It is in these micro level focused regulations that the main differences between the Hungarian and Dutch contexts can be observed. As to what individual sponsorship for educational events entails, the Dutch CGR Code, and the Hungarian GyKEK Code differentiate in definitions of events and individual financial sponsorship leniency. There is, however, a conundrum, which is how regulation seems to be all-encompassing, but in fact is not so in practical implementation. The regulation looks good on paper, and is very specific in terminology used; however, in practice these definitional categories which serve to draw a line between ethical and unethical financial relationships become blurred, and even entirely impotent in practice. To support this claim, I must discuss in detail what the Hungarian and the Dutch pharmaceutical industry codes on ethical promotion state, and then highlight how these strict regulatory definitions become obsolete in practical implementation, and visible only when we assess whether the

definition is reflected in the information made available in the transparency report on industry payments to physicians.

9.2.1. HUNGARIAN INDUSTRY SELF-REGULATION VERSUS DISCLOSURE

In Hungary, the GyKEK Code came into force on July 1st, 2014, and section 9.4 describes the rules for sponsoring individual physicians. The GyKEK Code states that Pharmaceutical companies may sponsor physicians for both "independent events" and "company events". Events that qualify as "professional" and have an "advanced training purpose (…) not qualifying as a promotional event" should be limited to financing "travel, meals and accommodation during the event and to the genuine registration fees." Additionally, sponsorship may only be given to healthcare professionals if the event that they wish to attend be within their specialist competencies (i.e. a cardiologist cannot be sponsored to attend an event on neurology unless proven that their professional competencies necessitate this). Funding for entertainment is prohibited. Previously touched upon was the fact that the GyKEK Code makes a distinction in the nomenclature i.e. "independent" and "company" event, the signification presuming separation of events based on the qualities of the *organizing partner*, either academic/medical institution, or private company. However, this distinction is later dropped altogether in section 9.7, which uses an integrated term in its statement that "Events for healthcare professionals shall be organized solely with professional, scientific, or educational purposes" which includes the totality of "promotional events, advance trainings, conferences, symposia, congresses" (GyKEK Code, 2014, section 9.7). This means, that regarding individual sponsorship, pharmaceutical companies may sponsor doctors for both CMEs and Conferences. This is also substantiated by the fact that pharmaceutical company disclosure reports in Hungary show that under "contribution of costs to events", reports identify separately whether a company sponsored an individual for registration fees, or travel and accommodation fees, but, whether this was for a CME or a Conference event is not disclosed, basically reaffirming that when it comes to individual industry funding, separating CME from Conference hospitality costs is unnecessary, allowing companies to sponsor any event.

Contribution to costs of Events		
Sponsorship agreements with HCOs / third parties appointed by HCOs to manage an event [HUF]	Registration fees [HUF]	Travel & Accommodation [HUF]

Source: EFPIA Disclosure template: https://www.efpia.eu

Additionally, in the GyKEK Code there is no defined cap or limitation regarding the amount that a physician may receive in a given year besides a loosely defined

requirement that individual sponsorship should not exceed the amount that the physician him/herself would pay, were they paying from their own pockets (GyKEK Code, 2014 section 9).

9.2.2. DUTCH INDUSTRY SELF-REGULATION VERSUS DISCLOSURE

In the CGR Code (2015) the textual differentiation between meetings (CMEs) and manifestations (conferences) is much more specific, the reason being that there are financial limitations/caps in place for just how much an individual doctor may claim from companies per calendar year for each type of event, rendering the Dutch Code slightly more financially defined than the Hungarian Code in this regard. The CGR Code allocates individual financial sponsoring of physicians permissible if they cover hospitality costs for both meetings (CME) and manifestations (industry sponsored conferences). Hospitality costs are "compensation of or paying for the travel expenses, accommodation costs or registration fees of a meeting/manifestation. Such hospitality may not include relaxation (sport, recreation and so on)" (CGR Code, 2015 section 6.4.3). Although allowing hospitality payments for both meetings and manifestations, the distinction becomes important for the defined amounts a physician may receive for each.

For meetings, a physician may receive €500 per occasion and a total of €1,500 per annum. In addition, payments for meetings are deemed "reasonable" only if the physician him/herself pays 50% of all costs (CGR Code, 2015 section 6.4.6). Hospitality for a manifestation on the other hand, must not exceed €75 per occasion, and €225 per year. For manifestations the regulatory text does not explicitly mention any mandatory out of pocket contributions by physicians rendering interpretation to assume that they are not required to do so. Meeting (CME) attendance is seemed to be prioritized over other events in terms of higher allowance rates regarding hospitality contributions, while simultaneously limiting complete financial dependency with the 50% out of pocket rule. In an almost ironic turn, however, differentiation is once again rendered pointless in that the transparency database of payments to individual doctors does not allocate whether hospitality costs were provided for meetings or manifestations, or whether it covered registration, travel or accommodation (such as the Hungarian reports) but simply discloses singular payments under the all-encompassing "hospitality compensation"[53] label. This may be perhaps due to the relatively novelty of disclosing hospitality payments which were not subject to disclosure until 2016.[54] Nevertheless, current format in the table below which shows the disclosed hospitality costs received by a Dutch specialist in Internal Medicine shows how these hospitality costs are disclosed as one sum. This physician received a total of 22 separate payments from a variety of companies for varying services, two of

[53] Vergoeding gastvrijheid

[54] http://transparantieregister.nl/Wat-wel-en-niet-geregistreerd: "For participation in meetings, healthcare providers can receive a travel, subsistence and subscription fee from a company for participation in this meeting. Individual hospitality will be part of the CGR's transparency rules from 2015 and these relations will be published for the first time in 2016."

which were registered as “hospitality costs”. One payments is a mere €30, while the other is much higher topping at €1,975, with no mention of whether these were for more than one event, or whether it was for a CME or a conference.

Farma/MD: Norgine BV	Type: Hospitality compensation € 30, 00
Farma/MD: Gilead Sciences Netherlands B.V.	Type: Hospitality compensation € 1.975, 00

Source: Transparantieregister at http://transparantieregister.nl/nl-NL/Zoeken-in-het-register/Big-nummer

This means of very superficial reporting effects the definitions of doctors of what companies can and cannot fund, as well as their perceptions of ethical financial ties showing that lots of words in law are useless if not reflected in practice.

9.3. REGULATORY DEFICIENCY AS PRODUCING INDIVIDUAL AMBIVALENCE AND QUANTITY OVER QUALITY EMPHASIS

Looking at the codified regulation, we come to the paradox, in that while regulation exudes an image of CMEs as being slightly more independent (both financially and intellectually) than conferences, and that industry funding (defined in financial caps or the expectation to attend events that are truly educational) should go towards increasing physician participation in these supposedly more independent events, available financial disclosure reports lack this type of definitional categorization. From an analytical perspective it is exceedingly interesting that despite literal clarity in regulatory differentiation between event categories, the differentiation was limited to the formal terrain of text. Even in the case of the Dutch CGR code where a cap would presume differences in industry sponsorship along CME and conferences, this all becomes unnecessary when looking at the transparency disclosure reports, because essentially one cannot check whether a doctor that received individual hospitality costs from industry was attending a ‘more independent’ CME, or a ‘less independent’ industry conference.

This discrepancy might not be perceived as important, since the payments are available, so technically the mission of transparency is solved. However, the lack of specification in the disclosure reports means that patients (ultimately whom disclosure serves) cannot evaluate specifically what doctors are being paid for, and disclosure of lump sums may simply be confirmation of large payments without context. In my opinion, this type of disclosure places a halo on industry (for being open about payments) while shifting negative judgement to the medical professional (the receiver of undesignated payments). Although this is an assumption which warrants future investigation, with regards to how this is reflected in the profession of medicine: physicians themselves do not differentiate between receiving funding for a CME or a Conference specifically. If industry provides hospitality for any and all types of medical educational events, it creates non-discrimination among physicians in turn.

Placing any accredited event under the non-discriminatory definition of 'education' translates education as simply a necessary practice, a means to an end instead of a professional quality maintenance activity which would warrant selection and assessment of its contents, validity, or independence. As such, lacking this critical oversight and revealing a sort of ambivalence (it counts as education if it provides credits) diminishes necessity of quality, and reinforces in physicians a view that makes education simply a question of quantity (point attainment), over an assessment of the nature (quality) of an event.

9.3.1. CREDITS GIVE CREDENCE: EXONERATION BY NECESSITY

Interviews revealed a propensity to either merge CMEs and Conferences under the all-encompassing definition of 'medical education', or if respondents maintained differentiation in definition, they interpret both categories of events to serve the same purpose – thus in practical understanding, there is little or no difference between the concept of a CME or a Conference. The absence of differentiation is not based on content or event characteristics, but on the credit system in place which I mentioned in the previous chapter – the self-regulated quality maintenance scheme of the profession itself. Thus not only do doctors themselves make no qualitative differentiation between the nature of the two categories of events: funding (hospitality) takes on a generalized interpretation, reinforcing in doctors the industry rhetoric as the patron of medical education – the possessor and provider of means of access to education. This reduces critical oversight by the doctors themselves, who are concerned rather with attaining credits than selecting events based on independence from industry. This is illustrated by the following interview when I asked a Dutch pulmonologist as to whether he participated in conferences outside of CME, to which he answered, that they do not exist, and even asked me what I meant by "*conferences outside of CMEs?*" [NLDR09]. Upon my explanation of the division to the respondent using the regulatory definitions, he blankly stated that industry sponsored conferences "*do not happen anymore*". This of course is not accurate. However, this account is a revelation not of a doctor's ignorance, but rather of how accreditation substitutes scrutiny of independence and/or guarantees (perceived) unbiased (non-promotional) content, thereby alleviating physicians from having to make their own assessments. Doctors rely instead on the mechanisms of accreditation to be a stamp of (quality) approval (much like the way physicians rely on regulatory authorization of medication as a stamp of approval regarding medication safety and efficacy).

This type of non-differentiation occurred many times, physician respondents specifically describing CMEs and Conferences as basically merging into one another [NLDR07], whether it be a 3 day training organized by a medical association on a specific disease, or a conference in a specific medical field [NLDR09], [NLDR07], [HUDR21], [HUDR07], [HUPA02]. Even if the physician respondents made some kind of differentiation between CME and Conference, emphasis was still placed on the educational value as being defined by the credit points that a physician must collect to

maintain their medical licence – the 150 credits required in Hungary per year, and the annual 40 credits required in the Netherlands.

"*The points you actually get at the conferences. So they consider a conference as an education for a doctor. So if you are a specialist you need to have so many points a year and you can attain them at different conferences or sometimes at an evening that's organized by physicians themselves, but mostly its conferences.*" [NLDR06].

Combining the fact that doctors need to attain credits for their licence, that CMEs and conferences cost money, and that the scientific/educational nature of the event is fortified by being accredited, it is quite rare that a practicing physician would necessarily opt for attending events that do not provide such credits. Regulatory distinction is thus restricted to the formal documents rather than that manifesting in the mind and interpretation of the physicians that ultimately partake of them. The focus is less on who organizes an event, who is the financier, and whether that may implicate the content or not, rendering the degree of promotional potential of an event less of a discretionary issue. Placing all events under the umbrella term of physician education fortifies interpretation of the role of industry in physician education to not solely something defined by pharmaceutical companies, but practicing physicians themselves. This renders individual financial support for educational event attendance described as a thing of general necessity.

9.3.2. EDUCATION COSTS MONEY: EXONERATION BY EXPENDITURE

It is in the interests of pharmaceutical companies to confound the term of education, despite the fact that the regulatory distinction is a product of their own industry self-regulation. This I came to experience in conversations with respondents from industry associations and companies alike [HUPA02], [NLPH04], and [NLPH06]. In Hungary, the low salary of doctors presents an extremely convenient rationalization of the inherent need to finance doctors. And the following quote illustrates this to an exact degree.

"*To be able to provide healthcare at the level (patients) expect, doctors need to partake in educational events (…). Education costs money, and (Hungarian) doctors, with their current salaries, cannot cover these costs themselves, so (funding) education is our task (as an industry).*" [HUPA02].

I then asked for clarification, what would fall under education: "*Do conferences count as education? Yes. Do symposia count as education? Yes*." [HUPA02]. In fact the line between educational information and promotional information is so blurred that not even those who are charged with evaluating the difference can delineate between the two [HUPA01], and it is left to be determined "case by case" (CGR Code), leaving the definition not only negotiable, but negotiated by the companies themselves. Since everything can be deciphered as educational, it leads me to ask whether "promotion" even exists at all, since education is a word applied to any event.

Speaking to physicians about the importance of educational events in general and their seeking out of pharmaceutical industry sponsorship of hospitality costs were closely linked to discussing the national salaries of medical doctors and the price of educational events. This is only normal, since individual discretion in medical educational event attendance relies on the financial resources of the individual. The issues of national income averages for the profession of medicine were more prominent in Hungary than the Netherlands from the perspective of exonerating financial dependencies.

Dutch doctors, both General Practitioners and Specialists, retain the position of highest paid among OECD countries, while Hungarian physicians are among the lowest paid (OECD website)[55]. Expressed in 2004 USD, the average annual income of GPs and Specialists in the two countries of analysis was the following:

Country	Specialists	General Practitioners
Netherlands	$253.000	$117.000
Hungary	$27.000	$26.000

Data source: Peterson, C. L. and Burton, R. (2007). US health care spending: Comparison with other OECD countries. *Federal Publications*: Table 2: p. 18

The European Federation of Salaried Doctors report on European Hospital Doctors' Salaries (F11-071 EN, 2011) placed the average monthly income of Dutch physicians at circa €4,925, and Hungarian physicians at €1,317. In fact the minimum salary of doctors in the Netherlands is equal to the national salary average of the country, while in Hungary the average maximum salary of doctors is lower than the national average salary (F11-071 EN, 2001, p. 7).

Among Hungarian doctors the "*tragic*" [HUDR14] and "*catastrophic*" [HUDR02] state of the Hungarian healthcare system and medical salaries was almost always the first issue to come up in conversations, as well as the subject of informal payments. This is a reoccurring motif throughout interviews as a general problem in Hungary, but was perhaps more so during the year I conducted fieldwork (2015) being the year that the public forum (group) "1001 Doctors against Informal Payments", was formed on Facebook and which currently has close to 3,000 members. The group also has an official website (www.halapenznelkul.hu), and in 2015 submitted an open letter to the State Secretary for Health Dr. Zoltán Ónodi-Szűcs demanding that specific issues in healthcare be addressed. The letter begins with the opening lines: "It is passing away right now"; referencing a Hungarian hit song with the same opening lyrics – a song about being able to remain happy in a state of misery. The letter continues with the sentence "Your health and that of your parents and children frays into nothingness, as

[55] http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_REAC#

our healthcare collapses"[56]. The letter addresses 3 points of concern: informal payments (referred to as "our common corruption"), the salaries of healthcare providers (doctors and nurses alike), and the dire state of resources in the healthcare delivery infrastructure. The letter also references the case of the Szent Imre Hospital, where two thirds of the hospital anaesthesiologists resigned in late 2015, claiming that hospital resources were such that they felt they could not carry out their work safely (Fábián, 2015). These events happened concurrently with fieldwork, making either this case specifically, or the 3 subjects discussed in the open letter, something that Hungarian respondents were very vocal about. In fact these problems trumped the problem of industry influence or financial relationships in medicine.

In contrast the wages of Dutch doctors did not come up as a problem or source of general complaint in any of the interviews I conducted. Problematic issues to be solved in healthcare were with regards to the administrative burden of doctors, and the need to reduce paperwork [NLDR06], [NLDR13], although negative comments about the Dutch healthcare system in general (access, resources, infrastructure) were rare and only came up if I asked respondents to specifically highlight any shortcomings. Wages in their general form, as being able to make a living in the Netherlands, were described as sufficient, and even residents stated that they made a decent amount from the perspective of good standard of life [NLDR01], [NLDR06].

The difference in self-regulatory documents in the two countries – the Netherlands having a cap on funding amount per year, as well as a 50% out of pocket rule, and Hungary having no defined limitations – may be explained by the higher salaries of Dutch doctors compared to that of Hungarian physicians. In addition to the regulation and wage differences, the theories that locate institutional corruption within financial dependencies would suggest in a simplistic form, that Hungarian doctors would be more dependent than those in the Dutch sample. However, it was enlightening to observe the same issues of lack of money came up in the Netherlands when interviews stepped into the realm of industry funding for medical education, expressed as anger towards a government that has left the profession to fend for itself.

9.3.3. FILLING IN THE "HOLES": EXONERATION BY ABANDONMENT

It is important to note here that it was right in the middle of fieldwork that a "carpet bombing" style Transparency Code was ratified (2014) by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and data regarding payments from industry to doctors and healthcare organizations was made available the year after (see Chapter 4). Making this information available to all has less to do with the industry suddenly growing a conscience, than with being spurred to do so due to a specific scandal. In 2012 the Drug Company GlaxoSmithKline (GSK) was found

[56] Most múlik pontosan. Az Ön, a Szülei és Gyermekei egészsége foszlik semmivé, ahogy egészségügyünk összecsuklik. Az 1001 orvos hálapénz nélkül csoport nyílt levele (2015) available at: https://www.peticiok.com/az_1001_orvos_halapenz_nelkul_csoport_nyilt_levele_2015

guilty in the United Stated for breaching the US Foreign Corrupt Practices Act. GSK was fined a record $3 billion for bribing doctors in China since 2007 to prescribe among other drugs Wellbutrin (an antidepressant, also the drug prescribed for smoking cessation), Avandia (a diabetes drug) and Advair (the ICS LABA medication for asthma already mentioned) (Thomas & Schmidt, 2012). GSK is also currently being investigated by the Serious Fraud Office in the UK; however, the investigation is, as of yet, on-going (UK Serious Fraud Office website). To restore its integrity, GlaxoSmithKline announced its intentions to stop financing individual doctors directly from the beginning of 2016 globally (Ward, 2016). The GSK bribery case sent a ripple through the industry, and respondents from pharmaceutical companies claimed that other global giants (e.g. AstraZeneca and (Eli) Lilly) have begun to take a similar approach, although as of yet they are still testing the waters by limiting the number of doctors they sponsor and not completely abstaining from individual payments as with GSK [HUPH12], [NLPH04].

It is thus that the pharmaceutical industry as a whole is taking steps to regain a lost trust (Kessel, 2014) by placing much focus on reducing individual financial relationships with doctors. Of all the various financial relationships, sponsorships, and services, it is the provision of hospitality costs for medical educational events that industry plans to clamp down on. Those that are the least enthusiastic about the trust-enhancing tactic of industry are the physicians themselves.

As mentioned in the above, in Hungary the low wages of doctors was a key narrative in discussions of financial dependency. Individual financial dependency was discussed as a forced situation, and not as a by-product of the creative doctor looking for alternative solutions to the low wage predicament. According to respondents [HUDR01], [HUDR17], [HUDR10] the source of dependency should not be sought in the loose morals of the profession, but rather in government negligence. Financial dependency was described not as a side-effect of lack of money, but as its solution. These respondents claimed that government purposefully tolerates industry financing because it alleviates having to increase the salaries of Hungarian physicians by having the pharmaceutical industry fill in the financial gaps in healthcare – one of which is medical event hospitality costs, and thus the absence of financial limits as to hospitality costs in the GyKEK Code. A pharmaceutical company compliance officer from Hungary provided affirmation of this claim, and stated that these industry payments were "*calculated into the healthcare budget by the government.*" [HUPH10]. This presents the state of financial dependency to one that is sanctioned, and even endorsed by government inaction. Justification of financial dependency on industry was thus seen as induced from the top down, and the individual responsibility of doctors to keep themselves independent as individuals was negated in explanations such as "*I did not sign up to be a revolutionary. I signed up to be a doctor*." [HUDR10] reflecting on his mandate to treat patients as sanctifying any and all means of being able to do so. The incredible anger at the dishevelled state of an underfunded healthcare system made this subject almost painful to discuss, rendering questions of individual personal

financial relationships that doctors had with industry taken as accusatory and inducing a defensive response. The role of the pharmaceutical industry in funding doctors to educate themselves remained constricted to filling in financial gaps, thus placing any undue influence that these dependencies may create last on the list of considerations. A Hungarian Neurologist explained:

"*It's not just promotion and information supplied (by industry) but many times they provide donations, and help the hospital if there is a problem. There are medications which are very important to have in stock, and if the (healthcare) system is not flexible, and we cannot fill the stockpile from one day to the next, then the industry will provide these. Without (the companies) the healthcare system would implode*." [HUDR14].

In a healthcare system which owes its daily functioning to industry action in times of shortage it is very difficult to identify industry as a potential threat to medical autonomy. In fact, at the micro level, financial independence as a prerequisite of autonomy is seen as a luxury that doctors cannot afford. Pharmaceutical companies in Hungary necessarily take advantage of a dire situation, so much so that when speaking to respondents from industry, many formulated statements along the lines of surprise, that people would actually still consider becoming a doctor at all, and those who knew the situation but remained committed to working as a physician must surely have within them a calling and integrity like no other [HUPH10].

In the Netherlands, where the healthcare system is ranked continuously among the best in Europe, topping the charts at number 1 in 2015 and 2016 by the Euro Health Consumer Index (Björnberg, 2015, 2016), and where respondents had no qualms as to financial deficiencies (wages, healthcare spending by the state, insurance company subsidising) it was intriguing to receive the same descriptions of the role of industry "filling in the gaps" with regards to medical education, as well as disgruntlement over industry intentions of closing shut its hospitality coffers to physicians in general.

"*The problem is that ideally post graduate (CME) courses should be (funded) by the government, (and be) totally independent. But we all know the government are a bunch of assholes that never do anything. So the pharmaceutical industry steps into that gap and they organize fantastic CME courses with the best of the best because they can pay the best of the best to come. You know I don't want to listen to some idiot telling me about how I should treat high blood pressure. I want to listen to Bryan Williams, from University College but then you need to fly Bryan Williams from London to Amsterdam, and he doesn't want to stay in a budget hotel, he wants to stay in a nice hotel because that's what he is used to, so for all of that you need money. And the pharma industry has that money and so they can have the best speakers and the nice environment. So in in practice it's never really independent of course*." [NLDR12].

This account is revealing from many aspects, and highlights what was described in Chapter 8 about educational events themselves being funded by pharmaceutical companies as well as KOLs who are invited to speak. Just to give an idea of how

prolific industry funding is, let me take a short detour based on the information provided in this account: Dr Williams is a member of, and regularly participates in, the European Society of Cardiology (ESC) Conferences. The sponsors of the ESC Congress are Bayer, Boehringer Ingelheim, BMS, Pfizer, Daiichi-Sankyo, and Novartis. Dr Williams received £22,280 for "Contribution to costs of Events" and £16,435 for "Fee for service and consultancy" from Daiichi-Sankyo in 2015. In 2016 he received £23,888 from Daiichi-Sankyo UK Ltd, £4,501 from Novartis Pharmaceuticals UK Ltd and £1,071 from Pfizer Ltd, all of these payments "fees for service and consultancy."[57] The ESC is accredited by the European Accreditation Council for Continuing Medical Education (EACCME), and awards credits equivalent to 26 hours of professional CME activity.[58] Conference fees for 2017 were between €195 and €975 depending on age, society membership, presentation type, and "early bird" registration. This example is a quick indication of the link between KOL position and the financial ties from the same companies that sponsor the entire conference, as well as how influence is easily exerted by pharmaceutical companies having contractual agreements with the speakers that physicians would likely see, and the fact that this event, an industry sponsored conference, is considered a CME due to the amount of points (hours) a physician can acquire. The conference is fully funded by companies and hosts a series of symposia within the conference which is designated as being sponsored or organized by a pharmaceutical company. For all this, doctors wishing to attend have to pay quite a sum.

A Dutch cardiology resident explained that a conference entry fee can easily be €500 or more, excluding the costs of travel and accommodation [NLDR06]. A Dutch pulmonologist described what he called "training events" which lasted roughly 3 days, amounting to €400 a day [NLDR09]. A specialist in pancreatic cancer cited his annual event spending to be roughly €5000 a year [NLDR10]. The same was reiterated in Hungary, where doctors expressed what could be described as anger when discussing the costs of educational events, which could easily amount to 40,000HUF per event [HUDR07] (roughly 120 euros in 2017 exchange rate), a laparoscopy conference registration fee was cited as being 200,000HUF [HUDR19] (roughly 640 euros in 2017 exchange rate, and over half of the Hungarian monthly income).

The price per one event is one thing; however the credit system requires multiple events to be attended which increases the yearly amount spent on education and hospitality. The presumable ethical initiative of downsizing on single doctor hospitality costs has been done without simultaneously revisiting the costs of attaining the mandatory credit numbers and the consequences of that are already visible. A Dutch resident cardiologist explained how the tightening of regulations restricted sponsorship opportunities and heavily impacts resident doctors specifically; the intention of limiting financial relationships for decreasing financial conflict of

[57] Source: British Transparency database: http://www.abpi.org.uk/our-work/disclosure/Pages/DocumentLibrary.aspx
[58] https://www.escardio.org/Congresses-&-Events/ESC-Congress/Registration

interests, simultaneously jeopardizing the number of educational events that residents can participate in.

"*The regulations are much more strict and I think from next year on (companies) can't take anybody to a conference anymore. So (now) it's once in your residency that you (can participate), while with pharmaceutical industry (sponsorship) it was easier to attend (more events)*." [NLDR06].

That residents are low on the list of doctors to sponsor for medical educational events was confirmed by a Hungarian pharmaceutical company respondent in discussing financial sponsorship preferences of a company.

"*The European and Hungarian regulation lists our (company) funding opportunities, of which there are not many. (Individual sponsorship) serves a scientific purpose, and so when we fund doctors, our main priority is not the residents*." [HUPH12].

One would assume that residents are the most in need of both education and funding. Residency implies a certain degree of studentship, in that their practice is still supervised, thus not quite fully autonomous when it comes to prescribing a drug. Additionally, they are situated lowest on the medical salary hierarchy. But herein lies the rub, because residents cannot supply treatment completely independently and are still in need of a superior to sign-off on clinical decisions, thus the statement of contributing to the education of physicians must be deciphered to mean preference for the fully autonomous prescriber.

Reiterating the 50% contribution rule in the Netherlands, and that additionally hospitals also provide a budget for doctors which must be spent on educational events. This budget was brought up by one respondent only, who said that doctors were allocated roughly €5-6.000 per person annually, however this hospital budget did not come up as a national given, dependent on the hospital or healthcare facility itself. In fact the use of it was not mandatory, this respondent saying that while he used hospital funding specifically, other colleagues may not be inclined to do so. Nevertheless, hospital budget or not, he maintained that the Dutch regulations were "overshooting" their target, and described again the inadvertent consequence of limiting physician subsidy by pharmaceutical companies. "*Looking at medical congresses, where you would see 3-4000 Dutch doctors attending, today you only see 10*." [NLDR05].

The belief in regulation as solving problems of influence by way of restriction or limitation without taking into consideration the expectations of physician quality maintenance requirements or the local context will result in unforeseen detriments, such as explained by a compliance officer from a pharmaceutical company in Hungary.

"*For example physicians from the United Kingdom only apply for industry funding for attendance at international events, since the healthcare institutions that provide local educational event either provide them for free, or physicians are able to finance themselves from their own salaries. It really weighs on your heart; the huge differences in the way things are thought out. And it shows, even in the internal regulations of our*

company that those who make the decisions come from a very different environment." [HUPH10].

9.4. COUNTING DEPENDENCY

Regarding payments to individuals for hospitality costs, hard data has only very recently become available (roughly since 2015 for both Hungary and the Netherlands). However, dissemination of financial payments is limited to the Netherlands. Despite Hungarian disclosures being available for 2 years now, as far as I know, the tables I have compiled in Chapter 8 are a first attempt of its kind. In the Netherlands, however, the subject of industry-medicine financial ties enjoys cyclical popularity. The CGR, which is responsible for managing the industry-financed transparency database, issued a report of the aggregate amounts of all types of financial relationships between doctors and industry. The CGR report (2016) provides a general overview of individual payments to doctors (Health Care Providers: HCP) and healthcare organizations (HCO) for the years 2015 and 2016 respectively. This is summarized in the graph below which has been taken directly from the CGR report:

	2015		2016	
	HCP	HCO	HCP	HCO
Number of HCP/HCO	3.814	1.091	3.659	1.101
Number of relationships	10.066	4.062	9.896	4.415
Total value	€8.761.753	€42.788.625	€8.347.627	€48.426.880
Average per HCP/HCO	€2.297	€39.220	€2.281	€44.192
Average value of relationship	€870	€10.534	€844	€11.021
1 relationship	2040	570	1.867	533
2 relationships	744	182	722	197
3-5 relationships	648	180	696	194
6-10 relationships	246	99	234	107
11-20 relationships	104	32	114	44
More than 20 relationships	32	26	26	26

Table source: Notitie kengetallen register 20130417. *Transparantieregisterzorg 2016* (11 mei 2017)

This table reflects what was stipulated by doctors and pharmaceutical company respondents in the Netherlands; that financial relationships are common for only a few physicians – indicated by inverse proportionality of the number of financial relationships to the number of doctors receiving these payments. These individuals, according to industry respondents, are and will remain the KOLs in medicine [NLPH06] [HUPH12]. Looking at the data more closely, the CGR also identified in percentage terms, the exact amounts paid per service rendered or type of sponsorship

awarded to HCPs and HCOs in the table below. When looking at the figures, it is important to note the "*educating the medical profession*" [HUPA02, NLPH04]) rhetoric to be reflected in the amounts of payments culminating in educational activities for both HCPs (reimbursement [hospitality] for medical education) and HCOs (sponsorship for meetings). These are highlighted in bold below.

Relationship types	2015		2016	
	HCP	HCO	HCP	HCO
Consultancy Services	6% 525.705, 18	2% 855.772, 5	7% 58.433, 89	2% 968.537, 6
Advisory Services	15% 1.314.262, 95	1% 427.886, 25	13% 1.085.191, 51	1% 484.268, 8
Speaker fees	20% 1.752.350, 6	2% 855.772, 5	18% 1.502.570, 86	2% 968.537, 6
Other Services	3% 262.852, 59	4% 1.711.545	3% 250.428, 81	6% 2.905.612, 8
Service Expenses	24% 2.102.820, 72	1% 427.886, 25	28% 2.337.335, 56	1% 484.268, 8
Reimbursement for continuing medical education	**30%** **2.628.525, 9**	0%	**30%** **2.504.288, 1**	1% 484.268, 8
Sponsorship for meetings	0%	**58%** **24.817.402, 5**	0%	**53%** **25.666.246, 4**
Sponsorship for projects	2% 175.235, 06	32% 13.692.360	1% 83.467, 27	34% 16.465.139, 2

Table source: Notitie kengetallen register 20130417. *Transparantieregisterzorg 2016* (11 mei 2017)

The CGR report does in fact paint a picture of declining trends, however what is not revealed by averages, and casts financial relationships in a new light, is the complementary research executed by Dutch Journalists from *de Volkskrant*. These journalists performed a 4 month manual search of individual payments in the transparency database. Results of their research confirmed the amounts of the CGR report[59], as well as the majority of payments going towards individual hospitality costs, but they added another variable: the specialist area of each doctor. In doing so the results challenge the generality of industry's slogan of educating the (entire) medical profession, showing that actually it was high prescribing specialists that received the most financial support. Accordingly, rheumatologists, urologists, pulmonologists, internists, dermatologists, gastroenterologists, and cardiologists (similar to the list of funding preference to medical associations by disease area in Chapter 8) received the most funding. This piece of information is crucial in destroying the idea that industry

[59] There is some slight variation between the exact amounts paid to doctors listed in the CGR report and *de Volkskrant* graphs for various types of sponsorship/service agreements. The journalists explain that this is because a complete list of physicians in the Netherlands is not accessible to the public, and that the list of physicians had to be constructed from a so-called "care card" and through the Dutch Patient's Organization. Additionally, journalists excluded General practitioners, vets, nurses, and dentists, and also chose 16 specialisms whom they deemed high prescribers excluding specialisms less interesting to industry (i.e. pathologists). Despite variations in methodologies, the amounts roughly converge with that of the CGR data, both in amounts, but also percentage dispersion. For additional confirmation I also contacted the CGR directly, who confirmed that the data from *de Volkskrant* were accurate (confirmation via email from CGR representative 17/05/2017).

has a general role of educating doctors, focusing predominantly on specialists and high prescribing disease areas.

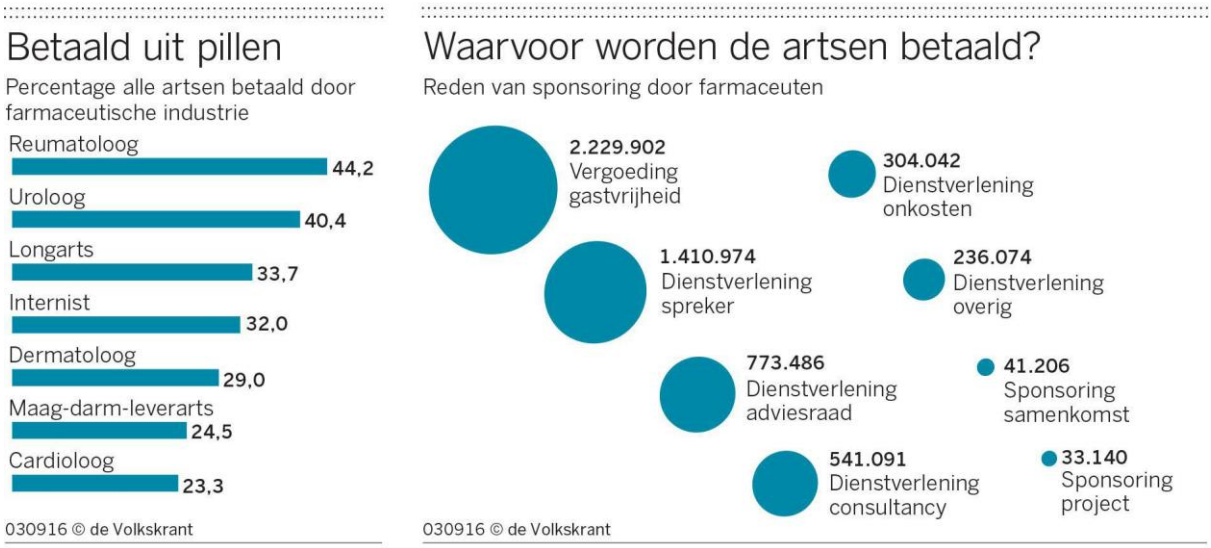


Image source: Tom Kreling, Ellen de Visser & Remy Koens: Farmaceuten betalen miljoenen aan artsen. Vooral reumatologen, longartsen en internisten profiteren. *De Volkskrant* (3 september 2016)

The article reveals more than one would initially think, and it requires some deeper analysis of what exactly these numbers mean in relation to sponsorship of specialists in the specific fields. The following analysis offers a return on investment explanation for why (certain) specialists are preferred for funding over other doctors.

9.5. THE STRATEGY BEHIND SPECIALIST PREFERENCE IN CME FUNDING

For innovative pharmaceutical companies, branded drugs are what essentially make profit. The cost of branded drugs is a highly controversial subject, and the pharmaceutical industry is accused of barring access to drugs at the cost of patient lives, while governments remain impotent in controlling the price of drugs on a free market.[60] The issue of drug pricing is not the specific subject of this thesis, but it is a contextual component. Citing the innovation crisis and the patent cliff discussed in Chapter 6, the pharmaceutical market is seeing the proliferation of generic drugs – copies of brand name drugs. The active ingredient in a generic drug, the disease that it targets, its mode of administration, and dosage is the same as its original (branded counterpart), while the inactive ingredient (components that do not affect the previously listed characteristics), name, appearance and packaging may be different than the branded version (EMA and FDA website). Generics are cheap because they are copies, and as such do not require all the clinical trials needed for original medications, but only need to prove that they work in the same way (bioequivalence). All brand patents expire, and this is when drugs can be copied and sold for a fraction

[60] http://www.who.int/medicines/areas/access/Medicine_Prices_and_Availability/en/

of the original price. The patent cliff enables governments and health insurance providers to take advantage of the cost reduction potential of generic drugs.

In Hungary and the Netherlands cost reduction incentives have lead both countries to adopt regulation or policies that seek to push prescribers towards the use of cheaper medication. In Hungary, where health insurance is mandatory, universal, and provided by the National Health Insurance Fund, law (Act XCVIII of 2006) favours reimbursement of the cheapest drug in a therapeutic class – meaning the generic version of medication unless a generic is not available (Gaál et al., 2011; Nagy-Koppány et al., 2013). In the Netherlands, healthcare insurance is mandatory, but provided by private insurance companies, among which citizens may choose. In 2013, Dutch insurance companies made it a policy to reimburse medication based on price, and thus again, cheaper generics tend to be favoured over brand name drugs (Wammes et al., 2014; Mw. drs. E.I. Schippers, open letter: Medicine's Policy Plan, 2016). This is where it gets interesting, and the strategies of industry influence are visible. We must invoke here the specific wording of institutional corruption theory, in that it is *systematic* and *strategic* influence that is exerted, and industry targets specific doctors to fund precisely because of their prescribing power, preferring certain doctors over others.

General Practitioners belong to the primary care sector, the so-called "first line" of healthcare service delivery. Their first line position is functional in the sense that they control access to specialized care. A patient must first visit a GP and obtain a referral to see a specialist, if the GP deems that the ailment warrants specialist discretion. Their function alongside provision of care is to lessen the burden of the healthcare system in making sure that patient ailments are specific, serious, or valid enough to warrant increased attention by specialists, simultaneously enforcing cost reduction, being that first line and general non-specialist care is characterized by higher generic medicines use. As such GPs are not the most common beneficiaries of industry funding for medical conferences.

"*In general companies (producing original, brand name drugs) don't interact with GPs, since the GP usually prescribes generics. Original companies focus on specialists*." [HUPH13]. "*GPs are not the main targets for (educational) funding but rather specialists*." [HUPH12]. "*Typically we wouldn't pay GPs to present (at conferences)*." [NLPH06]. "*Obviously (specialists) influence the (pharmaceutical) market more than GPs*." [HUDR20].

I was specifically told by an industry respondent not to bother speaking to GPs at all about financial ties with industry, because they did not execute the type of practice that would warrant investment in specialized knowledge [HUPH12]. This was supported by accounts from GPs with regards to financing medical educational events, a Dutch GP explaining how she would "allow (herself) the luxury" of attending one bigger international conference every year, because she had to finance these for herself

[NLDR03]. Preference is so obvious, that another GP described how this type of favouring manifested when GPs and specialists were attending the same event.

"*I once went to a conference which was in the Netherlands and it was about sports medicine, so it was attended by GPs and sports doctors and cardiologists. And I know that the cardiologists didn't have to pay at all because they were paid by the pharmaceutical industry and we paid our own attendance. (…) specialists have their own ways*." [NLDR02].

Why are specialists preferred over GPs? The limited answer would be what I encountered in the field; industry respondents claiming that GPs do not prescribe their innovative drugs; GPs will claim that they are in the business of providing a generalist, less specialized form of care, making knowledge on specialized drugs less pertinent, and specialists will cite their incredibly specialized knowledge as warranting attendance at the best (and most expensive) international conferences. Additionally, my fieldwork would propose an additional explanation, which identifies the specialists' ability to override generic preference.

Whatever the law may mandate, or what the reimbursement policies may be, professional, specialist opinion still overrides general limitations. The cost reduction policies of generic prescription are also like general guides, and although GPs' prescriptions are monitored by government bodies, every patient is an individualized case, and specific personal characteristics may still necessitate prescribing different drugs within a therapeutic class. This is where the GP-specialist power-play is important.

In the Netherlands and Hungary, GPs would complain about specialists prescribing branded versions of drugs, for which there is a less expensive generic version on the market, which was described as the problem of specialists changing medications for no apparent reason other than industry inducement. A Dutch GP [NLDR03], a Dutch cardiologist [NLDR06], and a Hungarian ex-GP now working for a pharmaceutical company [HUPH13] all used the example of a gastrointestinal medicine used to treat gastrointestinal reflux disease, peptic ulcer disease, heartburn, and Zollinger–Ellison syndrome. These respondents named 3 drugs available: the brand name Nexium® (Esomeprazole), another brand name Prilosec® (Omeprazole), and a generic version of these called Pantoprazole (sold under circa 800 names globally[61]), all of which are available by prescription only. The Dutch GP stated how she would always prescribe the cheaper Pantoprazole, basically because it was a general requirement of GPs to do so. However, the Dutch Cardiologist described how the general rule of prescribing the generic drug was commonly overridden in her hospital because specialists tended to prescribe Prilosec®. The new doctor may forget, overlook or generally trust that the specialist had a reason for prescribing the brand and not change it. The Hungarian industry respondent, in a reflection on his days as a GP, talked about how the

[61] https://www.drugs.com/international/pantoprazole.html

prescribing habits of specialist colleagues informed his own decisions to prescribe Nexium® and Prilosec® over other drugs.

Prilosec® and Nexium® have coincidently been used by Marcia Angell (2004) as an eloquent example of the pharmaceutical industry ever-greening patent extension, me-two medication tactic (Gagnon, 2013). Both branded drugs are manufactured by the same company AstraZeneca. Just before it lost the patent to its blockbuster Prilosec®, AstraZeneca placed Nexium® on the market which critics have called out for being nothing more that Prilosec® in a purple packaging, but more expensive. The above example, however, is more important from the perspectives of specialist override: the fact that whatever a specialist says goes, and this is maintained by their specialist status as well as the trust among colleagues, both regarding professional autonomy, and specialist status. Status within the profession of medicine itself is vitally important, especially along the lines of GP and specialist, because this is exactly what is being taken advantage of by the pharmaceutical industry. Among physicians themselves, GPs are slightly lower in rank, despite the very vital role that they have as the first line. Specialists would talk about GPs as generalist, and needing their specialist help due to lack of knowledge produced by generality [NLDR04], [NLDR09] or a specialist who described sales representative information as boring and simple, and not about innovation, so sales reps should rather "*go to the GPs*" [NLDR18], indirectly asserting that GPs would not be interested in anything other than basic medical information. Similarly GPs would describe specialists as "*limited in knowledge*" precisely due to specialization [NLDR03]. Responses in Hungary were similar, with GPs being described as "*bureaucrats*", doing no work of note other than deciding which competent person to pass the patient off to [HUDR16]. The following quote from Hungary provides a concise description of the friction respondents in both countries described.

"*General Practitioners are looked down upon, but to be honest I'm content with being a GP. This is a different world, where I am one on one with patients and I get to know them better. But the GP is always (seen as) being stupid, mainly because (specialists) know more about a small slice (of medicine). But we have to know a bit about everything*." [HUDR25].

Similarly to the Eso/Panto/Omeprazole use, another disease where the GP-specialist divergence caused tension was in relation to cholesterol-lowering medication (statins), emphasizing how this affects the patient. Saying that specialists always prescribe branded drugs, a Dutch GP [NLDR03] explained how her patients would become confused if suddenly their GP were to then prescribe its generic form.[62] In the case of medication prescribed initially by a specialist, patients will stick to it because they trust the specialist. The lack of reverence for the GP in comparison to a specialist does not help. They get used to a box cover, or a shape and colour of a pill, and when the GP

[62] A specialist may prescribe a drug, but if the medication is such that the patient has to take it for longer periods of time i.e. anti-cholesterol medication, then the patient simply goes to the GP to have the prescription re-filled.

or the pharmacist offers a generic, the patients usually prefer the medication prescribed by the specialist. [HUPH13] "*A patient will buy either what is cheapest, or what the doctor prescribed (for the first time). Ask any patient, which medication they take. They will probably say "that pink one*." [HUPA01]. Even if the GP and the pharmacist has the duty to inform the patient that a cheaper version may be available to them, the loophole is in the specialist override when a specialist might even say to a patient "*Listen Mrs X, stick to this specific drug, because this is the best*" [HUPH13]. Adding chaos to confusion is the lack of medical trust in generic drugs, a Dutch GP [NLDR02] citing how these drugs are supposedly manufactured in "*third-world*" countries which made this respondent sceptical of their safety. In Hungary, the allure of branded medication stems from the socialist era when there was a barrier to accessing pharmaceutical products, which produced an awe towards branded drugs; one specific example being the almost magical qualities of "*Swiss medication, and Bayer Aspirin*" [HUDR04]. While in Hungary the awe-clad nature of branded drugs sometimes induces scepticism towards generics, Dutch doctors' scepticism was slightly more orientated towards the supposed manufacturing countries such as "*India and China*" [NLDR02], although some see this scepticism as manufactured propaganda by the innovative industry [NLMJ01]. The distrust towards generics is ironic because they too are approved by the same regulatory authorities that approve the original drug. However, the preference towards generic prescription varied incredibly between respondents.

Placing this once again into the context of strategic influence by pharmaceutical companies, the specialist override presents an opportunity to maintain the use of branded drugs over generics. Revisiting payments for educational events, it becomes more a conscious *intention* to "educate" the *specialist* than fulfilling a more philanthropic role of ensuring that the profession of medicine can educate itself as a whole. The specialist override places industry ethicality rhetoric in a new light, because while companies advertise their intentions of reducing potential influence via financial dependency by downsizing financial support for conference attendance to only a few select physicians, influence itself remains because for industry, influence does not necessarily manifest by financing everyone, but by retaining financial ties with specialists who ultimately dictate what medicines will be prescribed. The specialist status serves to convince doctors of their skill and responsibility, unquestioningly accepting the role of industry in their 'education'.

9.6. DOCTORS AND SALES REPRESENTATIVES

The pharmaceutical sales representative is the most identifiable and most undisputed form of pharmaceutical industry advertising to physicians. Sales representatives are once again the main targets of pharmaceutical industry codes of ethical promotion, which devote much attention to defining what sales representatives can say to doctors, what information must be provided and what information is prohibited, what gifts can be given, what the monetary worth of those gifts can be, that gifts must be such that

can be used by the doctor in his/her practice, or the gift must be such that it informs the patient, that representatives can only visit doctors outside of working hours, etc.

Sales representatives are an interesting phenomenon to investigate, partly because their visibility makes them the subject of much criticism and consequently regulatory restriction, but also because sales representatives as per function do not directly fulfil the definition of a financial relationship. The giving of gifts to physicians (Wazana, 2009) to induce unconscious reciprocity or favouritism is not only less prolific today, but from a regulatory perspective is very restricted, and the scrutiny of sales representative promotion has enforced in physicians a conscious avoidance, and/or heightened sense of scrutiny. During interviews physicians were critical towards representatives, and were well aware of the marketing incentive and the promotional intentions of their visits. As to whether sales representative visitations have dropped in frequency, the majority of respondents, both physicians, regulatory authority respondents and industry employees, all concurred that promotion via representatives was dwindling, either citing stringent regulation and increased scrutiny towards obvious promotion to physicians (common in the Netherlands), or government restrictions (such as Hungarian law which mandates a sales representative tax to be paid by pharmaceutical companies for each representative they hire).[63] (PricewaterhouseCoopers, 2009)

During fieldwork, and particularly regarding interviews with doctors, I was more often than not invited to the hospital or clinic where the physician worked. There was no standard time slot for visits; practicing physicians trying to squeeze me in to their busy schedules and allowing me to steal an hour of their time. In a hospital or clinic, there will always be a secretary, or a medical assistant acting as a barrier between you and the doctor. These are the bureaucratic guardians, the "technostructure" (Mintzberg, 1983); those organizational members who work towards ensuring that the work of the organization is carried out in appropriate fashion by providing and controlling information flow, standardizing tasks, engaging in work allocation and scheduling etc. Getting through the technostructure required answering 3 standard questions: (1) whom am I looking for (2) do I have an appointment, and (3) which company am I representing? The technostructure staff confirmed that visits by representatives are not only common practice, but that representatives are among those who are traditionally allowed entry into the healthcare establishment, and so make up part of the physician informational/work routine. The number of representatives in total may be declining,

[63] "On 15 December 2008, the Hungarian Parliament adopted legislation amending Act XCVIII of 2006 on the safe and economical supply of medicinal products and medical devices and the general rules on the distribution of medicines (…) companies that distribute or manufacture medicinal products are again subject to a payment obligation for each medical sales representative they employ. (…) The monthly fee payable will be HUF 416,000 for each sales representative engaged in promotional activities for medicinal products and HUF 83,000 for medical device sales representatives." PricewaterhouseCoopers: Pharmaceutical Newsletter Hungary (2009)
As a result of these laws, the number of sales representatives in Hungary decreased by a third in 2012.
https://www.hrportal.hu/c/eltunt-az-orvoslatogatok-tobb-mint-harmada-20130910.html
http://medicalonline.hu/cikk/a_gyogyszerismertetok_alkalmazasanak_feltetelei

but a sales representative said that this really only meant that instead of having a daily quota of meeting 5-6 doctors, she now had to visit 9-10 a day [HUPH06]. Their purpose is to sell a medication by persuading doctors to prescribe specific drugs. To do this they are trained specifically in methods of persuasion. Exactly what they are trained to do and the actual training materials used, are company trade secrets and I could not manage to persuade any current or former sales representative to provide me with these for analysis. However, physicians were willing to discuss just how these sales representatives persuade doctors in practice.

9.6.1. TECHNIQUES OF SEDUCTION

Certain sales representative stereotypes still exist – stereotypes that emanate from the tactical methodologies of seduction and reciprocity which are designed to tempt doctors and sway prescribing habits. *Time Magazine* simply calls them "Pharma Babes" (Haig, 2007), and even in popular television series, attractive female sales representatives are filmed walking down hospital corridors in high heels, hair blowing in an uncommonly strong indoor wind, while Robert Palmer's "Bad Case of Loving You" plays in the background (Scene from the TV series "Scrubs").

"*The drug reps are like you. Most of them female, attractive, they know what they want and they are smart and young. And we are mostly middle-aged white men. Yeah, that's true. That's the truth of it. You don't send a grey old man to a grey old man to convince him. You send a 30 year old woman, and they all get these trainings in how to (initiate) conversation. It helps. If it didn't help they wouldn't be there. I mean they don't have to be blonde. But in general, I recognize them from a mile away in the hospital. So their gestalt is actually very typical of western Big Pharma*." [NLDR12].

Pertinent perhaps to mention, but it was usually male doctors, or male respondents that would emphasize the physical appeal of sales representatives [NLDR12], [HUDR10], [HUDR02], while female respondents would evaluate representatives based on age, or level of education [HUDR19], [HUDR14]. However, this does not mean that female doctors are less susceptible or more critical. Speaking to sales representatives about how their approach would mould itself to the physician, respondents cited successful relationships with female doctors to be due to common denominators, such as talking about family, child rearing, work-life balance etc.[HUPH04] [HUPH05] [HUPH06]. This is not to be confused with evidence of gender stereotypes, but, using an expression from the field, "*every doctor has his/her gummy bear*" – a special something that they like to talk about, an atmosphere they like to maintain [HUDR09]. It is the job of the sales representative to find this sweet spot and form a viable relationship with the physician. Doctors are burdened by heavy schedules, patients with complaints and high expectations, and sales representatives trained in relational tactics present a discussion partner for a few minutes, that break the monotonous cycle of clinical life.

"*For 7 years I visited gynaecologists, and by then I knew everything about them, from their grandchildren to their pets. Now I'm visiting pulmonologists and we're in the*

introduction phase. A lot depends on the quality of the relationship. There are doctors with whom I have a good relationship after one or two visits while for others it takes a couple more visits to finally start talking about something other than the profession." [HUPH06].

Personal connections and the social side of promotion are important especially when regulation has singled out the gift culture as the most problematic regarding influence. Gifts in their traditional forms are prohibited; instead, regulation makes attempts at controlling the value and nature of a "gift", setting caps on gift values, and maintaining that anything given to a doctor must be of use to, or aids the physician in the course of practice (GyKEK Code, 2014, CGR Code, 2015). Additionally, regulation prohibits any form of financial or in kind compensation for prescriptions. This in practice may not always be adhered to. In Hungary I spoke to a physician who openly showed me the laptop he was recently given by a pharmaceutical company [HUDR26] for advisory services. Fee for prescription, something legally outlawed may still happen – a Hungarian gynaecologist claimed that her colleague took advantage of the fee-per-prescription practice, even abusing it to her own advantage by lying to sales representatives about how many drugs she/he prescribed, receiving payments for phantom prescriptions [HUDR23]. "*It happens even today, rarely, perhaps once or twice that a sales representative will say they will pay you 1000HUF for every prescription you write*." [HUDR04]. During interviews I sometimes forgot my pen, and was immediately provided by some kind of industry emblem embossed biro. Pharmaceutical company logos were spotted on neglected stress-balls, folders on shelves, or on bags and satchels hung on hurried shoulders and streaming past my eye line as I sat in hospital waiting rooms.

In contrast to Hungary where reminiscence of the "*good old days*" of industry perks [HUDR02], [HUDR09] still popped up from time to time (a laptop here, the odd pen, calendar, notepad or payment per prescription), Dutch physicians are firm that this practice, gifts and money, has completely disappeared, and paraphernalia were limited to pens and mints at conferences – but not given by sales representatives. Fee-per-prescription is considered a bribe in its purest form and something that "*happens only in countries where oversight is less. A thing like fee-for-prescription could never ever happen in Britain or Holland. Impossible, because the first doctor that you would try to bribe would run to the newspapers*." [NLDR12]. In the Netherlands the tactics of social seduction for sales representatives is the baseline rule of engagement, as explained by a respondent from a Healthcare NGO.

"(Reps) are mostly blonde women (...) that cliché is really true. And that also has reason. It's all in the context of being influential. It's a kind of seduction. Even if you are not willing to introduce new medication in your arsenal of medications you normally use, you're sitting opposite a nice person who says "I know you. I know how you work, and I know you are a bit conservative." No one likes to be called conservative by the way. "So just promise me, the first time you have a patient who

doesn't react to your standard treatment, try this product. Just try it once and you'll see the results." [NLOO02].

By pure coincidence born of being very late to an interview with a Dutch pulmonologist, our meeting was cut short, when a knock on the door signalled that the meeting with a representative from Novartis was scheduled to begin. Being that we had discussed sales representatives only moments prior, the doctor invited me to stay and observe the meeting. A woman in her early 30s stepped into the office, startled at first by my presence, and genuinely uncomfortable with my being there, agreed that I stay, condolence given rather to appease the doctor than actually being happy to share. The sales representative then proceeded by giving the doctor an A2 size chart, a 3D depiction of the bronchial tract. This chart was actually a requested delivery, something the pulmonologist could use in explaining anatomical processes of asthma and COPD to patients. The doctor and the representative went on to tell me how nowadays only this type of informative, educational material was allowed. Time for the sales rep was also limited so she went directly into her presentation, providing pictorial aid via an iPad. Hindered at times by the physician explaining complex medical jargon for my benefit, the representative proceeded to discuss the subject of the day: a new study and treatment for COPD.

First things first: The name of the study is FLAME (which fits in nicely with the catchier studies titles mentioned in previous chapters (ADVANTAGE, or ENHANCE) the findings of which were presented by Dr Jadwiga Wedzicha (Key Opinion Leader and Clinical Chair in Respiratory Medicine at Imperial College London) at the American Thoracic Society Conference just a week ago (May 2016). After introducing the scientific validation, the representative asked the next question:

"*When you see patients which come from the General Practitioner, which medication are they on already (…) for COPD? "My question is, do you see patients who get a combination of LABA and ICS, for example Seretide® and they come to you with complaint that they don't need ICS?*" (Rep from interview [NLDR09])

This question does many things: it indirectly undermines GP prescription decisions, it pulls at the heartstrings of doctors by citing patients who complain when better treatment is actually available, and it places the name of the competitor drug Seretide® (manufactured by GlaxoSmithKline) in one sentence with patient complaints and unsuccessful prescribing. Proceeding on, the representative then takes us back to the FLAME study, and this is when the name of the medication being peddled comes up first: Ultibro® by Novartis. Factually laying out the success of Ultibro® she went on to talk of clinical end points and lower exacerbation rates and less frequent cases of pneumonia in comparison with Seretide®, the competitor and comparator drug in the trial. Finally, the close is the mention of the findings being published in the New England Journal of Medicine, and the question to the doctor of whether he knew of this study, and whether this information was helpful.

This encounter revealed much of what was said with regards to the tactics of successful seduction, delivering on requests (poster) maintaining that the doctor call the shots (letting me stay and elaborating on medical jargon if the doctor asked the rep to do so, even if it meant straying slightly from the core message to be conveyed) and providing hard evidence (trial findings) and veracity support (academic presentations, and KOL approval). This is an interesting peek into what remains interaction behind closed doors, and what a representative visit may entail. However, perhaps what is more important, was that all this was conveyed in a mere 15 minutes. The information condensed in a short presentation, the references given, the core message conveyed. It is this characteristic above all that makes sales representatives vital for doctors.

9.6.2. INFORMATION SATISFICING AND THE DOOR TO CME FUNDING

Whether or not doctors will see representatives, there are two things that detailers provide: accessible information, and network connection to CME sponsorship. These qualities become lost in analyses that study influence as the product of exchanging gifts or the power of personal sympathy and reciprocity. Not that one should dismiss these tactics, for they are part of the marketing mechanism and thus necessitated the description of the art of salesman seduction in the above, but regulatory restrictions are made without taking into account the context of the work of the doctor. As with downsizing CME sponsorship while maintaining a quality assurance system that places financial strain on doctors, a similar paradox occurs in the sales representative dilemma: expecting doctors to possess an enormous amount of information, while not taking into account their working environments and their human capacities.

Information overload is not characterize simply by the amount of scientific medical literature that is available, but also all the medication that is currently on the market. Between 2011 and 2015, a total of 144 new therapeutic agents were authorized by the European Medicines Agency (Downing et al., 2017). In 2013 alone, the EMA approved 30 new active ingredients (Bujar & McAuslane, 2014). To keep up with the constant flow of new drugs available, sales representatives provide accessible and current information, delivered to the doorstep of the physician. A Dutch GP's reaction to my question as to positive experiences with pharmaceutical sales representatives produced the following description:

"*Representatives are not all bad. And for me it's also good to know that there are new inventions. So I know that there is new ways of treating diabetes with medication, and a novel approach. I would like to know about new medicines and inventions, so I can make decisions about whether or not to prescribe new things for my patients*." [NLDR02].

The sales representative provides information in 15 minutes, and this is important even if only for the knowledge that there is a new medication on the list of many already available. If it seems like a legitimate improvement over current treatment, the doctor may then proceed to look into the medication in more detail [NLDR02], [HUDR19].

The regulatory stringency and the conscious decision of many doctors to decline representative visits out of fear of being accused of undue influence, was seen by this GP as beneficial for maintaining impartiality. Doctors themselves are very wary about discussing any reliance on the pharmaceutical sales representative, out of fear of being judged by patients, colleagues, or the media. However, the respondent expressed some anxiety regarding these restrictions (regulatory and public scrutiny), citing the confinement of a GP clinical practice necessitating visits from representatives who are the link with the outside world.

"*For me it's a link to the world, otherwise I'm sitting in my practice and I am seeing my patients and how can I know what's happening? (…) our (profession) is so protected from influence that you hardly know what's happening.*" [NLDR02].

A specialist in urology from Hungary described that representatives hardly come to their hospital, which he saw as a problem in that the existence of some medications only became apparent to him once he scoured the internet, dived into the literature, or came across the information by chance. The problem is the delay that this causes because time to spare for one's own research is rare if one is a practicing physician [HUDR11]. Limiting the number of sales representatives is a "*double edged sword*" said a cardiologist in the Netherlands [NLDR04] because while academic medical centres are the hubs of innovation and research, exposing physicians to novelty and innovation at the workplace, the isolated clinic, hospital, or practitioner cannot necessarily access new and vital information on a daily basis. This duality was expressed by a specialist in vascular medicine, when I asked whether sales representatives count as a viable source of information.

"*Oh Fuck no! I never see pharmaceutical sales representatives. No, I couldn't do that. It would be a terrible conflict of interest. They are an important source of information but not for my level. They are for the run of the mill cardiologists in a mid-sized town. For them, representatives are very important*." [NLDR12].

Being a KOL himself, this respondent claimed to not rely on sales representatives, being one who has direct contact with industry innovation via various consulting and advisory positions, but he yet again confirms their necessity for other professionals. Their vital role is reflected in their first line "operating core" (Mintzberg, 1983, p. 12) status – those that perform the "basic" work of the profession of medicine: "distributing the outputs" i.e. applying medical knowledge in the clinic.

Representatives are not only a source of, but a key to information manifesting as a gateway to medical education. Since doctors seek out industry compensation for hospitality, the sales representative presents an opportunity to acquire such funding. Asking respondents whether they sought out industry or industry invited them to events, doctors cited having good relationships with representatives [HUDR07] as one means of attaining CME sponsorship; "*What I've come across up to now is that we asked the company, usually a sales representative that is already closely related to*

what you know, and then you talked to them" [NLDR06], some sales representatives even proposing to meet the doctor at the CME and give further explanation of the product at the event itself [HUDR21]. A resident in neurology explained the link between sales representatives and conference funding opportunities;

"*I have contacted sales representatives asking them whether there is any possibility of sponsoring me financially to attend a congress. They evaluated my request. It wasn't a 100,000 HUF (approx. €320 in 2017) fee but a smaller amount, around 20,000 HUF (approx. €60 in 2017), so when I asked them, they were more than happy to help*." [HUDR18].

He went on to explain that although residents are not usually the targets of industry promotion or funding, his superior regularly introduced him to industry representatives, as contacts and networks for funding opportunities in the future. Thus representatives are not solely walking billboards for the industry, but act as links to resources for further information attainment. Shutting down sales representative activities, placing strict limitations on representative-doctor interactions may be rationalized as minimising influence and promoting physician independence, but simultaneously regulation does not consider the functional aspects and qualities that necessitate this interaction. Restrictions have been concocted without offering the medical professional alternative means of attaining the goal of self-education.

The incredible scrutiny that sales representatives, and physician financial ties with industry have received has unintended consequences, which have not been fairly addressed, and are based on assumptions of physician susceptibility to (assumed) sub-standard information. These shallow assumptions make it easy to criticize physician greed for their financial ties with industry, when in fact expectations (coming from the profession itself and patients) of doctors to constantly train and self-educate (**motive**) places pressure on them to find informational sources and financial support (**means**) to do so. The fact that financial ties to industry are seen as the main drivers of undue influence and industry manipulation, regulation and public scrutiny tend to focus on criticising and demanding a reduction in industry payments to physicians. Regulation and increasing moral judgment about accepting industry money places doctors in an impossible situation where the goal has remained unchanged while the tools to achieve it continue to become less accessible.

Merton claimed that when a goal is accepted, but the means by which to achieve it is unavailable, innovation will ensue (Lanier & Stuart, 2010, p. 266). In this case, when payments to doctors are perceived as a conflict of interests, one may devise ways in which to hide or confound financial ties. Loose regulation, as I have described in the above, creates loopholes (**opportunity**) within which one can do so (Punch, 2000, p. 244; Coleman, 1995; Friedrichs, 2010; p. 221). Two side-effects of uninformed regulatory stringency were identified in this research specifically: (1) modes of concealing direct-to-physician payments, and (2) the opportunities of rationalizing industry promotion-based prescription decisions. It is these that I shall discuss in the

following, and present the innovative means and rationalizations used by physicians to conceal payments, and claim minimized industry influence.

9.7. HIDING THE BODIES IN REGULATORY LOOPHOLES

Regarding industry-medicine relationships, transparency of industry-medicine financial ties is an important step forward, but one which has failed to take into consideration the entire construct of actors involved, and the opportunities hidden within the systems of disclosure. To understand the insufficiencies, and thus loopholes, we must take a closer look at the text and definition of the current regulation regarding disclosure and (self) regulation obligations in both countries.

The Dutch CGR Code (2015) states in Chapter I, Article 1.2: "The present code of conduct lays down standards for activities to ensure responsible interactions between authorization holders and healthcare professionals, professional carers, patient organizations and other interested parties". The GyKEK Code (2014) states in Chapter 3 Article 1.1: "The scope of this Code shall cover marketing practices undertaken with by companies' medicinal products as regulated in Act XCV of 2005 on Medicinal Products for Human Use and Amendments to Other Regulations on Medicinal Products". Act XCV of 2005 identifies as "authorization holders" those entities which have been granted medicines authorization by the competent authority (OGYÉI).

Transparency only applies to companies that have submitted and received authorization for marketing, those that have a medication on the market (not to be confused with a patent). Authorization holders manufacture, sell, and advertise drugs to consumers. So who falls out of the scope? The majority of biotechnology and university spin-out companies, clinical research organizations, site maintenance organizations, and medical conference catering companies: in short, non-authorization holders and middlemen service providers. These legal entities do not make up what is conventionally defined as healthcare system actors (EU Study, 2013) but they in fact are the "technostructure" and "support staff" (Mintzberg, 1983) which are active in contributing additional services to healthcare system actors in the execution of their professional activities. These legal entities provide means for pharmaceutical companies to hide their direct payments to physicians. While these entities serve as payment blind spots, which can easily be abused by companies, doctors also devised ways to, if not erase, but blur the direct nature of payments from pharmaceutical companies. Disclosing payments is largely (although not entirely) the duty of pharmaceutical companies. Most of this is done via the basis of individual physician names, and so for doctors, the goal is not necessarily to hide company payments, but make it less apparent that they as individuals are receiving the money, thereby confounding direct links to industry. In the following I shall discuss how regulatory loopholes in transparency regulation are used to both hide direct payments to physicians, as well as confound the direct link between a payment and an individual physician.

9.7.1. HIDING PAYMENTS

Pharmaceutical company respondents in the Netherlands and Hungary did not directly implicate themselves, but confirmed the regulatory loophole, that middlemen service provides such as clinical research organizations (CROs) and conference organization service providers are not covered by transparency requirements, and as such constitute indirect financial relationships whereby doctors receive payments through these companies [NLPH04], [HUPA02].

"*Often the CRO works on the assignments and is funded by the industry, (but) a company between (the pharmaceutical company and individual doctor) falls outside (of the regulations)*." [NLPA01].

Using the CRO as an example, this respondent from the Dutch pharmaceutical industry self-regulatory body explained how the scope of transparency regulation extending only to companies with medicines on the market leaves out companies that are hired to execute tasks on behalf of companies, such as the running of clinical trials. The outsourcing of certain industry tasks (Chapter 6) is becoming more common, especially for industry cost reduction and trial expediency reasons. The CROs are a good example of companies serving the needs of industry, but are not in the business of actually selling drugs. In effect a company can hire a CRO which ultimately ends up paying the doctor for services rendered (in this case clinical trial services). These payments are not entered into the disclosure reports, because essentially, the doctors are not paid directly by a pharmaceutical company. While one can argue that transparency reports do not disclose amounts spent on clinical trials in general (being that money spent on trials is not promotion) and so payments would effectively remain undisclosed even if trial services were paid by an authorization holder, CROs today do much more than simply run clinical trials. CROs now take part in many commercial advisory services, selling branding strategies, and advice on market positioning of products[64]. As to potentially hiding financial ties with physicians for services other than clinical trials, research could benefit from further investigation (Dehue, 2010). During fieldwork in Hungary, however, the above accounts fortify the potential of CROs as direct-to-physician payment cover-up entities, something confirmed by Dutch respondents.

A similar situation arises with Biotechnology companies which do not necessarily hold marketing authorization for medication, since they are located in the preclinical stages of drug development. Sometimes before an interview I would check the name of the doctor in the transparency register, and if pertinent, would confront the respondent

[64] CRO Quintiles (one of the largest CRO companies in the world) merged with IMS Health in 2016, and since November 2017 is known as IQVIA (www.iquivia.com), specializing in service provision across the board: medical research and development, real-world value outcomes, commercialization, and technology.

with the data to discuss the nature (and perhaps rationalizations) of their own financial ties. What I did not expect was the following statement:

"*And by the way these amounts are of course a fraction of the money that I really make. Because there are lots of biotech companies that I have positions in, but because they have no marketable drugs they don't have to put anything in the transparency register*." [NLDR12].

Many biotech companies are funded by venture capital, so not all income comes from big pharma. However, it becomes interesting when pharmaceutical companies decide to invest in a biotech company, without actually owning it. This presents a possible mode of concealing direct payments to physicians, as stated by another Dutch physician: "*The rule is that only those companies have to disclose that have a product in the pipeline, so if they are selling a product. I know that biotech companies don't have to disclose their payments*" [NLDR18]. Biotech companies as a means of hiding, or not disclosing entirely how much money doctors receive from industry, came up only in the Netherlands, which I attribute to what I stated in Chapter 6, namely that the biotech industry is not yet as prolific in Hungary as it is in the Netherlands. Hungarian research institutions choose PPPs and grants for research instead of fully spinning out a private company; however, it will be interesting to assess biotech company development in the future.

Additional service providers such as conference or CME organizers/catering companies also present an opportune third part non-transparent means of paying medical professionals, since these companies are active in providing services in the post-authorization stages. In The Netherlands, a physician [NLDR17] referred to marketing or PR firms being paid by the industry to participate in continuing medical education event organization and advertising, and invited physicians won't be paid directly by the company, but by the PR or marketing company, once again making the payment indirect through a middleman and circumventing disclosure requirements. Dutch self-regulatory experts confirmed this practice.

"*All these bypasses (come from) these independent organizations for organizing congresses sponsored by industry but (the independent organization) pays the doctor and these relations are not in there because then there is no relation between one (pharmaceutical) company and the person. Maybe this organization gets money from 5 companies and pays one person, but then (how do you know) which company the doctor got money from?*" ([NLPA01].

In Hungary it was a general problem at the time I conducted interviews, that almost no one apart from respondents from pharmaceutical companies knew what the EFPIA transparency register was or what it meant, even though EFPIA data collection had begun the year I conducted fieldwork. Sometimes even industry-connected respondents were lost as to what the EFPIA regulations were, such as when I asked a CRO manager, formerly a practicing physician, about the new regulations, to which

he answered "*No, but it seems like I'll learn something new today*" [HUPH11]. Doctors themselves were almost completely oblivious, some perhaps remembering they had to sign some kind of data release consent form, but could not explain why that was necessary [HUDR10]. As such, siphoning payments through conference organizations was not something that came up during interviews themselves, but something I looked into separately when this method of hiding payments to physicians presented itself during fieldwork in the Netherlands.

Regarding CMEs organized at teaching hospitals specifically (those that should be independent from industry), the website OFTEX.hu offers an overview, being a central database that lists all CMEs in Hungary for every half year. The sheer amount of CMEs per year is enormous (1643 CMEs in 2017, 1793 CMEs in 2016)[65], and being limited in time, a complete analysis could not be made. Nevertheless, an overview of the database which provides information as to the organizing partner reveals most are organized by the teaching hospital or medical associations (their financial relationships discussed in the Chapter 8). Some of the CME sponsors are pharmaceutical companies themselves (Johnson and Johnson, Boeringer Ingelheim, and EGIS appear as organizers for a few CMEs held in 2017). However, interesting for this analysis is that there are also very many limited liability (Ltd) companies which appear as event organizers, and a Google search will show most of them to be medical conference PR and event management firms – like the company "Congressline", an organizer of many conferences and CMEs in Budapest. Looking at the Congressline website and randomly selecting a CME like the Hungarian Gynaecological Society[66] 4th Annual Professional Continuing Medical Education Event[67], among the main sponsors are the pharmaceutical giants: Roche, Novartis Sandoz, and Merck. Of course, this only provides evidence that the CME itself was sponsored by industry, already problematic from a CME independence perspective, but not yet evidence of money being hidden. One must take to looking at the websites of event organizers themselves, where many of these medical event organizers have a tab on their websites labelled "references". Under this tab, one will either find a list of successful CMEs organized by the event organizer (and any link to pharmaceutical companies made apparent by scouring the website of the CME itself). Other event organizers, under the same tab will not list events, but partnering companies, and so the link is more visible. Such as "Convention Medical Training"[68], and "Promenade Publishing House"[69] (which appear in the OFTEX database as organisers of numerous CMEs) display their "partners" and "references" openly on their websites, listing almost all innovative pharmaceutical companies subject to disclosure regulations. This information, although not conclusive, still illustrates the many third party services which work with

[65]Hungarian Continuing Medical Education database: OFTEX: https://ww.oftex.hu
[66] See table on payments to Hungarian medical Associations: Hungarian Gynaecological Society received 86,614HUF of which 100% went to sponsoring of a medical educational event.
[67] Magyar Nőorvos Társaság IV.Szakmai Továbbképző Tanfolyama, 2017 Május 26-27, Siófok, Hotel Azúr: http://www.congressline.hu/mnt2017/szakmai-kiallitas.php
[68] http://cmt.info.hu/Nyitooldal
[69] http://www.promenade.hu/referenciak

pharmaceutical companies and are in the business of medical CME organization, making it highly probable that companies use these middlemen to hide direct payments to doctors as is the case in the Netherlands.

In Hungary, the practice of disclosing payments to doctors is in its first steps, and as I mentioned, during fieldwork the lack of knowledge among practicing physicians about the disclosure requirement in general meant that the question of hiding payments to physicians intentionally via third party service providers did not come up at all. This is not surprising because up until payments are actually disclosed, and patients or the public can access and critique these financial ties, the desire to "hide" payments does not make any sense. Now that the payments are accessible, it must remain to be seen what (if any criticism) will ensue. Asking former respondents about any effects or consequences of the transparency reports, one physician answered my inquiry by saying that "*No one cares. (At the moment) we don't even know if the hospital will exist tomorrow, or whether we will still have a job, or colleagues or even patients. If you ask 100 doctors, 99 won't know what the EFPIA disclosures are*" [HUDR10], while another physician and member of a clinical trial approval committee, simply had no idea, and even asked me to explain what these disclosures are and where to find them [HUREG02].

As to revealing regulatory loophole abuse and hidden payment mechanisms, the Dutch media is an important actor, given that the subject of pharmaceutical industry influence in the medical profession, and the ethicalities of these relationships can be said to be a reoccurring hot topic for the news. "*We need journalists, to ensure what payments are in the register and which are not*" said the one respondent, rendering the task of locating deficiencies to people not necessarily part of the self-regulatory structure, which is slightly ironic [NLPA01]. Nevertheless, reporters from the Netherlands published an article in *de Volkskrant* newspaper, describing how many of the payments form pharmaceutical companies are not in the transparency register thanks to a "network of commercial agencies" (Kreling & de Visser, 2016) acting as payment middlemen. The image below shows exactly how individual payments are concealed through third party service providers.

Image source: Tom Kreling and Ellen de Visser (2016) De verborgen betalingen van farmaceuten. *De Volkskrant*, 14 mei

The fact that this is a problem that needs to be addressed is validated by the fact that in the Netherlands, where transparency has been the norm since 2012, the CGR has already published its intentions to investigate and devise means of including these indirect financial transactions within the disclosure database (CGR website). However, the question as to how this will be done specifically will only become apparent in 2018 [NLPA01], [NLPA03].

9.7.2. CONFOUNDING PAYMENTS

If not to hide completely, but to confound financial relationships with individual doctors, foundations, organizations, and private companies are great ways to divert attention from direct payments to physicians. Industry payments to healthcare organizations are also subject to transparency obligations. HCOs are defined by EFPIA as "Any legal person (i) that is a healthcare, medical or scientific association or organisation (irrespective of the legal or organisational form) such as a hospital, clinic, foundation, university or other teaching institution whose business address, place of incorporation or primary place of operation is in Europe or (ii) through which one or more HCPs provide services" (EFPIA Disclosure Code, Schedule 1). A Doctor may create a foundation or Ltd company, a private enterprise[70] which is a legal entity owned by a doctor or many doctors. These legal entities appear in the transparency registers, however any link between a legal entity and a medical professional is quite difficult to make, since it is not necessarily general knowledge as to whether your doctor has

[70] Besloten Vennootschap (NL), Egyéni Vállakozó (HUN)

his/her own HCO. In the Netherlands, journalists from *de Volkskrant* and the radio channel *Argos* were the first to tell me about these Ltd. companies, and how difficult it is to trace back whether a doctor might have a company or a foundation of his/her own – since HCO disclosures are completely separate from those of HCPs, patients for whose benefit transparency registers are claimed to have been created, are more likely to search for the name of their doctors in these transparency databases. Payments to HCOs confound direct payments, and make it more difficult, if not impossible, for patients to assess exactly how much money their physician gets. While Doctor X may have received a certain amount of money for various services rendered, or hospitality costs paid, the same Dr X may have shares in a company, or may be the chairman of a medical foundation also the recipient of industry money. This is what is not hidden, but made all the more difficult to assess, which becomes apparent when trying to search the databases or disclosure reports.

In the Netherlands, to search for payments to HCPs, a patient must first find the licence number (BIG[71] Number) of the doctor in a separate register (BIG register) and then type the licence number into the transparency database and enter a captcha code to see the payments. For Ltd. companies, the patient must first know the name of the company, and search the Dutch Chamber of Commerce (Kamer van Koophandel) website for the company's KvK number. Then the process of entering the KvK number and a captcha code begins again. In Hungary there is no centralized database, but disclosures are made public via complete lists of HCOs and HCP names on company websites. This makes the process simpler in that all HCP and HCO payments by one company are disclosed together in a list. However, there are currently 26 companies obligated to provide HCP/HCO disclosures, meaning that a patient would have to search across 26 company websites (minimum, because for example Novartis has its own disclosures, but so do its subsidiaries, Novartis-Sandoz, and Novartis-Alcon, which provide disclosure reports, but are not listed as separate companies on the AIPM website). A disclosure report can be anywhere between 1-2 pages (IBSA, Biogen) to 58-66 pages (Sanofi, Lilly), and can only be searched manually. Thus not only are HCPs are difficult to find, but Ltd. companies even more so.

In the Netherlands, this form of evading disclosing payments under the name of the physician personally came up when I asked a Dutch specialist about the successfulness of the transparency obligations. His reaction was that it was useless because methods like Ltd. companies were a relatively easy method of confounding.

"*There are many ways around (transparency). You can actually start with 3 or 4 people; you can start a teaching foundation, and the money goes to the foundation and doesn't (seem) to go (directly) to the doctor*." [NLDR13].

How this affects the complete nature of individual physician payment disclosures was detailed by a Dutch physician, who claimed that about 80% of his payments were not

[71] Beroepen in de individuele gezondheidszorg (individual occupational registration number)

in the register. As to whether this was specific to him, he said that he had no way of knowing, but that he knew of many colleagues who had no payments disclosed at all even though he knew that they worked closely with pharmaceutical companies [NLDR18], insinuating that these payments might be disclosed as payments via Ltd entities.

Hungarian physicians, not in relation to the transparency obligations (due to lack of awareness about its existence), but in discussions about accepting payments from sales representatives directly, stated that while they did not accept any type of financial compensation personally, payments to their foundation were accepted [HUDR09], [HUDR10], making this not just a Dutch phenomenon. Hungarian physicians do in fact run private practices more commonly than the Dutch, and these individual enterprises are sometimes not given abstract names, but are simply named after the doctor to whom the enterprise belongs. These "HCOs" are simply called Dr XZ Ltd., and sometimes both the doctor and his/her Ltd. appear in the same list with only slight variation in operational address such as: HCP: Dr P(…) Gy(…) (Békéscsaba) 20,000 HUF registration fees and HCO: Dr P(…) Gy(…) Ltd. (Békéscsaba) 60,000HUF for services provided (Bayer disclosure report Hungary, 2016).[72]

One other mode of confounding is related to the regulatory limitations, which could provide another means of transparency evasion by physicians. In the Netherlands disclosure of financial payments to HCOs and HCPs is mandatory, and done by the companies themselves, however only for companies that are based in the country.

"*Reporting is a dual responsibility, it has been agreed and also put in the code that it's expected that the pharmaceutical company will do the reporting if we have the contract directly with the HCP on a local level. And it's also expected that the contract with the HCP and the pharmaceutical company is done on a global level as well, let's say the United States contracts the HCP and the payment comes from the United States, then the HCP is responsible for reporting the payment himself. That is the expectation*." [NLPH04].

Payments by foreign companies, or payments received from the parent company (e.g. AstraZeneca UK) would have to be reported by the doctor him/herself, which many might simply not do, overlook, or report it on other websites such as a university hospital declaration of funding. The multiple other platforms of financial disclosure (university, publications, and presentations) may easily lead to lack of oversight, since all of this comes with added administration, and thus added possibility of forgetfulness, or in a worst case scenario, intentional non-disclosure.

"*I can't remember, but if I have a scientific paper I want to publish, I always have to disclose my conflicts of interests. And every time, I have to think: "Oh what are my conflicts", and sometimes I forgot one or they as: "what is you conflict with this*

[72] http://transparency.bayer.com/omr/online/2016/HU/Transparency_Report_HU_2016_en.pdf

product?" and every paper is asking different questions about your conflict of interests. I'm not sure I'm in an official register; although I had to fill in some data about this." [NLDR18].

Similarly, the novelty of transparency introduction has also worn off, causing physicians to forget to update their profiles as frequently as they used to at the time of the transparency database implementation [NLEX01]; but forgetfulness can also be a farce such as a Dutch physician stating that you can always use the excuse of forgetfulness that a company "*helped you out*" with something financially [NLDR13].

In Hungary, transparency is not mandatory in the sense that a doctor's explicit consent must be given to have payments disclosed under his/her name. If such consent is not obtained, the payments will still be disclosed but as an aggregate amount in one lump sum, and allocate how many single payments make up this total, as well as what percentage of all paid doctors did not give consent. Asking doctors whether they would agree to have their payments disclosed, I received mixed answers, many agreeing to the idea behind transparency as a means to promote independence and reduce potential conflict of interest, but simultaneously indignant about the violation of personal dignity, or an excuse used to direct scrutiny towards individuals, instead of actually changing the system of financial dependency [HUDR20], [HUPH11]. "*Who would be so stupid as to give consent?*" said a Hungarian GP [HUDR25]. While some see transparency as a step to maintaining trust, other respondents felt that this is just another excuse to blame doctors, on top of informal payments. "Stupidity" of disclosure came up in the Netherlands, as to my question of whether doctors are comfortable in disclosing their payments or not. A Dutch gynaecologist stated that it borders on stupidity to "*disclose all your secrets*" to others, because this creates misplaced judgement [NLDR18]. A cardiologist then explained how transparency of payments by a company renders an automatic assumption of manipulation. In the end, if he receives funding from company X, his prescription of the drug manufactured by company X is treated as a product of industry manipulation even if his professional opinion is such that the drug is the best on the market [NLDR12]. Transparency itself, touted as the solution to minimizing undue influence of industry by opening up payment amounts to patients and the public, supposedly aims to increase trust via openness, and enable patients to make decisions about whether or not they can trust the independence of their doctor. This, however, bears little necessity, because as Freidson (1970, p. 22) states, what patients ask of doctors is "Doctor, do something!" not "tell me if this is true or not" – thus implying that the patient is generally less concerned with how much payment a doctor receives, as long as what the doctor does actually ends up in the patient feeling better. Sismondo (2013) states that in fact transparency does little to change the culture of receiving payments from industry, and I feel that this analysis shows exactly that: the culture of relying on industry money and access to medical knowledge has not changed with transparency. The only thing that has changed, is devising new (hidden or confounded) means of continuing a normalized practice.

9.8. EFFECTS ON PRESCRIPTION PRACTICES: EXPLANATIONS FROM THE FIELD

Last but not least, the question of influencing prescribing habits of doctors must be addressed, ultimately because as (critical) patients ourselves, the core problematic is whether or not our doctors are still keeping our best interests at heart. Much research has been done to excavate correlations linking advertising exposure of physicians and representative visit frequency. Other studies locate financial dependency and the promise of future financial support as the driver behind prescription loyalty to a specific company's drug. Doctors do not intentionally harm their patients by prescribing wrong or knowingly harmful medication. Those that do are "*psychopaths*" [HUDR25], or at the very least can be called criminals. A superficial understanding of undue industry influence by way of creating corrupt doctors who prescribes deadly medicines purposefully is an inaccurate and doltish conclusion to draw, but one that is inevitable when we assume corruption and undue influence to be a product of a morally bankrupt individual. In this thesis the intention has been to locate corruption as being a product of institutional characteristics of the medical profession – characteristics that enable relationships with industry to divert the profession of medicine from its institutional purpose – requiring identification of contextual and professional factors that enable influence, and limit the capacities of medical professionals to be a countervailing power to pharmaceutical companies. It is in this light that doctors' prescribing decisions shall be addressed.

Interview questions aimed to discuss whether doctors trusted pharmaceutical companies and whether that trust (or lack thereof) translates into decisions in the clinic, whether industry scandals have any effect on how they view the criminogenic company wares, asking doctors in both countries to explain to me what influenced their prescribing habits, what made them choose to use one drug over the other. Patient's needs, medical guidelines, and trust in certain medication based on positive feedback from patients and colleagues were dominant factors for treatment decisions, as well as cost reduction considerations. Other less obvious, but just as vital components of prescription decisions, were located in medicine characteristics, and market availability: what exactly the drug does, how many similar drugs were available, and whether or not to trust generic medication or its brand name counterpart. It is these latter considerations that are pertinent to this thesis and important in that they reflect that treatment decisions, however closely related to the individual patient qualities, are still made with consideration to larger pharmaceutical market factors, and these are what I will discuss, since they are closely linked to phenomena I described in previous chapters.

Reiterating the "*formal position*" of the Dutch Medicines Regulatory Authority – and one that takes the European Medicines Agency as its policy guide [NLREG01] – having many products that essentially do the same thing but vary slightly serve the consensus that disease is individual, and variety in one treatment area ensures that if a

patient does not react well to e.g. beta-blocker A, then perhaps beta-blocker B might be a better fit. This formal position is not just that of the Dutch MEB, but a general medicines authorization policy embodied in the ICH GCP and medicines authorization procedures in which proving that a medicine submitted for authorization (should ideally but) is not formally required to prove superiority against medicines already on the market. What this "formal position" and general authorization policy does not address, however, is that this type of approach may cause market saturation, which may be a good thing from the consumer choice abundance perspective, but which has very interesting unintended consequences for prescription decisions in the clinic.

Market saturation is used here to describe the situation wherein multiple drugs are available for the treatment of one specific ailment. This does not mean that there is no more space for innovation, that a disease should be seen as "*solved*" [NLPH06] because there are many drugs available, nor that there is no need for the development of another painkiller, another SSRI, another statin, another cough medication, etc. There is of course always room for development, side effect reduction, added efficacy, safety, or convenience in administration of the pharmaceutical product. However, in Chapter 7, I already discussed the enormous problem caused by no official regulatory requirement to prove superiority of a new drug in relation what is already on the market – statements from doctors illustrating that while they may know of many existing drugs that could be prescribed for a disease, they cannot know which one is the best, since all are tested against placebos. Thus we simply have a market in which there are many drugs for one condition which, for lack of clinical evidence are assumed to basically do the same thing, at least looking at the interpretations of practicing physicians. The following quote specifies how a saturated market affects the treatment decisions of doctors.

"*Let's take the example of multiple myeloma patients, who've had their cancers spread to the bone. One of the treatments for this is Zoledronic Acid. When the patent for the brand name expired, suddenly many generic and other brands became available, and now there are say 11 companies manufacturing the same drug. Since they all have the same (active) ingredients, it makes no difference to me or the patient which drug is prescribed.*" [HUDR10].

In the previous sections I discussed the phenomenon of specialist override, and how the status hierarchy of specialist versus GP provides a possible explanation of industry tendencies to financially engage with specialists more assiduously, as well as with specialists in certain fields, and provided the examples of Panto/Ome/Esomeprazole as an example of specialist preference (and override) of prescribing the brand name over the generic. In this example, one step further than brand preference is the explanation as to the rationale behind preference, which is located in the market saturation argument. What does it matter which drug I prescribe if they are all the same? In this scenario the decision to prescribe one brand of the same drug over another is a cost-benefit calculation, enabled by the fact that the market is full of

medicines that do the same thing. This same respondent went on to say, that since all drugs are the same, "*(…) who am I to tell a colleague to prescribe one drug over another, especially if that colleague receives funding from a particular company?*" [HUDR10]. When all treatments are the same, this leaves room for other non-medical qualities to be taken into consideration. Making sure to cross reference the claim of indifference by similarity, I asked pharmacists in both countries to verify drug similarity, which they did. A Dutch pharmacist reiterated that the market for some drugs was full, and so it made little difference if doctors were to prescribe one brand over another. A Hungarian pharmacist stated the same thing, saying that drugs today are so similar in dosage, strength, and efficacy, that in essence prescription decisions can certainly be based on supra-medical considerations, such as relationships with sales representatives, or financial compensation for CMEs. In conclusion, thanks to market saturation, this type of decision making "*fits into normal behaviour*" [HUPH02].

The normality, and hence acceptability of supra-medical incentive based decision-making, was described by a Dutch specialist in the context of whether financially-motivated prescribing could be seen as corruption – especially since Dutch doctors consider payment-per-prescription to be outright "*bribery*" [NLDR12].

"*I am not sure how much corruption is going on, I could imagine though that if there are two similar products with similar patient benefit (…), value per cost, I would advise the hospital to take the one from the company that I work best with. (The company) that funded two of my studies. But by doing that I am not harming the patient. So I have no problem with that. So say there are two companies both with identical products with identical price but one product pays for the trainings we do and helps us with surgeon resident training program and funds that, then I will say 'Oh well the (drugs) are the same but I will go for (prescribe) that company's medicine because we have the best relationship with them". I don't think that's corruption personally.*" [NLDR10].

While pay-per-prescription is considered to be corruption among Dutch doctors, exhibiting prescription preference for payments to the hospital to run physician training programs, or to finance research, is not considered bribery. It is enlightening to read this account because it reflects again the association of improper financial dependency, bribery, and corruption to manifest in the mind and action of individuals. When payments are made to institutions, foundations, or organizations i.e. collectives, then accusations of bribery and corruption tend to dissipate. Ironically, the decision process of drug preference based on financial incentives is the same, while the ethicality of this is supported by reference to a saturated market.

I had many an informal discussion with colleagues, friends, and family to assess how they see this reasoning as patients themselves. I admit to having difficulty in challenging these doctors, as did those with whom I raised this scenario as a hypothetical, because in essence if the medication is the same, does it really make a

difference to me which one the doctor prescribes? If I'm treated well, do I really care that the drug which saved my health also produced some financial gain for my doctor? In a very candid interview, however, a Hungarian Nephrologist revealed how the "what does it matter" rational is not completely without harm.

"*The situation is very delicate. If I know that I help the patient with drug A and also with drug B, but one drug helps the patient ever so slightly more, say the chances of the patient being cured with the use of drug A is 65%, and 75% with the use of drug B, these are small differences, but then someone says, you can get 150,000HUF if you prescribe drug B, and 1.5 million HUF if you prescribe drug A. I would say I always prescribe the drug with the higher efficacy percentage, but I think that many people are 'holier-than-thou' and they will find an excuse or a medical reason to validate and persuade him/herself that the more lucrative drug is truly the best decision.*" [HUDR09].

This is an extreme account not because of rarity, but rather because it would presume that doctors know precisely the percentage of variation in efficacy of drugs, which due to continued clinical testing against placebos, as well as the inability to disseminate, and compare statistical significances in the medical literature on a daily basis, were challenged in this analysis. However, this only solves the question of intentionality. The evidence that all drugs are the same is not a definite given, but a regulatory policy that only considers safety and efficacy over superiority, which supports a presumption of equality. In conclusion, the problem is not that harmful or less efficacious drugs are being prescribed by a Mr Hyde. It is rather that Dr Jekyll is operating in a market environment that enables profit-based decisions to drive prescribing decisions, eradicating the need to remain financially independent, further normalizing industry-medicine relationships and, more importantly, industry influence in clinical decision-making.

9.9. CONCLUSION

Corporate crime research, its uptake by the media, and the awareness among patients and NGOs regarding industry-medicine financial relationships, has had immense regulatory and industry policy impact: its main product being increased transparency requirements regarding financial payments by industry to physicians. Again, this all began in America with the introduction of the Physician Sunshine Act, which provided an example to follow in the Netherlands, when former Minister of Health, Abraham Klink, initiated implementation of similar transparency requirements for Dutch physicians and healthcare organizations. Europe, and thus Hungary, followed suit in 2014 after the adoption of the EFPIA Transparency Code. Corporate compliance officers stepped into their own golden age in the late 1990s and early 2000s (Baer, 2009). In fact regulation, its promotion and development is very much "in" and will continue to be a new rhetoric entering the conversation as a means of regaining Big Pharma's lost trust (Parker, 2007). Solace is found in increased regulation and severity

of punishment, despite criminology having already accepted that regulation alone does not decrease crime, and severity does not deter (Lanier & Stuart, 2010; Braithwaite, 1989). In fact, increased regulation may spur individuals to find "new ways of committing old crimes" (Nelken, 2012, p. 630). Regulation is sadly slow, and superficial, shifting focus on medical professionals as to ties with industry, naming and shaming them into independence without taking the professional requirements of continuing education, time limitations of full-time clinical practice, and the costs of education into context. Keeping goals high while cutting away at the means of achieving them is what leads doctors to devise modes of hiding, confounding and/or normalizing ties with industry.

CHAPTER 10: CONCLUSION

This thesis has provided a comprehensive and in-depth analysis of relationships between the pharmaceutical industry and the medical profession, examining undue industry influence exerted within the knowledge production, interpretation, and application activities of professional medical conduct in Hungary and the Netherlands. The goal of this thesis has been to apply the theory of institutional corruption to the industry corruption of medicine – the systematic and strategic influence, which is currently legal and ethical, which undermines the institution's effectiveness, by weakening its ability to achieve its purpose, resulting in the loss of the institution's inherent trustworthiness (Lessing, 2013). Through application, the question of whether the profession of medicine has become institutionally corrupted was assessed, and if so, how has it been systematically, strategically, legally, and ethically weakened in achieving its institutional purpose.

The purpose of medicine is to promote the health and well-being of society, according to the principles of beneficence, non-maleficence, respect for patient autonomy, and justice. Despite criticisms as to its application outside of its original use (the institutional corruption of the American Congress In: Newhouse, 2014; Dawood, 2014) I have argued that institutional corruption theory is applicable to the analysis of industry-medicine relationships and the medical profession, given that the professional mandate to provide healthcare is a fiduciary duty. The institutional purpose of medicine, using Giddens' (1984) definition of institutions as societal systems reproduced over space and time, is the promotion of health, but cannot be studied in this abstract form. Provided in Chapter 3 was a conceptual framework within which institutional corruption can be studied, establishing that professional trust (and fiduciary obligation) is based in the conditionally determinant qualities of authority maintained by autonomy of medical practice. The concept of medical practice (as a system reproduced) in this thesis does not limit itself to clinical practice, but envelops the knowledge production, interpretation, and application activities of the medical profession. These were allocated as macro, meso, and micro levels of autonomy in theory, and manifest in medical research and development, evidence-based medicine, and clinical practice respectively.

A problem of conclusion emerges. Institutional corruption of the medical profession would be established (as by the dictates of Lessing's general theory) upon some indication that the purpose of the institution remains partially or wholly unattained, and that it has consequently lost its inherent trustworthiness. Patients are still getting better, and doctors are still among the most trusted professions. The logical conclusion would be to establish that the institutional corruption of medicine has not occurred. What of the cases and examples of undue influence provided in the cases analysed? One may interpret these as lucky coincidences which neatly fall within Nelken's (2012) proposition that "scandals" or instances of unethical or deviant conduct are not representative of normal functioning, but simply deviant conduct redefined as normal

behaviour within the context of medical practice, giving basis to an approach of a normalized, institutionalized culture of deviance which provides rationalizations for doctors to pursue financial incentives in the course of their occupation instead of societal interests – an approach I have argued against.

I will, however, argue that institutional corruption has befallen the profession of medicine, and that these scandals are not just (happy) coincidences that (luckily) prove a momentary point of individual deviance institutionally rationalized. I will indulge in one final argument, one that assesses institutional corruption as a "problem of institutional design" (Oliveira, 2014). This argument is important not only for substantiating the theory of institutional corruption, but also for a claim that purports institutional corruption to be present in both countries of analysis, with no substantial variation in descriptions of how the pharmaceutical industry is corrupting the institution of medicine, or why it is successful in doing so. The majority of literature presented in Chapter 2 originates from, or analysed cases in, the US. However, I have found that industry influence so described manifests itself in Hungary and the Netherlands. I believe that this can be explained by, firstly, the international nature of pharmaceutical companies, and their market activities, but also by the incredible harmonization that has befallen both the pharmaceutical product lifecycle (ICH GCP, 1996), and the centralization and harmonization of drug regulation and approval (EMA). The European Innovative Medicines Initiative (IMI) promotes PPPs and valorisation of academic knowledge (actively pursuing a Bayh-Dole-type exploitation of research) as well as the practice and standardization of the medical profession as both regards ethical practice (WMA Declaration of Geneva, 1948) as well as the internationalization of medical research and knowledge (harmonization of clinical guidelines). This lays the ground for assertions as to congruence in the organization of the system of pharmaceutical product delivery, the professional practice of western medicine, as well as the role of industry in medicine.

During fieldwork, sometimes after rich discussions as to how industry may influence medical practice generally in the country of analysis, or colleagues specifically, respondents in both Hungary and the Netherlands regardless of sector, concluded that pharmaceutical industry influence was "*an American problem*" [HUDR10], [NLDR18]. Respondents did not claim variation of influence (intention of industry to influence), or degree of susceptibility to industry influence as varying between European Union member states, not even in the axiomatic form of Eastern European corruption versus Western European wholesomeness (TI CPI, 2016). Although Hungarian respondents commonly referred to low medical salaries as rationalization for necessary industry patronage, when asking them whether this made industry influence more prolific in Hungary, respondents dismissed the proposition altogether, claiming that the only difference is that susceptibility only differs in price, and not integrity.

Differences between the two countries under analysis emerged in 3 areas: (1) University spin-out/off companies, academic technology transfer, and biotech start-up

endeavours were more common in the Netherlands than in Hungary. This is supported by the literature and studies in Chapter 6, as well as assessment of the accounts from the field: in the Netherlands, academic and research institutions featuring commonly in discussions, whereas in Hungary, to a substantially lesser degree. In Hungary PPPs are suggested to be the preferred industry-medical research interaction, although the literature suggests that this is a delay in university economic presence only expected in a country where capitalism is but a couple of decades old, proposing this difference to be a question of time to catch up.

(2) Low salaries of Hungarian doctors presented another difference between the economic statuses of physicians between the two countries. Pay-per-prescription practices were described as being a result of low wages in Hungary, possibly bolstered by a tradition of accepting informal payments, however the degree of susceptibility or dependence on industry funding was not quoted as diverging. Legal differences are substantially limited to industry self-regulatory codes, such as the financial caps for industry funding of hospitality costs in the Netherlands and analysis suggests only formal differentiation, as Dutch physicians reiterated similar problems of CME cost coverage, abandonment of government in research and education funding, and the necessity of medical quality assurance made possible by pharmaceutical industry funding (Chapter 6, 8 & 9).

(3) A final major difference between the two countries is the implementation, and formal execution of pharmaceutical transfer of value to HCPs and HCOs. In the Netherlands, early adoption of transparency has made disclosure a normal practice among doctors, while in Hungary its novelty requires comprehension, acceptance, but most pressingly, awareness among physicians and patients. The Dutch CGR has undoubtedly achieved awareness, and fashioned an accessible and relatively easy to use central database for the curious patient. In Hungary, disclosure was not a national initiative as in the Netherlands, but the result of simply implementing EFPIA regulation: voluntary disclosure, executed in such a complicated manner (a search would require a patient to sift through the reports of 2015 and 2016, currently around 900 pages of PDF and JPEG format files) that to describe its worth to the patient would require all the possible synonyms for useless. Apart from differences in time of implementation, mode, and accessibility issues, analysis revealed the ways in which transparency may be evaded (Chapter 9) using examples and testimonies predominantly from the Netherlands. I also included some suggestive indication that hiding and confounding payments to doctors is not only a characteristic of the Netherlands, but also quite possible in Hungary. The fact that until 2014, there was no transparency at all, simply means that such concealment and confounding were not necessary. Only now, and in ensuing years can we fully assess whether this will occur in Hungary.

These differences are acknowledged, yet they do not implicate the validity of assertions that institutional corruption of medicine is a product of institutional design. Although this analysis was executed in two European Union member states, global

exportation of the Bayh-Dole Act, EU-wide policy endorsement of industry funding of translational research, harmonization and internationalization of the pharmaceutical product delivery chain, the phases of clinical testing, the standards and requirements for regulatory approval across US, EU and Japan, mutual recognition of national regulatory approval in the EU, the synthesis of US and EU pharmaceutical markets, the globalization of clinical trials, international harmonization of clinical guidelines and standardization of medical practice embodied in EBM, render this analysis an important consideration for an international context. Oliveira (2014) suggests that the nature of institutional corruption as being *systematic and strategic influence* that is currently *legal and ethical* already renders it an institutional design problem, one that is being internationally harmonized. "Even perfect execution" as following clinical trial protocols, achieving efficient translation of data into EBM, and application in practice "would not achieve desired goals" (Oliveira, 2014, p. 15) i.e. precision of technical process (instrumentalism) does not substitute for the ethicality of conduct or autonomy in decision-making.

Not a new argument, but an attempt to validate the generalizability of institutional corruption theory, Oliveira (2014) suggests that to qualify institutional *purpose* as the baseline from which deviation verifies institutional corruption is far too abstract a concept for methodological examination. Institutional purposes may be immortalized in text but a purpose is achieved via human action, something that purpose does not define. Take the example of a dentist and a decaying tooth. Although the purpose of dental intervention is the promotion of health i.e. removal of the caries tooth, achievement of the purpose would legitimize removal with a wrench, and the use of whiskey as an anaesthetic.

> "It is in the formulation of specific goals and the definition of goal achieving behaviour that we may begin to decipher how a purpose should be achieved. The analyst observes only the achievement of goals, but wants to make claims about the purpose; in this sense, the analyst is interpreting goals from the ground up, verifying their compatibility with the purpose; it is a process of synthesis, of combining the multiple specific goals to evaluate if the purpose that this combination implies is the same as the institutional purpose" (Oliveira, 2014, p. 14).

The multiplicity of goals is embodied again in Shapiro's (1990) description of goal attainment in complex societies, where principal-agent relationships are born as a mode of coping with division of knowledge and capabilities, providing the rationale behind the increased role of industry in medical practice – the relationship itself enabling goal attainment. The purpose of healthcare provision within the paradigm of medical care with pharmaceutical products is thus achieved by breaking down this purpose into defined goals of chronological sequence, standard operating procedures, as reflected by the medicines delivery chain – knowledge production (R&D), knowledge interpretation (EBM), and knowledge application (clinical practice). The decision to use forceps and anaesthetics instead of wrenches and whiskey in a dental

intervention, is defined by the principles of medicine embodied in the Hippocratic traditions of medical practice.

A focus on purpose achievement of an institution (whether or not patients are benefiting from treatment or not) would require the assessment of individual action that manifests an outcome in opposition to the purpose i.e. promotion of health versus detriment of health. This places the actions, decisions, and rationalizations of the individual as the unit of analysis. However, once again the argument of embeddedness (Granovetter, 1985), as does the theory of institutional corruption, dismisses individual culpability without blaming a distorted organizational culture for the normalization of deviance. Oliveira suggests that institutional corruption is not a problem of institutional performance but a problem of institutional design "in which the very design aimed at achieving the goal undermines its achievement" (Oliveira 2014, p. 16), and describes 3 mechanisms which induce institutional corruption: 1) the work breakdown structure, 2) motivating for the goal, and 3) formalization and communication. These mechanisms will be explained and applied to the data collected and described in this thesis.

10.1. INSTITUTIONAL CORRUPTION IN THE WORK BREAKDOWN STRUCTURE

The work breakdown structure refers to the process of translating an abstract institutional purpose into fathomable and executable goal attainment. The work breakdown structure (division of knowledge and labour) is created by breaking down institutional purpose into smaller "granular goals" (Oliveira, 2014, p. 17) – goals that the institutional members may comprehend, physically execute, and the achievement of which contributes to the achievement of the institutional purpose. To achieve a goal, one must be in possession of, or have access to the means (Merton, 1938), which Oliveira calls "adequate means-ends pairing" (2014, p. 18). Goal achievement must be preceded by means accomplishment. If only one means exists of goal achievement, individuals wanting to pursue granular goals by other means will not be able to do so, meaning that means attainment will consume the actions of the individual, replacing pursuance of granular goals with the pursuance of means attainment.

Institutional corruption as a result of means achievement over granular goal manifest in medical knowledge production in many ways. The institutional purpose of promoting health is realised in the granular goal of making drugs available to patients i.e. regulatory approval. The prerequisite means are the enormous financial resources needed for conducting clinical trials. Funding needs to be attracted which requires that the subject of research hold enough lucrative possibility to persuade pharmaceutical company investment. The pursuit of means, pursuing research that is financially attractive for investors, means the pursuit of financial investment trumps the goal of research dictated by patient needs. Similarly, the problem of CRO outsourcing, where the pursuit of maintaining the position of a research site and continued selection as such by CROs ensures attainment of means to participate in research and gain prowess,

provide patients with the medication they need, and ensure financial reward for doctors. The CRO presses upon doctors the protocols designed by the sponsoring company, adherence to instrumentalist qualities of clinical trial execution and research expedience manifest means accomplishment over critical clinical oversight, and allow biases in research to be overlooked in the desire to adhere to trial design. Inadequate means pairing also manifests in the CME system; the goal of medical associations in finding resources to maintain continuous training similarly shows means attainment surpass the goal of independent information sharing among colleagues. The accreditation system which is meant to be a sign of CME content quality, is less a measure of scientific credibility than it is a means – attaining credits to maintain medical licensure. Doctors' continued reliance on sales representatives follows an identical logic, detailers being a means of getting CME attendance funding, as well as an easily accessible means of self-education.

10.2. INSTITUTIONAL CORRUPTION IN GOAL MOTIVATION

Distinguished here are direct and indirect motivation for individuals to work towards the realization of a granular goal. Direct reward comes with personal gain from the accomplishment of a specific institutional goal, while indirect rewards are given for the individuals' contributions (work) to an organization indirectly related to the institutional goal achievement. Institutional corruption manifests when individuals are directed to work for defined rewards, which place the reward of achieving the granular goals or larger purpose of the institution second to what is won in an indirect reward system (Oliveira, 2014; see also Merton, 1938 self-contained reward system). This explanation bears some similarity to the previous section on means-ends pairing – the pursuit of a means eclipsing the pursuit of a goal. Oliveira describes performance measurement systems, qualitative output indicators, as "sabotaging the very goal it aims to promote" (2014, p. 21) such as CME credit attainment promoting quantity of education over quality.

Manifesting in medical research the birth of the enterprising university described how academic and research institutions are invested in turning a profit from the fruits of scholarly labour. Investment, royalties, or a financial stake in an innovation brings money, prowess and recognition to institutions, which inevitably leads to further investment. While researchers themselves may dream of accomplishing market success in a start-up or spin-out company, universities are now invested in researchers attracting investment. Translational research has surely thawed frozen science in the ivory tower, but the purpose of achieving socially available and applicable science has been turned to the pursuit of researching potentially lucrative instead of socially necessitated products. The same can be said for the KOL phenomenon, where status is no longer consummated in the professional prowess of peer acknowledgement, but by the recognition and financial reward received from pharmaceutical companies in the form of consultancy contracts and speaking invitations.

EBM is also a victim of both work breakdown structure, and goal motivation, since the requirement that all guidelines be based on clinical evidence abdicates considering the necessity of medicalization or pharmaceuticalization in patient care, focusing only upon what is concurred as scientific proof established by randomized control trials already biased by industry sponsors.

10.3. INSTITUTIONAL CORRUPTION IN FORMALIZATION AND COMMUNICATION

Finally, institutional corruption occurs when there is a gap between regulatory text and its communication towards the individuals and institutions that it regulates. Rules, regulations, and codes aimed at providing institutional members with pragmatic explanations of what is acceptable and legal, ethical behaviour in line with the achievement of the abstract organizational purpose is not communicated in an applicable fashion, or that the text itself reproduces ambiguities in interpretation of acceptable means for achieving institutional purpose. In this analysis ambiguities of means in achieving granular goals, and consequently institutional purpose, I found in varying modes of all the stages of medical practice, not limited to legal text, but also in interpretation of ethical duties of the profession. In medical R&D, helping patients was understood as linked to market access i.e. "*sellable*" [NLDR14], subsuming research to market potential was seen not as a loss of autonomy, but as a valid means of serving society. Similarly to the doctors who engage in research, and spend less time evaluating the nature of research (i.e. CRO made-to-order trials, or seeding trials), scrutiny is lost in the pursuit of means to contribute to medical knowledge production.

In medical knowledge interpretation, the same focus on technically sound evidence, as opposed to the evaluation of societally beneficial evidence, and the ever increasing standardization of medical practice, is the pursuance of scientific validation without considering issues of medicalization or pharmaceuticalization, which as shown, may lead to cases of treatment doctors themselves deem unnecessary for patients. KOLs who devise these guidelines, speak at conferences, and are paid to favour the employer's products see this not as "*pharma-whoring*" [NLDR12], [NLDR10] but as a deserved, and valid status, capitalizing on the ability to influence others.

Looking at specifically regulatory textual documents, the areas that are self-regulated reveal the gap between text and interpretation, such as the ambiguities surrounding the classification of medical CMEs. In practice, the accreditation system replaces or confounds any inspection as to the surety of absence of industry marketing or promotional tactics, rendering the regulatory distinction between ideally independent CMEs and less independent medical conferences ambiguous. The ambiguities are solved by accreditation which is less inclined to take into consideration the financial independence of an event. In transparency reports payments to doctors, and the superficial labels of hospitality funding, meeting sponsorship, or other costs etc. add another layer of ambiguous interpretation to what is and what is not ethical. Although

the Dutch self-regulatory code defines financial caps for payment to doctors, it is pragmatic idealism, because it assumes that corruption has a monetary limit of 50% out-of-pocket cost sharing, or till the €500 mark. Additionally, and this ties into means-ends pairing, regulation that restricts sponsorship of hospitality to doctors has been executed in a move towards increased independence of medical professionals, but limiting industry financial support for CME attendance has been done without changing the high and still costly licence retention requirements of doctors. This is a step beyond inadequate rule communication, since it shows complete regulatory disregard and abuse discussed in Chapter 9, when doctors will go so far as to hide or confound payments from pharmaceutical companies.

EPILOGUE

As the story goes, Dr Jekyll created his potion with the intention of breaking the duality of good and evil encased physically in the singular human body. Such a duality in his philosophy, limited man, in that existing as a singular box within which good and bad are encased, placed man at the mercy of his context, the titillation of his surrounding provoking evil or good. His concoction divided the heinous from the moral, ceasing simultaneous duality for complete separation, changing from purely good and evil with a self-determined swig of a potion. Criminological study is a Jekyllian pursuit of the boundaries of criminal and non-criminal conduct, and this is an obsession in corporate, white collar, and organizational criminological inquiry, because the foothold of criminal law is not definitive for the crimes of individuals, organizations, and institutions which are entrusted with the promotion and protection of social interests. The tale of Dr Jekyll and his demise as Mr Hyde concludes that one cannot choose separation. Although I have challenged the Bad Pharma-Good Doctor duality, this thesis does not conclude with the identification of evil physicians, or that the institution of medicine aims to harm. Consequently, I do not see a solution in sequestration of industry and medicine as the only option for medical autonomy and practice in the service of patients. Perhaps one should indulge in solutions that do not divide good and bad in regulation, punishment and reward, but promote a means-ends paring which strengthens the connection between granular goals to that of the abstract institutional purpose - being able to place the consequences of one's singular decisions into the larger system of institutional purpose achievement. In the pursuit of granular goals, immediate achievements legitimize means not worthy of the institutional purpose, which limit the capability of medicine to remain a countervailing power to pharmaceutical industry interests – its institutional corruption.

> Strange as my circumstances were, the terms of this debate are as old and commonplace as man; much the same inducements and alarms cast the die for any tempted and trembling sinner; and it fell out with me, as it falls with so vast a majority of my fellows, that I chose the better part and was found wanting in the strength to keep to it.
>
> — Robert Louis Stevenson: The Strange Case of Dr Jekyll and Mr. Hyde

BIBLIOGRAPHY

PUBLICATIONS

(F11-071 EN 2011) The European Federation of Salaried Doctors (2011) *Report on European Hospital Doctors' Salaries. Paris, France*. [Online] http://www.liganet.hu/news/6205/F11-071_EN_European_Hospital_Doctors_Salaries.pdf

Abraham, J. & Davis, C. (2013) Science, Law, and the Medical-Industrial Complex in EU Pharmaceutical Regulation: The Deferiprone Controversy. In: *European law and new health technologies*. 1st Edition, Oxford University Press, Oxford, USA, pp. 240-255

Abraham, J. (1994) Bias in Science and Medical Knowledge: The Opren controversy. *Sociology*, 28(3), pp. 717-736.

Abraham, J. (1997) 6. The Science and Politics of Medicines Regulation. *Sociology of Health & Illness*, 19 (19B), pp. 153-182.

Abraham, J. (2010) Pharmaceuticalization of Society in Context: Theoretical, empirical and health dimensions. *Sociology*, 44(4), pp. 603-622.

Adams, S. (1984) *Roche versus Adams*. Johnathan Cape Ltd. UK, London.

Agres, T. (2002) Euros for Discoveries? *The Scientist*, 16(9) [Online] http://www.the-scientist.com/?articles.view/articleNo/14003/title/Euros-for-Discoveries-/

Akdim, F., Kastelein, J. J. P. & Gaudet, D. (2008) The ENHANCE Study and Marketing Ezetimibe. *JAMA*, 299(23), pp. 2747–2748.

Akobeng, A. K. (2005) Understanding Randomized Control Trials. *Archives of Disease in Childhood*, 90(8), pp. 840-844

Albanese, J. S. (1984) Corporate Criminology: Explaining Deviance of Business and Political Organizations. *Journal of Criminal Justice*, 12(1), pp. 11-19.

Aldridge, S., Parascandola, J., & Sturchio, J. L. (1999) *The Discovery and Development of Penicillin 1928-1945*. International Historic Chemical Landmark. American Chemical Society. The Alexander Fleming Laboratory Museum, London, UK.

Alper, B. S., Hand, J. A., Elliott, S. G., Kinkade, S., Hauan, M. J., Onion, D. K., & Sklar, B. M. (2004) How Much Effort is Needed to Keep Up with the Literature

Relevant for Primary Care? *Journal of the Medical Library Association*, 92(4), pp. 429–437.

Angell, M. (2000) Is Academic Medicine for Sale? Editorial, *NEJM*, 342(20), pp. 1516-1518.

Angell, M. (2004) *The Truth About the Drug Companies. How they deceive us and what to do about it*. Random House Publishing, New York, USA

Atal, I., Trinquart, L., Procher, R. & Ravaud, P. (2015) Differential Globalization of Industry and Non-Industry-Sponsored Clinical Trials. *PLoS One*, 10(12)

Axelrod, R. (1967) Conflict of Interest: An axiomatic approach. *Journal of Conflict Resolution*, 11(1), pp. 87-99.

Baer, M. H. (2009) Governing Corporate Compliance. *Boston College Law Review*, 50, pp. 949-1019.

Baghdadi-Sebeti & Serhan (2010) WHO Good Governance for Medicines Programme: an innovative approach to prevent corruption in the pharmaceutical sector. *World Health Report Background paper 25*. [Online] http://www.who.int/healthsystems/topics/financing/healthreport/25GGM.pdf

Ball, R. (2006) The Logic of White Collar Crime Definition. *Kriminologija i socijalna integracija*, l4, pp. 23-32.

Barabási, A.L. (2016) *Network Science*. Cambridge University Press, Cambridge, UK.

Barak, G. (Ed.) (2015) *The Routledge International Handbook of the Crimes of the Powerful*. Routledge, New York, NY, USA.

Bawden, D. & Robinson, L. (2008) The Dark Side of Information: Overload, anxiety and other paradoxes and pathologies. *Journal of Information Science*, 35(2), pp.180-191.

Baylis, F. (2004) The Olivieri Debacle: Where were the heroes of bioethics? J*ournal of Medical Ethics*, 30, pp. 44-49.

Beauchamp, T. L. & Childress, J. F. (2001) *Principles of Biomedical Ethics*. Oxford University Press, New York, USA.

Beauchamp, T. L. (2007) The 'Four Principles' Approach to Health Care Ethics. In: Ashcroft, R. E., Dawson, E., Draper, H., McMillan, J. (Eds.), *Principles of Health Care Ethics*, 2nd Edition, John Wiley & Sons, Ltd, Chichester, UK.

Becker, H. S. (1963) *Outsiders: Studies in the Sociology of Deviance*. The Free Press, New York, USA.

Becker, H. S. (1967) Who's Side Are We On? *Social Problems*, 14(3), pp. 239-247.

Becker, M. H., (1970) Sociometric Location and Innovativeness: Reformulation and extension of the diffusion model. *American Sociological Review*, 35(2), pp. 267-282.

Benson, M. L. (1985) Denying the Guilty Mind: Accounting for involvement in a white-collar crime. *Criminology*, 23(4), pp. 583-607.

Bjork, B. C., Roos, A. & Lauri, M. (2009) Scientific Journal Publishing: yearly volume and open access availability. *Information Research: An International Electronic Journal*, 14(1) paper 391.

Björnberg, A. (2015) Euro Health Consumer Index Report. *Health Consumer Powerhouse.* [Online]
https://healthpowerhouse.com/files/EHCI_2015/EHCI_2015_report.pdf

Björnberg, A. (2016) Euro Health Consumer Index Report. *Health Consumer Powerhouse.* [Online]
https://healthpowerhouse.com/files/EHCI_2016/EHCI_2016_report.pdf

Blaskó, G. (2011) *Selected Topics of Pharmaceutical Management.* Debrecen University of Pharmacy, Department of Pharmaceutical Management and Organization. [Online]
http://gyogyszertankonyv.med.unideb.hu/files/TAMOP_Blasko_angol.pdf

Bodenheimer, T. (2000) Uneasy Alliance – Clinical Investigators and the Pharmaceutical Industry. *NEJM*, 342(20), pp. 1539-1544.

Borrett, D. S. (2013) Heidegger, Gestell and Rehabilitation of the Biomedical Model, *Journal of Evaluation in Clinical Practice*, 19(3), pp. 497-500.

Bothwell, L. E., Greene, J. A., Podolsky, S. H. & Jones, D. S. (2016) Assessing the Gold Standard – Lessons from the History of RCTs. *NEJM*, 374(22), pp. 2175-2181.

Bourdieu, P. (1968) Forms of Capital, In: Richardson, J. G. (Ed.) (1986) *Handbook of Theory and Research for the Sociology of Education*, Greenwood Press, New York, NY, USA.

Bourdieu, P., Accardo, A. & Ferguson, P.P. (1999) *The Weight of the World. Social suffering in contemporary society*. Stanford University Press, Stanford, CA, USA.

Bradshaw, J. (2015) AstraZeneca to buy Takeda's lung business for £383m. *The Telegraph* [Online]

http://www.telegraph.co.uk/finance/newsbysector/pharmaceuticalsandchemicals/12052991/AstraZeneca-to-buy-Takedas-lung-business-for-383m.html

Braithwaite, J. (1984) *Corporate Crime in the Pharmaceutical Industry*, Routledge & Kegan Paul, London, UK. [

Braithwaite, J. (1985) White collar crime. *Annual Review of Sociology*, 11(1), pp. 1-25.

Brennan, T. A., Rothman, D. J., Blank, L., Blumenthal, D., Chimonas, S. C., Cohen, J. J., Goldman, J., Kassirer, J. P., Kimball, H., Naughton, J. & Smelser, N. (2006) Health Industry Practices That Create Conflicts of Interest. A Policy Proposal for Academic Medical Centers. *JAMA*. 295(4), pp. 429–433.

Brinkmann, S. (2007) Could Interview be Epistemic? An alternative to qualitative opinion polling. *Qualitative Inquiry*, 3(8), pp. 116-1138.

Brittenham, G. M., Nathan, D. G., Olivieri, N. F., Porter, J. B., Pippard, M., Vichinsky, E. P. & Weatherall, D. J. (2003) Deferiprone and Hepatic Fibrosis. *Blood*, 101(12), pp. 5089-5091.

Brooks, G. (2016) *Criminology of Corruption*. Chapter 4: Explaining Corruption: Differential Association, pp. 67-86. Palgrave Macmillan UK.

Brown, A. (2013) Understanding Pharmaceutical Research Manipulation in the Context of Accounting Manipulation. *Journal of Law, Medicine & Ethics*, 41(3), pp. 611-619.

Bruner, J. (1991) The Narrative Construction of Reality. *Critical Inquiry*, 18(1), pp. 1-21.

Bujar, M. & McAuslane, N. (2014) New Drug Approvals in ICH Countries 2004-2013. Focus on 2013. *CIRS: Centre for Innovation in Regulatory Science.*

Busfield, J. (2006) Pills, Power, People: Sociological understandings of the pharmaceutical industry. *Sociology*, 40(2), pp. 297-314.

Calnan, M. & Spyridonidis, D. (2011) Are New Forms of Professionalism Emerging in Medicine? The Case of the Implementation of NICE guidelines. *Health Sociology Review*, 20(4), pp. 394-409.

Calnan, M. (2015) Eliot Freidson: Sociological narratives of professionalism and modern medicine. In: Collyer, F. (Ed.) *The Palgrave Handbook of Social Theory in Health, Illness and Medicine.* Palgrave Macmillan, Gordonsville, USA. pp. 287-305.

Carroll, J. (2005) CRO Crowing About Their Growth. *Biotechnology Healthcare*, 2(6), pp. 46–50.

Chavannes, N. H., Kaper, J., Frijling, B. D., Van der Laan, J. R., Jansen, P. W. M., Guerrouj, S., Drenthen, A. J. M., Bax, W. & Wind, L. A. (2007) NHG-Standaard Stoppen met roken. *Huisarts Wet*. 50(7), pp. 306-314.

Cheraghi-Sohi, S. & Calnan, M. (2013) Discretion or Discretions? Delineating Professional Discretion: The case of English medical practice. *Social Science & Medicine*, 96, pp. 52-59.

Chimonas, S., Brennan, T. A. & Rothman, D. J. (2007) Physicians and Drug Representatives: Exploring the dynamics of the relationship. *Journal of General Internal Medicine*, 22(2), pp. 184–190.

Chopra, S. S. (2003) Industry Funding of Clinical Trials: Benefit or Bias? *JAMA*, 290(1), pp.113-114.

Choudhry, N. K., Stelfox, H. T. & Detsky, A. S. (2002) Relationships between Authors of Clinical Guidelines and the Pharmaceutical Industry. *JAMA*, 287(5), pp. 612-617.

Clinard, M. & Yeager, P. (1980) *Corporate Crime*. Free Press, New York, USA.

Cockerham, W. C. (2016) *Medical Sociology*. 13th Edition, Routledge, New York, USA.

Cohen, D. (2010) Rosiglitazone: What went wrong? *BMJ*, 341, pp. c4848.

Coleman, J., Katz, E. & Menzel, H. (1957) The Diffusion of an Innovation among Physicians. *Sociometry*, 20(4), pp. 253-270.

Coleman, J.W. (1995) Motivation and Opportunity: Understanding the causes of white-collar crime. In: Geis, G., Meier, R. & Salinger, L. (Eds.) *White Collar Crime. Classic and Contemporary Views.* 3rd Edition, Free Press, New York, USA, pp. 360-381.

Coleman, S. (1982) Organizational Actors and Irrelevance of Persons, In: Ermann, M. D. & Lundman R. J. (Eds.) (2002) *Corporate and Governmental Deviance. Problems of Organizational Behaviour in Contemporary Society.* 6th Edition. Oxford University Press, New York, USA, pp. 95- 104.

Colquhoun, D. (2011) Publish-or-Perish: Peer review and the corruption of science. *The Guardian.* [Online] https://www.theguardian.com/science/2011/sep/05/publish-perish-peer-review-science

Colvin, E. (1995) Corporate Personality and Criminal Liability. *Criminal Law Forum*, 6(1), pp. 1-44.

Cressey, D. R. (1986) The Poverty of Theory in White Collar Crime Research. In: Laufer, W. S. & Adler, F. (Eds.) (1995) *Advances in Criminological Theory*. Vol. 1 Transaction Publishers, New Brunswick, USA.

Croall, H. (2001) *Understanding White Collar Crime*. Open University Press, Buckingham, USA.

Cruess, S. R., Johnston, S. & Cruess, R.L. (2004) "Profession": A working definition for medical educators. *Teaching and Learning in Medicine*, 16(1), pp. 74-76.

Danzinger, S. K. (1979) On Doctor Watching: Fieldwork in medical settings. *Journal of Contemporary Ethnography (formerly Urban Life)*, 7(4), pp. 513-532.

Davidson, R. A. (1986) Source of Funding and Outcome of Clinical Trials. *Journal of General Internal Medicine*, 1(3), pp. 155-158.

Davis, D. A. (2004) CME and the Pharmaceutical Industry: Two worlds, three views, four steps. *CMAJ*, 171(2), pp. 149–150.

Dawood, Y. (2014) Classifying Corruption. *Duke Journal of Constitutional Law & Public Policy*, 9(1), pp. 103-134.

De Jonge, B. & Louwaars, N. (2009) Valorizing Science: Whose values? Science & Society Series on Convergence Research. *European Molecular Biology Organization Reports*, 10(6), pp. 535-539.

Dehue, T. (2010) Selling Sickness. *Gezonde Scepsis*, Presentation Slides. [Online] https://www.slideshare.net/Gezondescepsis/trudy-dehue-selling-sickness-2010-5417129

DiMasi, J. A., Grabowski, H. G. & Hansen, R. W. (2016) Innovation in the Pharmaceutical Industry: New estimates of R&D costs. *Journal of Health Economics*, 47, pp. 20-33.

DiMasi, J.A., Hansen, R. W., Grabowski, H. G. & Lasagna, L. (1991) Cost of Innovation in the Pharmaceutical Industry. *Journal of Health Economics*; 10(2), pp. 107-42.

Dinkins, C. S. (2005) Shared Inquiry: Socratic-hermeneutic interpre-viewing. In: Ironside, P. (Ed.) *Beyond Method: Philosophical conversations in healthcare research and scholarship* University of Wisconsin Press, USA, pp. 111-147.

Doty, K. & Kouchaki, M. (2015) *Commitments Disrupted: Understanding and addressing commitment drift in for-profit enterprises*. Edmond J. Safra Working Papers, No.64, Harvard University.

Dove, F. (2011) What's happened to Thaidomide babies? BBC World Service [Online] http://www.bbc.com/news/magazine-15536544

Downing, N. S., Zhang, A. D. & Ross, J. S. (2017) Regulatory Review of New Therapeutic Agents—FDA versus EMA, 2011-2015. *NEJM*, 376(14), pp. 1386-1387.

Drain, P. K., Robine, M., Holmes, K. K. & Bassett, I. V. (2014) Global Migration of Clinical Trials in the Era of Trial Registration. *Nature Reviews. Drug Discovery*, 13(3), pp. 166–167.

Drazen, J. M., Morrissey, S. & Curfman, G. D. (2007) Rosiglitazone — Continued Uncertainty about Safety. *NEJM*; 357(1), pp. 63-64.

Drews, J. (2005) Drug Research: Between ethical demands and economic constraints. In: Santoro M. A. & Gorrie T. M. (Eds.) (2005) *Ethics and the Pharmaceutical Industry*, Cambridge University Press, New York, USA, pp. 21-36.

Dukes, G., Braithwaite, J. & Moloney, J. P. (2014) *Pharmaceuticals, Corporate Crime and Public Health*. Edward Elgar Publishing UK.

Dutta, K. A. (2015) Identifying Key Opinion Leaders Using Social Network Analysis, *Cognizant 20-20 insights*, pp. 1-12. [Online] https://www.cognizant.com/whitepapers/identifying-key-opinion-leaders-using-social-network-analysis-codex1234.pdf

EC study (2013) *Corruption in the Healthcare Sector*. HOME/2011/ISEC/PR/047-A2, European Commission – Directorate-General Home Affairs. Luxembourg, Publications Office of the European Union. [Online] https://www.stt.lt/documents/soc_tyrimai/20131219_study_on_corruption_in_the_healthcare_sector_en.pdf

Edwards, N. (2011) Using Stories to Increase Sales at Pfizer. How "Anecdote Circles" Led to an Engaged Sales Force and Improved Business Results. *Strategic Communication Management*, 15(2), pp. 30-33.

EFPIA (2017) *The Pharmaceutical Industry in Figures. Key Data 2017*. European Federation of Pharmaceutical Industries and Associations, Belgium. [Online] https://www.efpia.eu/media/219735/efpia-pharmafigures2017_statisticbroch_v04-final.pdf

Egészségügyi Közlöny (2014) *Egészségügyi szakmai irányelv – A dohányzásról való leszokás támogatásáról*. Emberi Erőforrások Miniszteriuma – Egészségügyi Államtitkárság, Egészségügyi Szakmai Kollégum.

Ehrhardt, S., Appel, L. J. & Meinert, C. L. (2015) Trends in National Institutes of Health Funding for Clinical Trials Registered in ClinicalTrials.gov. *JAMA*, 314(23), pp. 2566-2567.

Emanuel, E. J., Wendler, D., Killen, J. & Grady, C. (2004) What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research. *Journal of Infectious Disease*; 189 (5), pp. 930-937.

Eppler, M.J. & Mengis, J. (2003) A Framework for Information Overload Research in Organizations. Insights from Organization Science, Accounting, and Marketing, *Working Paper ICA*, pp. 1-42.

EU Anti-Corruption Report (2014) *Report from the Commission to the Council and the European Parliament*. European Commission, Brussels, 3.2.2014 COM (2014) 38 final [Online] https://ec.europa.eu/home-affairs/sites/homeaffairs/files/e-library/documents/policies/organized-crime-and-human-trafficking/corruption/docs/acr_2014_en.pdf

EU WG Report (2002) *Report on Research and Development*. Economic Committee, Working Group on Research and Development, Brussels, Belgium. [Online] http://register.consilium.eu.int/pdf/en/02/st05/05402-r1en2.pdf

European Parliament Working Paper (1998) *Health Care Systems in the EU. A comparative study*. European Parliament, Directorate General for Research, Luxembourg. [Online] http://www.europarl.europa.eu/workingpapers/saco/pdf/101_en.pdf

Fábián, T. (2015) Tömeges Felmondás Budapest Legjobb Kórházában. *Index*. [Online] http://index.hu/belfold/2015/12/02/szent_imre_aneszteziologus_felmondas/

Fair, B. (2010) Morgellons: Contested illness, diagnostic compromise and medicalization. *Sociology of Health & Illness*, 32(4), pp. 597-612.

Ferrell, J. & Hamm, M. (Eds.) (1998) *Ethnography at the Edge: Crime, Deviance and Field Research*. Northeastern University Press, USA.

Ferrell. J., Hayward. K. & Young. J. (2008) *Cultural Criminology: An invitation*, Sage Publications, London, UK.

Field, M. J. & Lo, B. (Eds.) (2009) *Conflict of Interest in Medical Research, Education, and Practice*. National Academies Press. Washington DC. US.

Fischer, M. A., Keough, M. E., Baril, J. L., Saccoccio, L., Mazor, K. M., Ladd, E., Von Worlez, A. & Gurwitz, J. H. (2009) Prescribers and Pharmaceutical Representatives: Why are we still meeting? *Journal of General Internal Medicine,* 24(7), pp. 795–801.

Fishman, J. R. (2004) Manufacturing Desire: The commodification of female sexual dysfunction. *Social Studies of Science,* 34(2), pp. 187-218.

Francer, J., Izquierdo, J. Z., Music, T., Narsai, K., Nikidis, C., Simmonds, H. & Woods, P. (2014). Ethical Pharmaceutical Promotion and Communications Worldwide: Codes and regulations. *Philosophy, Ethics, and Humanities in Medicine*, 9(1), p. 7.

Freidson, E. (1970) *Profession of Medicine. A Study of the Sociology of Applied Knowledge*. University of Chicago Press, Chicago, USA.

Freidson, E. (1983) Viewpoint. Sociology and Medicine: A polemic. *Sociology of Health & Illness*, 5(2), pp. 208-219.

Freidson, E. (1984) The Changing Nature of Professional Control. *Annual Review of Sociology*, 10, pp. 1-20. [

Friedrichs, D. O. (2010) *Trusted Criminals: White collar crime in contemporary society*. 4th Edition. Cengage Learning, Wadsworth, USA.

Fugh-Berman, A. J. (2010) The Haunting of Medical Journals: How ghostwriting sold "HRT". *PLoS Med,* 7(9), e1000335.

Gaál, P., Szigeti, S., Csere, M., Gaskins, M., & Panteli, D. (2011) Hungary Health System Review. Health Systems in Transition. *European Observatory on Health Systems and Policies*, 13(5), pp. 1-266.

Gabe, J., Bury, M. & Elston, M. A. (Eds.) (2004) *Key concepts in Medical Sociology*. Sage Publications, London, UK.

Gagnon, M. A. (2013) Corruption of Pharmaceutical Markets: Addressing the misalignment of financial incentives and public health. *Journal of Law, Medicine & Ethics*, 41(3), pp. 571-580.

Garba, S., Ahmed, A., Mai, A., Makama, G. & Odigie, V. (2010) Proliferations of Scientific Medical Journals: A burden or a blessing. *Oman Medical Journal*, 25(4), pp. 311–314.

Gardiner, J. (1993) Defining Corruption. In: Heidenheimer, A. J., & Johnston, M. (Eds.) (2002) *Political Corruption: Concepts and contexts* (Vol. 1). Transaction Publishers, New Brunswick, USA.

Gauthier, D. K. (2001) Professional Lapses: Occupational deviance and neutralization techniques in veterinary medical practice, *Deviant Behaviour*, 22(6), pp. 467-490.

GfK Verein (2016) *Trust in Professions 2016 – a GfK Verein Study*. [Online] http://www.gfk.com/fileadmin/user_upload/dyna_content/GB/documents/Press_Releases/2016/Trust_in_Professions_2016_Sweden_EN.pdf

Giddens, A. (1984) *The Constitution of Society. Outline of the Theory of Structuration*. University of California Press, USA.

Gilmore, S. & Kenny, K. (2014) Work-Worlds Colliding. Self-Reflexivity, Power and Emotion in Organizational Ethnography. *Human Relations*, Vol. 68(1), pp. 55-78.

Gobert, J. & Punch, M. (2003) *Rethinking Corporate Crime*. Cambridge University Press, LexisNexis, UK.

Goldacre, B. (2008) *Bad Science*. Fourth Estate, London, UK.

Goldacre, B. (2012) *Bad Pharma. How Drug Companies Mislead Doctors and Harm Patients*. Fourth Estate, London, UK.

Gómez-Jara Diez, C. (2011) Corporate Criminal Liability in the Twenty-First Century: Are all corporations capable of wrongdoing? *Stetson Law Review*, 41(1), pp. 41-61.

Goodman, L. A. (1961) Snowball Sampling. *Annals of Mathematical Statistics*, 32(1), pp. 148-170.

Gøtzsche, P. C. (2013) *Deadly Medicines and Organised Crime: How Big Pharma Has Corrupted Healthcare*. Radcliff Publishing, London, UK.

Gøtzsche, P. C., Hróbjartsson, A., Johansen, H. K., Haahr, M. T., Altman, D. G. & Chan, A. W. (2007) Ghost Authorship in Industry-Initiated Randomised Trials. *PLoS Med*, 4(1), p. e19.

Gouldner, A. W. (1967) Anti-Minotaur: The myth of a value-free sociology. *Social Problem*s, 9(3), pp. 199-213.

Goulielmos, A. M. & Goulielmos, M. A. (2005) The Accident of the m/v Herald of Free Enterprise. A Failure of the Ship or of the Management? *Disaster Prevention and Management*, 14(4), pp. 479-492.

Granovetter, M. (1973) The Strength of Weak Ties. *American Journal of Sociology*, 78(6), pp. 1360-1380.

Granovetter, M. (1985) Economic Action and Social Structure: The problem of embeddedness. *American journal of sociology*, 91(3), pp. 481-510.

Gray, G. C. (2013a) Insider Accounts of Institutional Corruption: Examining the social organization of unethical behaviour. *British Journal of Criminology*, 53(4), pp. 533-551.

Gray, G. C. (2013b) The Ethics of Pharmaceutical Research Funding: A social organization approach. *Journal of Law, Medicine & Ethics*, 41(3), pp. 629-634.

Greene, J. A. & Podolsky, S. H. (2012) Reform, Regulation, and Pharmaceuticals — The Kefauver-Harris Amendments at 50. *NEJM*, 367, pp. 1481-1483.

Greenland, P. & Lloyd-Jones, D. (2008a) Critical Lessons From the ENHANCE Trial. *JAMA*, 299(8), pp. 953–955.

Greenland, P. Lloyd-Jones, D. (2008b) The ENHANCE Study and Marketing Ezetimibe—Reply. *JAMA*; 299(23), pp. 2747–2748.

Gusterson, H. (1997) Studying Up Revisited. *Political and Legal Anthropology Review*. 20(1), pp. 114-119.

Haig, D (2007) Attack of the Pharma Babes. *Time Magazine*. [Online] http://content.time.com/time/health/article/0,8599,1573327,00.html

Hall, R. (1999) Organizations: Structures, processes, and outcomes, In: Jaffee, D. (2000) *Organization Theory: Tension and Change*. McGraw Hill, New York, USA.

Hamburg, M. (2012) 50 Years after Thalidomide: Why regulation matters. *FDA Voice*. [Online] https://blogs.fda.gov/fdavoice/index.php/2012/02/50-years-after-thalidomide-why-regulation-matters/

Hammersley, M. (2001) Which Side was Becker On? Questioning Political and Epistemological Radicalism. *Qualitative Research*, 1(1), pp. 91-110.

Harrison, S. & Ahmad, W. I. U. (2000) Medical Autonomy and the UK State 1975-2025. *Sociology*, 34(1), pp. 129-146.

Healy, D. (1997) *The Anti-Depressant Era*. Harvard University Press, Boston, USA.

Healy, D. (2004) *Let them eat Prozac: The unhealthy relationship between the pharmaceutical industry and depression*. New York University Press, NY, USA.

Heckathorn, D. D. (1997) Respondent Driven Sampling: A new approach to the study of hidden populations. *Social Problems*, 44(2), pp. 174-199.

Heidenheimer, A. J. (2002) Perspectives on the Perception of Corruption. Political corruption: Concepts and contexts, In: Heidenheimer, A. J. & Johnston, M. (Eds.) (2002) *Political Corruption: Concepts and Contexts* (Vol. 1). Transaction Publishers, New Brunswick, USA.

Hellman, D. (2013) Defining Corruption and Constitutionalizing Democracy. *Michigan Law Review*, 111(8), pp. 1385-1422.

Henry, S. & Einstadter, W. J. (2006) *Criminological Theory: An analysis of its underlying assumptions*. Rowman & Littlefield Publishers, USA.

Herper, M. (2005) David Graham on the Vioxx Verdict. *Forbes*. [Online] https://www.forbes.com/2005/08/19/merck-vioxx-graham_cx_mh_0819graham.html#443785b55698

Hill, K. P., Ross, J. S., Egilman, D. S. & Krumholz, H. M. (2008) The ADVANTAGE Seeding Trial: A review of internal documents. *Annals of Internal Medicine*, 149(4), pp. 251-258.

Hirschler, B. (2016) GSK and J&J back $1 billion biotech spin-off from Index Ventures. *Reuters* [Online] http://www.reuters.com/article/us-biotech-venture-gsk-johnson-johnson-idUSKCN0VB0XD

Hoffmann, D. E. (2009) Physicians Who Break the Law. University of Maryland Legal Studies Research Paper, *St. Louis University Law Journal*, 53(4), pp. 1049-1088.

Holloway, W. & Jefferson, T. (2000) *Doing Qualitative Research Differently: Free association, narrative and the interview method*. 1st Edition, Sage Publications, London, UK.

Holstein, A. & Gubrium, J. F. (2004) The Active Interview. In: Silverman D. (Ed.) (2004) *Qualitative Research: Theory, Method and Practice*, 2nd Edition, Sage, pp. 138-161.

Hoogland, J. & Jochemsen, H. (2000) Professional Autonomy and the Normative Structure of Medical Practice. *Theoretical Medicine and Bioethics*, 21(5), pp. 457-475.

Hu, M., Schultz, K., Sheu, J. & Tschopp, D. (2007) The Innovation Gap in Pharmaceutical Drug Discovery & New Models for R&D Success. *Kellogg School of Management.* [Online] http://www.kellogg.northwestern.edu/academic/biotech/faculty/articles/NewRDModel.pdf

Hughes, J. R., Stead, L. F., Hartmann-Boyce, J., Cahill, K. & Lancaster, T. (2014) Antidepressants for Smoking Cessation. *Cochrane Database of Systematic Reviews*, (1) Art. No.: CD000031

Human Rights Fact Sheet 31 (2008) *The Right to Health*. Office of the United Nations High Commissioner for Human Rights, World Health Organization. [Online] http://www.ohchr.org/Documents/Publications/Factsheet31.pdf

IGZ Report (2009) (2009) *Fase IV-onderzoek als marketinginstrument: beïnvloeding van voorschrijfgedrag door combinatie van elementen. Marketingdoeleinden bij onderzoek met geregistreerde geneesmiddelen*. Inspectie voor de Gezondheidzorg, Den Haag. [Online] https://www.igz.nl/zoeken/document.aspx?doc=Fase+IV-onderzoek+als+marketingonderzoek&URL

Internal email communications "ADVANTAGE ideas" email thread (1999) University of California San Francisco Library Archives [Online] https://www.industrydocumentslibrary.ucsf.edu/drug/docs/#id=kshw0217

Jacobs, J. J., Galante, J. O., Mirza, S. K. & Zdeblick, T. (2006) Symposium: Relationships with Industry: Critical for New Technology or an Unnecessary Evil? *Journal of Bone and Joint* Surgery, 88(7), pp. 1650-1651.

Jadad, A. R. & Enkin, M. W. (2008) *Randomized Controlled Trials: Questions, Answers, and Musings*, 2nd Edition, BMJ Books, Blackwell Publishing Ltd, Oxford, UK.

Jaffee D. (2001) *Organization Theory: Tension and change*. McGraw Hill, New York, USA.

Jaffee, D. (2000) *Organization Theory: Tension and Change*. McGraw Hill, New York, USA

Jain, S. S. L. (2006) *Injury. The Politics of Product Design and Safety Law in the United States.* Princeton University Press, USA.

Jancsics, D. (2014) Interdisciplinary Perspectives on Corruption. *Sociology Compass*, 8(4), pp. 358-372.

Jesilow P.D., Pontell H.N. & Geis G. (1985) Medical Criminals: Physicians and white-collar offenses. *Justice Quarterly*, 2, pp. 149-165

Karanth, B. M. (2010) A Symbol of Our Profession: White coat ceremony address to the class of 2014, *Journal of General Internal Medicine*, 26(6), pp. 679-674.

Karreman, D., Sveningsson, S. & Alvesson, M. (2002) The Return of Machine Bureaucracy? Management Control in the Work Settings of Professionals, *International Studies of Management and Organization*, 32 (2), pp. 70-92.

Kellner, T. (2010) Funding Models of CME and CPD in Europe, In: *Continuing Medical Education in Europe: Evolution or Revolution?* MedEd Global Solutions.

Kendel, D. A. (1990) Professional Autonomy in Medicine. *Canadian Family Physician*, 36, pp. 1115-1117.

Kennedy, P. (2015) The Contradictions of Capitalist Healthcare Systems. *Journal of Socialist Theory*, Critique 42(2), pp. 211-231.

Kessel, M. (2014) Restoring the Pharmaceutical Industry's Reputation. *Nature Biotechnology*, 32(10), pp. 983-990.

Khalil, E. L. (1995) Organizations versus Institutions. *Journal of Institutional and Theoretical Economics*/Zeitschrift für die gesamte Staatswissenschaft, 51(3), pp. 445-466

Kitsis, A. E. (2011) The Pharmaceutical Industry's Role in Defining Illness. *Virtual Mentor AMA Journal of Ethics*, 13 (12), pp. 906-911.

Kjaergard, L. L. & Als-Nielsen, B. (2002) Association between Competing Interests and Author's Conclusions: Epidemiological study of randomized clinical trials published in the BMJ. *BMJ*, 325, pp. 249.

Klein, N. & Epley, N. (2017) Less Evil than You: Bounded self-righteousness in character inferences, emotional reactions, and behavioural extremes. *Personality and Social Psychology Bulletin*, 43(8), pp. 1202-1212.

Knaapen, L. (2014) Evidence-Based Medicine or Cookbook Medicine? Addressing concerns over the standardization of care. *Sociology Compass*, 8(6), pp. 823-836.

KNAW (2014) Koninklijke Nederlandes Akademie van Wetenschappen. *Benutting van octrooien op resultaten van wetenschappelijk Onderzoek.* Amsterdam, (with English Summary) [Online] https://www.knaw.nl/en/news/publications/benutting-van-octrooien-op-resultaten-van-wetenschappelijk-onderzoek

Knightly, P., Evans, H., Potter, E. & Wallace, M. (1979) *Suffer the children: The story of thalidomide*. Viking Press, USA.

Kramer, R. C., Michalowski, R. J. & Kauzlarich, D. (2002) The Origins and Development of the Concept and Theory of State-Corporate Crime. *Crime & Delinquency,* 48(2), pp. 263-282.

Kreling, T. & de Visser, E. (2016) De verborgen betalingen van farmaceuten. *De Volkskrant* [Online] https://www.volkskrant.nl/wetenschap/de-verborgen-betalingen-van-farmaceuten~a4300650/

Kreling, T., de Visser, E. & Koens, R (2016) Farmaceuten betalen miljoenen aan artsen. Vooral reumatologen, longartsen en internisten profiteren. *De Volkskrant*. [Online] https://www.volkskrant.nl/4369431

Lambert, H. (2009) Evidentiary Truths? The Evidence of Anthropology through the Anthropology of Medical Evidence. *Anthropology Today*, 25(1), pp. 16-20.

Lambsdorff, J. F. (2015) Preventing Corruption by Promoting Trust: Insights from behavioral science. *Passauer Diskussionspapiere: Volkswirtschaftliche Reihe*, 69(15), pp. 1-16.

Lanier, M. M. & Stuart, H. (2010) *Essential Criminology.* 3rd Edition, Westview Press, USA.

Law, J. (2006) *Big Pharma: How the world's biggest drug companies control illness*. Constable & Robinson Ltd, London, UK.

Lee, P. I. & Tham, J. L. C. (2014) Industrialization of Medicine and Medical Professionalism: Bioethical critiques. *Studia Bioethica*, 7(3), pp. 44-51.

Lehman, B. (2003) The Pharmaceutical Industry and the Patent System. *International Intellectual Property Institute*. Washington D.C., USA. [Online] https://users.wfu.edu/mcfallta/DIR0/pharma_patents.pdf

Lessing, L. (2011) *Republic, Lost. How Money Corrupts Congress – and a Plan to Stop It.* Twelve, Hachette Book Group, New York, USA.

Lessing, L. (2013) Foreword: 'Institutional Corruption' Defined. *Journal of Law, Medicine & Ethics*, 41(3), pp. 2-4.

Lewis S., Baird P., Evans R. G., Ghali W. A., Wright C. J., Gibson E. & Baylis F. (2001) Dancing with the Porcupine: Rules for governing the university-industry relationship, *CMAJ*, 6(18), pp. 783-785.

Lewis, G. & Abraham, J. (1998) Making Harmonization Work: The politics of scientific expertise in European medicines regulation. *Science and Public Policy*, 25(3), pp. 155-169.

Lexchin J. (1993) Interactions between Physicians and the Pharmaceutical Industry: What does the literature say? *CMAJ*, 149(10), pp. 1401-1407.

Lexchin, J. (2012) Those Who have the Gold make the Evidence: How the pharmaceutical industry biases the outcomes of clinical trials of medications. *Science and Engineering Ethics*, 18(2), pp. 247-261.

Lexchin, J., Bero, L. A., Djulbegovic, B. & Clark, O. (2003) Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic review. *BMJ* , 326(7400), pp. 1167-1170.

Liazos, A. (1972) The Poverty of the Sociology of Deviance: Nuts, sluts, and perverts. *Social Problems*, 20(1), pp. 103-120.

Liberati, A. & Magrini, N. (2003) Information from Drug Companies and Opinion Leaders: Double standards in information for medical journals and practitioners should go. *BMJ*, 326, pp. 1156-1157.

Light, D. & Levine, S. (1988) The Changing Character of the Medical Profession: A theoretical overview. *The Milbank Quarterly*, 66 Supplement (2), pp. 10-32.

Light, D. (2001) Managed Competition, Governmentality and Institutional Response in the United Kingdom. *Social Science & Medicine*, 52(8), pp. 1167-1181.

Light, D. (2010) Health-Care Professions, Markets, and Countervailing Powers. In: Bird, C. E., Conrad, P., Fremont, A. M., & Timmermans, S. (Eds.) (2010) *Handbook of Medical Sociology*. 6th Edition. Vanderbilt University Press, Nashville, pp. 270-289

Light, D., Lexchin, J. & Darrow, J. J. (2013) Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs. *Journal of Law, Medicine & Ethics*, 14(3), pp. 590-610.

Lippens, R. (2001) Rethinking Organizational Crime and Organizational Criminology. *Crime, Law and Social* Change, 35(4), pp. 319-331.

Lockett, A., Wright, M. & Franklin, S. (2003) Technology Transfer and Universities' Spin-Out Strategies. *Small Business Economics*, 20(2), pp. 185-200.

Loewy, E. H. (2007) Oaths for Physicians – Necessary Protection or Elaborate Hoax? *Medscape General Medicine*, 9(1), pp.7.

Longo, V. D. & Mattson, M. P. (2014) Fasting: Molecular mechanisms and clinical applications. *Cell Metabolism*, 19(2), pp. 181-192.

Lundh, A., Lexchin, J., Mintzes, B., Schroll, J. B. & Bero, L. (2017) Industry Sponsorship and Research Outcome. *Cochrane Database of Systematic Reviews*, Issue 2. Art. No.: MR000033.

Lundh, A., Sismondo, S., Lexchin, J., Busuioc, O. A. & Bero, L. (2012) Industry Sponsorship and Research Outcome. *Cochrane Database of Systematic Reviews*, Issue 12. Art. No.: MR000033.

Maisonneuve, H (2010) The Role of the Pharmaceutical and Medical Devices Industry in Continuing Medical Education of European Physicians. In: *Continuing Medical Education in Europe: Evolution or Revolution?* MedEd Global Solutions

Makra, Zs. (2013) Az Egyetemi Spin-Off Vállalkozások Jellegzetességei és Alapításának Folyamata a Nemzetközi Szakirodalom Tükrében. In: Inzelt, A. & Bajmócy, Z. (Eds.) *Innovációs rendszerek. Szereplők, kapcsolatok és intézmények*. JATE Press, Szeged, pp. 57-70

Marks, J. M. (2013) *What's the Big Deal? The Ethics of Public-Private Partnerships Related to Food and Health.* Edmond J Safra Working Papers, No.11, Harvard University

McFadden, D. W., Calvario, E. & Graves, C. (2007) The Devil is in the Details: The pharmaceutical industry's use of gifts to physicians as marketing strategy. *Journal of Surgical Research*, 104(1), pp. 1-5.

McFadden, R. D. (2015) Frances Oldham Kelsey, Who Saved U.S. Babies from Thalidomide, Dies at 101. *The New York Times* [Online] https://www.nytimes.com/2015/08/08/science/frances-oldham-kelsey-fda-doctor-who-exposed-danger-of-thalidomide-dies-at-101.html?_r=0

McHenry L. (2010) Of Sophists and Spin-Doctors: Industry-sponsored ghostwriting and the crisis of academic medicine. *Mens Sana Monographs*, 8(1), pp.129-145.

McKinley, J. B. & Marceau, L. D. (2002) The End of the Golden Age of Doctoring. *International Journal of Health Services*, 32(2), pp. 379-416.

Melander, H., Ahlqvist-Rastad, J., Meijer, G. & Beerman, B. (2003) Evidence B(i)ased Medicine – Selective Reporting from Studies Sponsored by Pharmaceutical Industry: Review of studies in new drug applications. *BMJ*, 326(7400), pp. 1171-1173

Merton R. K. (1957) Priorities in Scientific Discovery. Chapter 14, In: Merton R. K. & Storer, N. W. (Eds.) (1973) *The Sociology of Science. Theoretical and Empirical Investigations*. University of Chicago Press, USA, pp. 286-324

Merton, R. K. (1938) Science and the Social Order. Chapter 12, In: Merton R.K. & Storer, N. W. (Eds.) (1973) *The Sociology of Science. Theoretical and Empirical Investigations*. University of Chicago Press, USA, pp 254-266

Miller A. (2013) White Coats and White-Collar Crime. *CMAJ*, 185(1), pp. E19-E20.

Mintzberg, H. (1983) *Structure in Fives: Designing effective organizations*. Prentice-Hall, USA.

Mintzes, B. (2005) *Educational Initiatives for medical and pharmacy students about drug promotion: an international cross-sectional survey*. World Health Organization & Health Action International. WHO/PSM/PAR/2005.2. [Online] http://apps.who.int/medicinedocs/pdf/s8110e/s8110e.pdf

Mintzes, B. (2012) Advertising of Prescription Only Medicines to the Public: Does evidence of benefit counterbalance harm? *Annual Review of Public Health*, 33, pp.259-277.

Misra, S. (2012) Randomized Double Blind Placebo Control Studies: The "Gold Standard" in intervention based studies. *Indian Journal of Sexually Transmitted Diseases, 33*(2), pp. 131-134.

Moynihan, R. (2003) Drug Company Sponsorship of Education could be replaced at a Fraction of its Cost. *BMJ*, 326, p. 1163.

Moynihan, R. (2008) Key Opinion Leaders. Independent Experts or Drug Representatives in Disguise? *BJM*, 336, pp. 1402-1403.

Moynihan, R., Heath, I. & Henry, D. (2002) Selling Sickness: The pharmaceutical industry and disease mongering. *BMJ*, 324(7342): 886-891.

Murad, M. H., Asi, N., Alsawas, M. & Alahdab, F. (2016) New Evidence Pyramid. *Evidence-Based Medicine, BMJ Journals,* 21(4), pp. 125-127.

Mw. drs. E.I. Schippers Minister of Health, Welfare and Sport letter to The Speaker of the Lower House of Parliament, The States-General regarding the Medicines Policy Plan (20/01/2016) [Online] https://www.government.nl/binaries/government/documents/letters/2016/03/07/medicines-policy-plan-new-drugs-available-to-patients-fast-at-an-acceptable-cost/medicines-policy-plan.pdf

Mykhalovskiy, E. & Weir, L. (2004) The Problem of Evidence-Based Medicine: Directions for social science. *Social Science & Medicine*, 59(5), pp. 1059-1069.

Nader, L. (1972) Up the Anthropologist: Perspectives gained from 'studying up' In: Dell H. Hymes (Ed.) *Reinventing Anthropology.* Panthenon Books, New York, USA, pp. 284-311.

Nader, L. (2011) Ethnography as Theory. *Journal of Ethnographic Theory*. 1(1), pp. 200-219

Nagy-Koppány, K., Nemeth, E. & Csurdi, A. (2013) *Life Sciences in Hungary: Overview*. KNP LAW, Nagy Koppany Varga and Partners, Thompson Reuters Practical Law. Life Sciences Country Q&A. [Online] http://www.knplaw.com/wp-content/uploads/2014/02/Hungary-KNP.pdf

Needleman, L. M. & Needleman, C. (1979) Organizational Crime: Two models of criminogenesis. *The Sociological Quarterly*, 20(4), pp. 517-528.

Nelken D. (2012) White-Collar and Corporate Crime, In: Maguire M., Morgan R. & Reiner R. (2012) *The Oxford Handbook of Criminology*. 5th Edition, Oxford University Press

Nesi, T. (2008) *Poison pills. The Untold Story of the Vioxx Drug Scandal*. Thomas Dunne Books. New York, USA.

Netherlands Pharma Report (2011) Focus Reports [Online] https://issuu.com/focusreports/docs/phex_nl_2011

Newhouse, M. E. (2014) Institutional Corruption: A fiduciary theory. *Cornell Journal of Law and Public Policy*, 23 (3), pp. 553-594.

Nielsen, N. (2017) EU commission Drops Anti-Corruption Report. *EUObserver* [Online] https://euobserver.com/institutional/136775

Noaks, L. & Wincup, E. (2004) *Criminological Research – Understanding Qualitative Methods*. Sage Publications, London, UK.

Norris, P., Herxheimer, A., Lexchin, J. & Mansfield, P. (2005) *Drug Promotion: What we know, what we have yet to learn*: *Reviews of materials in the WHO/HAI database on drug promotion*. World Health Organization & Health Action International. [Online] http://www.who.int/medicinedocs/collect/medicinedocs/pdf/s8109e/s8109e.pdf.

Novo Nordisk (2015) A*nimals in Pharmaceutical Research. A responsible approach*. Company Brochure. [Online] https://www.novonordisk.com/content/dam/Denmark/HQ/RND/Documents/Bioethics_Animal%20research%20UK_Dec%202015.pdf

Novotny, Á. (2013) Az Egyetemi-Ipari Technológiatranszfer Sajátosságai Magyarországon. *Közgazdasági Szemle*, LX, pp. 1119-1139

Noy, C. (2008) Sampling Knowledge: The hermeneutics of snowball sampling in qualitative research. *International Journal of Social Research Methodology*, 11, pp. 327-344.

OECD (2014) *Health at a Glance: Europe 2014*. OECD Publishing, Paris. [Online] http://dx.doi.org/10.1787/health_glance_eur-2014-en

Oldani, M. J. (2004) Thick Prescriptions: Toward an interpretation of pharmaceutical sales practices. *Medical Anthropology Quarterly*, 18(3), pp. 325-356.

Oliveira, G. (2014) *Institutional Corruption as a Problem of Institutional Design: A General Framework*. Edmond J. Safra Working Papers, No. 41, Harvard University

Pammolli, F., Magazzini, L. & Riccaboni, M. (2011) The Productivity Crisis in Pharmaceutical R&D. *Nature Reviews, Drug Discovery* 10, pp. 428-438.

Pardell, H. & Negri, A. (2010) Current Climate and Opportunities in Europe. In: *Continuing Medical Education in Europe: Evolution or Revolution?* MedEd Global Solutions.

Parker, J. (2007) The Reputation, Image and Influence of the Pharmaceutical Industry: Regaining credibility. *Journal of Medical Marketing*, 7(4), pp. 309-313.

Pattnaik, P. N. & Pandey, S. C. (2014) University Spinoffs: What, why, and how? *Technology Innovation Management Review*, 4(12), pp. 44-50.

Pearson, A., Jordan, Z. & Munn, Z. (2012) Translational Science and Evidence-Based Healthcare: A clarification and reconceptualization of how knowledge is generated and used in healthcare. *Nursing Research and Practice*, 2012, pp. 1-6.

Peterson, C. L. and Burton, R. (2007) US Health Care Spending: Comparison with other OECD countries. *Federal Publications.* Congressional Research Service, Washington, DC, USA.

Pharmaceutical Research and Manufacturers of America (PhARMA) (2015) *Biopharmaceutical Research and Development. The Process behind New Medicines* [Online] http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf

Piquero, N. L., Tibbetts, S. G. & Blankenship, M. B. (2005) Examining the Role of Differential Association and Techniques of Neutralization in Explaining Corporate Crime. *Deviant Behaviour*, 26(2), pp. 159-188.

Pirnay, F. & Surlemont, B. (2003) Toward a Typology of University Spin-Offs. *Small Business Economics*, 21(4), pp. 355-369.

Pollack, A. (2009) Roche Agrees to Buy Genentech for $46.8 Billion. *The New York Times*. [Online] http://www.nytimes.com/2009/03/13/business/worldbusiness/13drugs.html

Price, M. & Norris, D. M. (2009) Health Care Fraud: Physicians as white collar criminals? *Journal of the American Academy of Psychiatry and the Law*. 37(3), pp. 286-289

Punch, M. (2000) Why Managers Murder and Corporation Kill. *Crime, Law & Social Change*, 2000, 33(243), pp. 243-280.

Quinn, R. (2013) Rethinking Antibiotic Research and Development: World War II and the Penicillin Collaborative. *American Journal of Public Health*, 103(3), pp. 426-434.

Rani, S. (2015) An Overview of Top Clinical CROs. *Clinical Leader.* [Online] https://www.clinicalleader.com/doc/an-overview-of-top-clinical-cros-0001

Rastegar, D. A. (2004) Healthcare Becomes an Industry. *Annals of Family Medicine*, 2(1), pp. 79-83.

Rawat, S. & Meena, S. (2014) Publish or Perish: Where are we heading? *Journal of Research in Medical Sciences*, 19(2), pp. 87-89.

Rees, J. L. (2008) Evidence and the Industrialization of Medicine. *Clinical and Experimental Dermatology*, 33(4), pp. 390-393.

Reiss Jr, A. J. & Tonry, M. (1993) Organizational crime. *Crime and Justice*, 18, pp. 1-10.

Relman, A. S. (1980) The New Medical-Industrial Complex. *NEJM*, 303, pp. 963-970.

Ridker, P. & Torres, J. (2006) Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations: 2000-2005. *JAMA*; 295(19), pp. 2270-2274.

Robbins, S. P. (1990) *Organization Theory: Structure, design, and applications.* Prentice-Hall International Editions, Englewood Cliffs, USA.

Rocca, J. (2008) Inventing an Ethical Tradition: A brief history of the Hippocratic Oath. *Legal Ethics*, 11(1), pp. 23-40.

Rodwin, M. A. (2012) Conflicts of Interest, Institutional Corruption, and Pharma: An agenda for reform. *Journal of Law, Medicine & Ethics*, 41(3), pp. 511.522

Rodwin, M. A. (2013) Rooting Out Institutional Corruption to Manage Inappropriate Off-Label Drug Use. *Journal of Law, Medicine & Ethics*, 41 (3), pp. 654-664

Ross, J. S., Hill, K. P., Egilman, D. S. & Krumholz, H. M. (2008) Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: A case study of industry documents from Rofecoxib litigation. *JAMA*, 299(15), pp. 1800-1812.

Rost, P. (2006) *The Whistleblower: Confessions of a healthcare hitman*. Soft Skull Press, Brooklyn, USA.

Rothman, D. J., McDonald, W. J., Berkowitz, C. D., Chimonas, S. C., DeAngelis, C. D., Hale, R. W., Nissen, S. E., Osborn, J. E., Scully Jr. J. H., Thomson, G. E. & Wofsy, D. (2009) Professional Medical Associations and their Relationships with Industry. A proposal for controlling conflict of interest. *JAMA*, 301(13), pp. 1367-1372.

Roulston, K. (2010) *Reflective Interviewing. A guide to theory and practice*. Sage Publications, London, UK.

Ruggiero, V. (2007) It's the Economy, Stupid! Classifying Power Crimes, *International Journal of the Sociology of Law*, 35(4), pp. 163-177.

Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B. & Richardson, W. S. (1996) Evidence-Based Medicine: What it is and what it isn't. *BMJ*, 312(7023), pp. 71-72.

Sackett, D.L. (1997) Evidence-Based Medicine. *Seminars in Perinatology*. 21(1), pp 3-5.

Sah, S. & Fugh-Berman, A. (2013) Physicians under the Influence: Social psychology and industry marketing strategies. *Journal of Law, Medicine, & Ethics*, 41(3), pp. 665-672.

Sah, S. & Loewenstein, G. (2010) Effects of Reminders of Personal Sacrifice and Suggested Rationalizations on Residents' Self-Reported Willingness to Accept Gifts. *JAMA*, 304(11), pp. 1204-1211

Salmon, J. W., White, W. & Feinglass, J. (1990) The Futures of Physicians: Agency and autonomy reconsidered. *Theoretical Medicine*, 11(4), pp. 261-274.

Schafer, A. (2004) Biomedical Conflicts of Interest: A defence of the sequestration thesis – learning from the cases of Nancy Olivieri and David Healy. *Journal of Medical Ethics*, 30(1), pp. 8-24.

Schuhmacher, A., Gassmann, O. & Hinder, M. (2016) Changing R&D Models in Research-Based Pharmaceutical Companies. *Journal of Translational Medicine.* 14(105), pp. 1-11.

Scott, M. B. & Lyman, S. M. (1968) Accounts. *American Sociological Review*. 33(1), pp. 46-62.

Seife, C. (2015) Research Misconduct Identified by the US Food and Drug Administration. Out of Sight, Out of Mind, Out of Peer-Reviewed Literature. *JAMA Internal Medicine*, 175(4), pp.567-77.

Shapiro, S. P. (1987) The Social Control of Interpersonal Trust. *American Journal of Sociology*, 93(3), pp. 623-658.

Shapiro, S. P. (1990) Collaring the Crime, not the Criminal: Reconsidering the concept of white-collar crime. *American Sociological Review*, 55(3), pp. 346-365

Shapiro, S. P. (2005) Agency Theory. *Annual Review of Sociology*, 31, pp. 263-284.

Siepmann, T. J. (2004) The Global Exportation of the US Bayh-Dole Act. *University of Dayton Law Review*, 30, pp. 209.243.

Silverstein, K. & Taylor, J. (2004) Profiting through Influence. The pharmaceutical and lobbying industries. In Passas, N. (Ed.) *It's Legal but it Ain't Right*. University of Michigan Press, USA, pp. 253-276

Sismondo, S. (2007) Pharmaceutical Company Funding and its Consequences. A Qualitative Systematic Review. *Contemporary Clinical Trials*, 29(2), pp. 109-113.

Sismondo, S. (2008) How Pharmaceutical Industry Funding Affects Trial Outcomes: Causal structures and responses. *Social Science and Medicine*, 66(9), pp. 1909-1914.

Sismondo, S. (2013) Key Opinion Leaders and the Corruption of Medical Knowledge: What the Sunshine Act will and won't cast light on. *The Journal of Law, Medicine & Ethics*, 41(3) pp. 635-643.

Slapper, G. & Tombs, S. (1999) *Corporate Crime*. Longman Criminology Series, Pearson Education, Canada.

Smith, A. (2006) The Big Threat to Big Pharma. Patent Expirations are Poison for Brand-Name Drugmakers, but Manna for Generics. *CNN Money*. [Online] http://money.cnn.com/2006/10/31/news/companies/generics/index.htm

Smith, R. (2006) The Trouble with Medical Journals. *Journal of the Royal Society of Medicine*, 99(3), pp. 115–119.

Song, C. H. & Han, J. W. (2016) Patent Cliff and Strategic Switch: Exploring strategic design possibilities in the pharmaceutical industry. *Springer Plus*, *5*(1), p. 692.

Sox, H. C. & Rennie, D. (2008) Seeding Trials: Just Say “No”. *Annals of Internal Medicine*, 149(4), pp. 279-280.

Spurling, G. K., Mansfield, P. R., Montgomery, B. D., Lexchin, J. & Doust, J. (2010) Information from Pharmaceutical Companies and the Quality, Quantity, and Cost of Physicians' Prescribing: A systematic review. *PLoS Med 7*, p. e1000352.

Sritharan, K., Russell, G., Fritz, Z., Wong, D., Rollin, M., Dunning, J. & Sheehan, C. (2001) Medical Oaths and Declarations : A Declaration marks an explicit commitment to ethical behaviour. *BMJ*, 323(7327), pp. 1440–1441.

Stamatakis, E., Weiler, R. & Ioannidis, J. P. A. (2013) Undue Industry Influences that Distort Healthcare Research, Strategy, Expenditure and Practice: A review. *European Journal of Clinical Investigation* 43(5), pp. 469-475.

Steinbrook, R. (2008) Financial Support of Continuing Medical Education. *JAMA*, 299(9), pp. 1060-1062

Stewart, J. G. (2012) *A Pragmatic Critique of Corporate Criminal Theory: Lessons from the extremity*. NYU School of Law Public Law Research Paper No. 12, 54, pp. 1-38.

Stichting Transparantieregister Zorg 2016 (2017) *Stichting Financiële relaties tussen zorgprofessionals en geneesmiddelenbedrijven*. Notitie kengetallen register 20130417. (11 mei 2017) [Online] http://www.transparantieregister.nl/nl-NL/Nieuwsberichten/2017/Transparantieregister-Zorg-2016

Subramanyam, R. (2013) Art of Reading a Journal Article Methodically and Effectively. *Journal of Oral and Maxillofacial Pathology*, 17(1), pp. 65-70.

Sugarman, J. (2016) Are there any Proven Benefits to Fasting? *John Hopkins Health Review*, 3(1), pp. 9-10

Sullivan, W. M. (2000) Medicine under Threat: Professionalism and professional identity. *CMAJ*, 162(5), pp. 673-675.

Sutherland, E. H. (1940) White-Collar Criminality. *American Sociological Review*, 5(1), pp. 1-12.

Sutherland, E. H. (1945) Is" White Collar Crime" Crime? *American Sociological Review*, 10(2), pp. 132-139.

Sutherland, E. H. (1983) *White Collar Crime – The Uncut Version*. Yale University Press, New Haven, USA.

Suvarna, V. (2010) Phase IV of Drug Development. *Perspectives in Clinical Research, 1*(2), pp. 57–60.

Tappan, P. W. (1947) Who is the Criminal? *American Sociological Review*, 12(1), pp. 96-102.

Terry, R. F., Salm, J. F., Nannei, C. & Dye, C. (2014) Creating a Global Observatory for Health R&D. *Science*, 345(6202), pp. 1302-1304.

The PLoS Medicine Editors (2009) Ghostwriting: The dirty little secret of medical publishing that just got bigger. *PLoS Med*, 6(9), p. e1000156.

Thomas, K. & Schmidt, M. S. (2012) Glaxo Agrees to Pay $3 Billion in Fraud Settlement. *The New York Times.* [Online] http://www.nytimes.com/2012/07/03/business/glaxosmithkline-agrees-to-pay-3-billion-in-fraud-settlement.html

Thomas, R. J. (1993) Interviewing Important People in Big Companies. *Journal of Contemporary Ethnography*, 22(1), pp. 80-96.

Thompson J., Baird, P. & Downie, J. (2001) *Report of the Committee of Inquiry on the Case involving D. Nancy Olivieri, the Hospital for Sick Children the University of Toronto and Apotex Inc*. Canadian Association of. University Teachers, James Lortimer & Co. Canada.

Thompson, D. F. (1993) Understanding Financial Conflicts of Interest. *NEJM*, 329(8), pp. 573-573.

Thompson, D. F. (1995) *Ethics in Congress: From individual to institutional corruption*. Brookings Institution Press, Washington, D.C., USA.

TI GCR (2006) *Transparency International Global Corruption Report*. Pluto Press, London, UK. [Online] https://www.transparency.org/whatwedo/publication/global_corruption_report_2006_corruption_and_health

TI Study (2016a) *Corruption in the Pharmaceutical Sector. Diagnosing the Challenges.* Transparency International's Pharmaceuticals & Healthcare Programme, Transparency International, UK. [Online] http://apps.who.int/medicinedocs/documents/s22500en/s22500en.pdf

TI Study (2016b) *Diagnosing Corruption in Healthcare*. Transparency International's Pharmaceuticals & Healthcare Programme, Transparency International, UK. [Online] http://www.transparency.org.uk/publications/diagnosing-corruption-in-healthcare/#.Wh7yHkqnE2w

Timmermans, S. & Oh, H. (2010) The Continued Social Transformation of the Medical Profession. *Journal of Health and Social Behaviour*, 51 Supplement, pp. S94-S106.

Topalli, V. (2005) When Being Good is Bad. An expansion of neutralization theory. *Criminology*, 43(3), pp. 787-835.

Tuhoy, C. V. & Dodson J. A. (2015) Statins for Primary Prevention in Older Adults. Expert Analysis. *American College of Cardiology*. [Online] http://www.acc.org/latest-in-cardiology/articles/2015/03/10/07/46/statins-for-primary-prevention-in-older-adults

US Preventive Services Task Force Recommendation Statement (2016) Statin Use for the Primary Prevention of Cardiovascular Disease in Adults. *JAMA*. 2016, 316(19), pp. 1997–2007

Van Dalen, H. P. & Henkens, K. (2012), Intended and Unintended Consequences of a Publish-or-Perish Culture: A worldwide survey. *Journal of the Association for Information Science and Technology*, 63(7), pp. 1282–1293.

Van Huijstee, M. & Schipper, I. (Eds.) (2011) *Putting Contract Research Organisations on the Radar. An Exploratory Study on the Outsourcing of Clinical Trials by Pharmaceutical Companies to Contract Research Organisations in Non-Traditional Trial Regions.* Centre for Research on Multinational Corporations (SOMO), Amsterdam [Online] https://www.somo.nl/wp-content/uploads/2011/02/Putting-Contract-Research-Organisations-on-the-Radar.pdf

Vaughan, D. (1996) *The Challenger Launch Decision: Risky technology, culture, and deviance at NASA*. University of Chicago Press, USA.

Vaughan, D. (1997) The Trickle-Down Effect: Policy decisions, risky work, and the"Challenger" tragedy. *California Management Review*, 39(2), pp. 80-102.

Vaughan, D. (1999). The Dark Side of Organizations: Mistake, misconduct, and disaster. *Annual Review of Sociology*, 25, pp. 271-305.

Wade, D.T. & Halligan, P.W. (2004) Do Biomedical Models of Illness Make for Good Healthcare Systems? *BMJ*, 329(7479), pp. 1398-1401.

Wammes, J., Jeurissen, P. & Westert, G. (2014) The Dutch Health System. *Radboud University Medical Centre*, Utrecht: NVAG. [Online] http://www.nvag.nl/afbeeldingen/2015/nscholing/Netherlands%20Health%20Care%20System%202014%20(PDF).pdf

Ward, A. (2016) GSK Confident Halting Payments to Doctors will Pay Off. *The Financial Times*. [Online] https://www.ft.com/content/7a0643c2-b52d-11e5-b147-e5e5bba42e51

Warzynski, C. & Noble, D. (1976) The Ideology of Professionalization and HRD. *Training and Development Journal*, 30(10), pp. 12-17.

Watkins, C., Moore, L., Harvey, I., Carthy, P., Robinson, E. & Brawn, R. (2003) Characteristics of General Practitioners who frequently see Drug Industry Representatives: National cross sectional study. *BMJ* , 326(7400), pp. 1178–1179.

Watts, D. & Peretti, J. (2007) Viral Marketing for the Real World. *Harvard Business Review*, May Issue. [Online] https://hbr.org/2007/05/viral-marketing-for-the-real-world

Wazana, A. (2000) Physicians and the Pharmaceutical Industry: Is a gift ever just a gift? *JAMA*, 283(3), pp. 391-393.

Weber, J. (2010) Assessing the "Tone at the Top": The moral reasoning of CEOs in the automobile industry. *Journal of Business Ethics*, 92(2), pp. 167-182.

Weber, M. (1949) *The Methodology of the Social Sciences*. Free Press, New York, USA.

Whitaker, R. & Cosgrove, L. (2015) *Psychiatry Under the Influence: Institutional corruption, social injury, and prescriptions for reform*. Palgrave McMillan, New York, USA.

Whitaker, R. (2001) *Mad in America: Bad Science, Bad Medicine, and the Enduring Mistreatment of the Mentally Ill*. Basic Books, USA.

Whitaker, R. (2010) *Anatomy of an Epidemic*. Broadway Books, USA.

WHO (2000) *World Health Report. Health systems: Improving performance*. World Health Organization, Geneva, Switzerland. [Online] http://www.who.int/whr/2000/en/whr00_en.pdf?ua=1

WHO/HAI Collaborative Project (2010) *Understanding and Responding to Pharmaceutical Promotion. A practical Guide*. 1st Edition. [Online] http://haiweb.org/wp-content/uploads/2015/05/Pharma-Promotion-Guide-English.pdf

Wilensky, H. L. (1964) The Professionalization of Everyone? *American Journal of Sociology*, Volume 70(2), pp. 137-158.

Wilson, D. (2011) Drug Firms Face Billions in Losses in '11 as Patents End, *New York Times* [Online] http://www.nytimes.com/2011/03/07/business/07drug.html

World Bank (2007) *Healthy Development. The World Bank Strategy for Health, Nutrition, and Population Results*. Washington, DC, USA. [Online] http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1154048816360/HNPStrategyFINALApril302007.pdf

REGULATION

Act XCV of 2005 on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products. 2005. évi XCV. Törvény az emberi alkalmazásra kerülő gyógyszerekről és egyéb, a gyógyszerpiacot szabályozó törvények módosításáról.

Act XCVIII of 2006 on the General Provisions Relating to the Reliable and Economically Feasible Supply of Medicinal Products and Medical Aids and on the Distribution of Medicinal Products. 2006. évi XCVIII. Törvény a biztonságos és gazdaságos gyógyszer- és gyógyászatisegédeszköz-ellátás, valamint a gyógyszerforgalmazás általános szabályairól.

CGR Code of Conduct for Pharmaceutical Advertising (2015) Gedragscode Geneesmiddelenreclame. De Stichting Code Geneesmiddelenreclame (amended 2017)

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. *Official Journal of the European Union,* L – 91: p. 13 – 19.

Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products. *Official Journal of the European Communities*, L – 369/65.

Council Directive 84/450/EEC of 10 September 1984 relating to the approximation of the laws, regulations and administrative provisions of the Member States concerning misleading advertising (Directive 84/450/EEC). *Official Journal of the European Communities,* L – 250/17.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Union*, L – 121, 1.5.2001, p. 34.

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. *Official Journal of the European Union*, L – 311, 28/11-2004: p. 67 – 128

Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal of the European Union*, L – 136, 30/04/2004, p. 34 – 57.

Dutch Medicines Act (2007) Regeling van de Minister van Volksgezondheid, Welzijn en Sport van 25 juni 2007, nr.GMT/MVG 2780607, houdende uitvoering van bepalingen van de Geneesmiddelenwet (GnW).

Edict 12/2011. (III. 30.) of the Hungarian Ministry of Human Capacities (12/2011. (III. 30.) NEFMI rendelet 235/2009. (X. 20) Korm. rendelet az emberen végzett orvostudományi kutatások, az emberi felhasználásra kerülő vizsgálati készítmények klinikai vizsgálata, valamint az emberen történő alkalmazásra szolgáló, klinikai vizsgálatra szánt orvostechnikai eszközök klinikai vizsgálata engedélyezési eljárásának szabályairól.

Edict 12/2011. (III. 30.) of the Hungarian Ministry of Human Capacities. 12/2011. (III. 30) NEFMI rendelet az egészségügyi szakmai kollégium működéséről.

Edict 25/2005. (II.25.) of the Hungarian Government: 235/2009. (X. 20) Korm. rendelet az emberen végzett orvostudományi kutatások, az emberi felhasználásra kerülő vizsgálati készítmények klinikai vizsgálata, valamint az emberen történő alkalmazásra szolgáló, klinikai vizsgálatra szánt orvostechnikai eszközök klinikai vizsgálata engedélyezési eljárásának szabályairól.

Edict 25/2005. (II.25.) of the Hungarian Government: 28/2015. (II. 25.) Korm. Rendelet az Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézetről.

Edict 3/2009. (II. 25.) of the Hungarian Ministry of Health: EüM rendelet az emberi felhasználásra kerülő gyógyszer, illetve gyógyászati segédeszköz ismertetésére, az ismertetői tevékenységet végző személyek nyilvántartására, és a gyógyszerrel, gyógyászati segédeszközzel kapcsolatos, fogyasztókkal szembeni kereskedelmi gyakorlatra vonatkozó részletes szabályokról.

EFPIA HCP Code (2014) EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals. European Federation of Pharmaceutical Industries and Associations, Brussels.

EFPIA HCP/HCO Disclosure Code (2014) EFPIA Code on Disclosure of Transfer of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations. European Federation of Pharmaceutical Industries and Associations, Brussels.

EMA CHMP (2010) Guideline of the Investigation for Bioequivalence. European Medicines Agency Committee for Medicinal Products for Human Use, London, UK. [Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr]

GnW Policy Rules (2012) Beleidsregels van de Minister van Volksgezondheid, Welzijn en Sport, van 9 januari 2012, inzake gunstbetoon als bedoeld in artikel 94 van de Geneesmiddelenwet: Beleidsregels gunstbetoon Geneesmiddelenwet.

GyKEK Code (2014) Code of Conduct for Ethical Pharmaceutical Marketing and Communications. A Gyógyszer-Kommunikáció Etikai Kódexe.

Hungarian Criminal Code: 2012. évi C. törvény a Büntető Törvénykönyvről.

Hungarian Medical Chamber Code of Medical Ethics (2012) Magyar Orvosi Kamara Etikai Kódexe.

ICH GCP Guideline (1996) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline. Guideline for Good Clinical Practice. E6(R1)

Judgment of 18 December Fern Olivieri v Commission and EMEA: ECLI: EU: T: 2003:351.

KNMG Code on Medical Professionalism (2007) Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling, Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst.

KNMG COI Code (2012) Code for the Prevention of Improper Influence due to Conflict of Interest. Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling.

KNMG Doctor's rules of Conduct (2013 version 3.1) Gedragsregels voor Artsen, Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst.

Law on Medical Research Involving Human Subjects. (1998) Wet van februari, 1998, Wet Medisch-Wetenschappelijk onderzoek met mensen.

Physician Payments Sunshine Act: Patient Protection and Affordable Care Act, 42 U.S.C. § 18001 (2010) US Public Law 111–148, 111th Congress, Section 6002.

Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.

PricewaterhouseCoopers (2009) Pharmaceutical Newsletter7, (29), Hungary. [Online]
https://www.pwc.com/hu/hu/publications/assets/7th_pwc_pharma_newsletter.pdf

The Dutch Hippocratic Oath, KNMG Artseneed (2010) Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst.

LINKS

[Accreditation Council for Continuing Medical Education]
https://www.uems.eu/areas-of-expertise/cme-cpd/eaccme

[British Transparency database] http://www.abpi.org.uk/

[CGR Dutch Disclosure of payments to Physicians, Transparency Database]
http://www.transparantieregister.nl

[Congressline. Medical Event Organizer] http://www.congressline.hu

[Dutch Association of Innovative Medicines. (Formerly Nefarma) De Vereniging Innovatieve Geneesmiddelen] http://www.verenigginnovatievegeneesmiddelen.nl

[Dutch Association of Physicians for Lung Disease and Tuberculosis, Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT)]
https://www.nvalt.nl/

[Dutch Chamber of Commerce: KvK] https://www.kvk.nl/

[Dutch College of General Practitioners NGH] https://www.nhg.org/

[Dutch Database of Licenced Physicians: BIG register] https://www.bigregister.nl/

[Dutch Federation of Medical Specialists: FMS] https://www.demedischspecialist.nl/

[Dutch guideline for Severe Asthma]
https://richtlijnendatabase.nl/richtlijn/ernstig_astma/ernstig_astma_-_startpagina.html#verantwoording

[Dutch Healthcare Inspectorate: IGZJ formerly IGZ] https://www.igzj.nl/

[Dutch Knowledge Institute: Kennisinstituut] www.kennisinstituut.nl

[Dutch Medical Guideline database] https://richtlijnendatabase.nl/

[Dutch Medical Guidelines for General Practitioners database]
https://www.nhg.org/thema/nhg-behandelrichtlijnen

[Dutch Medicines Evaluation Board: MEB-CGB] www.cbg-meb.nl/over-cbg

[Dutch National Family Practice Association: LHV] https://www.lhv.nl/

[EMA versus Abbvie and InterMune] http://www.raps.org/Regulatory-Focus/News/2014/10/02/20472/In-Landmark-Decision-EMA-Adopts-Clinical-Trials-Transparency-Plan/
http://www.alltrials.net/news/ema-important-european-ruling-abbvie-intermune-cases/
http://www.sciencemag.org/news/2013/04/european-court-wants-drug-data-kept-secret
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001779.jsp&mid=WC0b01ac058004d5c1

[EurdaCT: EMA Clinical Trial database] https://eudract.ema.europa.eu/

[European Federation of Pharmaceutical Industries and Associations] http://www.efpia.eu

[European Innovative Medicines Initiative] http://www.imi.europa.eu/

[European Medicines Agency EudraCT Public Web Reports (May) from 2011 to 2017] https://eudract.ema.europa.eu/statistics.html

[European Medicines Agency] http://www.ema.europa.eu

[European Society of Cardiology] https://www.escardio.org

[European Union of Medical Specialists] http://www.uems.eu

[Frans Timmermans' letter to the chair of the EU parliament's civil liberty committee, and the Presidency of the Council of the European Union] http://transparency.eu/wp-content/uploads/2017/02/20170130-Letter-FVP-LIBE-Chair.pdf

[Hungarian Association of Innovative Pharmaceutical Manufacturers: Innovatív Gyógyszergyártók Egyesülete] http://www.aipm.hu

[Hungarian Association of Medical Societies: MOTESZ] http://www.motesz.hu/

[Hungarian Chamber of Medicine] https://www.mok.hu

[Hungarian Continuing Medical Education database: OFTEX] https://ww.oftex.hu

[Hungarian Database of Medical Guidelines] https://kollegium.aeek.hu/Iranyelvek

[Hungarian National Healthcare Service website] http://www.enkk.hu

[Hungarian national institute for Pharmacy and Nutrition OGYÉI] https://www.ogyei.gov.hu

[ICTRP: World Health Organization International Clinical Trials Registry] http://www.who.int/ictrp/en/

[International Federation of Pharmaceutical Manufacturers and Associations] https://www.ifpma.org

[Pharmaceutical products directory] https://www.drugs.com

[Scene from the TV series "Scrubs"] https://www.youtube.com/watch?v=VMXa0U4WZyU

[TEDx (2014) *Dr Mark Mattson TED Talk: Neuroscientist Shows What Fasting Does To Your Brain*. John Hopkins University] https://www.youtube.com/watch?v=4UkZAwKoCP8

[Transparency International] https://www.transparency.org/

[U.S. Food and Drug Administration] https://www.fda.gov/

[UK Serious Fraud Office] https://www.sfo.gov.uk

[US Clinical Trial database] www.clinicaltrials.gov

[World Health Organization] http://www.who.int

[World Medical Association] https://www.wma.net/

ANNEX

Annex 1: World Medical Association Hippocratic Oath Declaration of Geneva, 1948

At the time of being admitted as a member of the medical profession:

- *I solemnly pledge myself to consecrate my life to the service of humanity;*
- *I will give to my teachers the respect and gratitude which is their due;*
- *I will practice my profession with conscience and dignity; the health of my patient will be my first consideration;*
- *I will maintain by all the means in my power, the honour and the noble traditions of the medical profession; my colleagues will be my brothers;*
- *I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient;*
- *I will maintain the utmost respect for human life from the time of conception, even under threat, I will not use my medical knowledge contrary to the laws of humanity;*
- *I make these promises solemnly, freely and upon my honour.*

Annex 2: Respondents Codes [Hungary]

Date of Interview	Interview method	Occupation	Codes Medicine	Codes Industry	Codes Regulators/ Associations	Codes Other
20/04/2015	face-to-face	Clinical Research Organization		HUPH01		
02/05/2015	face-to-face	Otolaryngology/ Healthcare Politics	HUDR01			
17/06/2015	face-to-face	Otolaryngology	HUDR02			
19/06/2015	face-to-face	Cardiology	HUDR03			
19/06/2015	face-to-face	Endocrinology	HUDR04			
20/06/2015	face-to-face	Anaesthesiology	HUDR05			
22/06/2015	face-to-face	Anaesthesiology	HUDR06			
29/06/2015	face-to-face	Pharmacist Generic Pharmaceutical Company		HUPH02		
30/06/2015	face-to-face	Cardiology	HUDR07			
16/08/2015	face-to-face	Surgery (resident)	HUDR08			
16/09/2015	face-to-face	Nephrology	HUDR09			
24/09/2015	face-to-face	Urology	HUDR10			
30/09/2015	face-to-face	Paediatrics	HUDR11			
01/10/2015	face-to-face	Pharmacist Generic Pharmaceutical Company		HUPH03		
01/10/2015	face-to-face	Sales Representative (Innovative Pharmaceutical Company)		HUPH04		
02/10/2015	face-to-face	Sales Representative (Innovative Pharmaceutical Company)		HUPH05		
05/10/2015	face-to-face	Sales Representative (Innovative Pharmaceutical Company)		HUPH06		
14/10/2015	face-to-face	Clinical Research Organization		HUPH07		
18/10/2015	face-to-face	Rheumatology	HUDR12			
21/10/2015	face-to-face	Psychiatry	HUDR13			
22/10/2015	face-to-face	Neurology	HUDR14			
27/10/2015	face-to-face	Neurology (resident)	HUDR15			
29/10/2015	face-to-face	Urology	HUDR16			

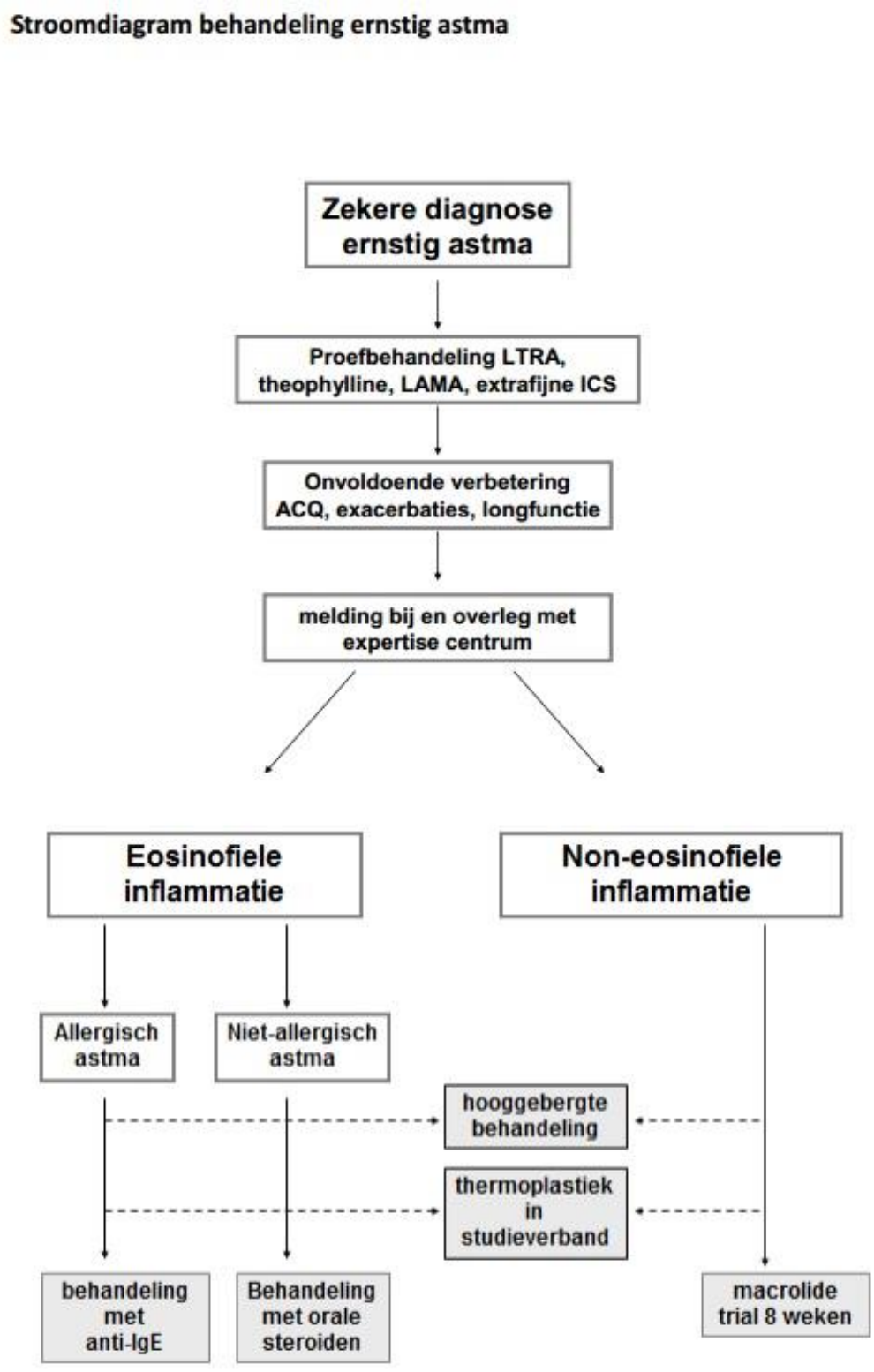
03/11/2015	face-to-face	Psychiatry	HUDR17			
05/11/2015	face-to-face	Neurology (resident)	HUDR18			
06/11/2015	face-to-face	Gynaecology	HUDR19			
10/11/2015	face-to-face (no record-ing allowed)	Pharmaceutical Companies' Association Committee for Ethical Marketing			HUPA01	
16/11/2015	face-to-face	Clinical Research Organization		HUPH08		
16/11/2015	face-to-face	Hospital Clinical Trial Manager	HUDR20			
17/11/2015	face-to-face	Innovative Pharmaceutical Company Compliance Officer		HUPH10		
20/11/2015	face-to-face	National Association of Hungarian Pharmaceutical Manufacturers			HUPA02	
14/12/2015	face-to-face	Clinical Research Organization		HUPH11		
14/12/2015	face-to-face	Urology (resident)	HUDR21			
21/12/2015	face-to-face	Innovative Pharmaceutical Company Legal Counsel		HUPH12		
12/01/2016	face-to-face	Hungarian Medicines Regulatory Authority			HUREG01	
13/01/2016	face-to-face	Urology (resident)	HUDR22			
15/01/2016	face-to-face	Gynaecology	HUDR23			
19/01/2016	face-to-face	Internal Medicine	HUDR24			
19/01/2016	face-to-face (no record-ing allowed)	Hungarian Medical Association			HUMA01	
22/01/2016	face-to-face	General Practice	HUDR25			
29/03/2016	face-to-face	Hungarian Clinical Trial Ethics Committee			HUREG02	
03/04/2016	face-to-face	Psychiatry	HUDR26			
02/08/2015/ 16/09/2015	face-to-face	Hungarian Medicines Regulatory Authority			HUREG03	
04/06/2015/ 29/10/2015	face-to-face	Generic Pharmaceutical Company		HUPH13		

Annex 2: Respondents Codes [Netherlands]

26/02/2016	face-to-face	Gynaecology	NLDR01			
09/03/2016	face-to-face	Medical Journal Editor				NLMJ01
10/03/2016	face-to-face	Healthcare Economist				NLEX01
11/03/2016	face-to-face	General Practice	NLDR02			
12/03/2016	face-to-face (no record-ing allowed)	General Practice	NLDR03			
14/03/2016	face-to-face	Cardiology	NLDR04			
14/03/2016	face-to-face	Cardiology	NLDR05			
11/04/2016	face-to-face	Dutch Medicines Regulatory Authority			NLREG01	
25/04/2016	face-to-face	Cardiology	NLDR06			
26/04/2016	face-to-face	Geriatrics	NLDR07			
11/05/2016	face-to-face	Biopharmaceutical Company		NLPH01		
17/05/2016	face-to-face	Journalist				NLJO01
19/05/2016	face-to-face	General Practice	NLDR08			
25/05/2016	face-to-face	Pulmonology	NLDR09			
02/06/2016	face-to-face	Pharmaceutical Industry Foundation for Ethical Advertising Legal Counsel			NLPA01	
03/06/2016	Telephone	Innovative Pharmaceutical Company		NLPH02		
07/06/2016	face-to-face	Internal Medicine	NLDR10			
13/06/2016	face-to-face	Biopharmaceutical Company		NLPH03		
16/06/2016	face-to-face	Innovative Pharmaceutical Company Compliance Officer		NLPH04		
20/06/2016	face-to-face	Virology	NLDR11			
21/06/2016	face-to-face	Dutch Medicines Regulatory Authority			NLREG02	
23/06/2016	face-to-face	Pharmacist Healthcare NGO				NLOO01
29/06/2016	face-to-face	Cardiology	NLDR12			
18/07/2016	Telephone	Innovative Pharmaceutical Company Compliance Officer		NLPH05		
19/07/2016	face-to-face	Innovative Pharmaceutical Company Manager		NLPH06		

27/07/2016	face-to-face	Other Healthcare Organization				NLOO02
08/08/2016	face-to-face	Internal Medicine	NLDR13			
09/08/2016	face-to-face	Oncology	NLDR14			
11/08/2016	face-to-face	Dutch Association for Innovative Pharmaceutical Companies			NLPA02	
29/08/2016	face-to-face	Pulmonology	NLDR15			
13/10/2016	face-to-face	Healthcare Economist				NLEX02
18/10/2016	face-to-face	Cardiology	NLDR16			
01/02/2017	face-to-face	Innovative Pharmaceutical Company Compliance Officer		NLPH07		
02/03/2017	e-mail and telephone	Journalist				NLJO02
24/03/2017	face-to-face	Pharmaceutical Industry Foundation for Ethical Advertising Legal Counsel			NLPA03	
27/03/2017	face-to-face	Medical Association for General Practitioners			NLMA01	
05/04/2017	face-to-face	Federation for Medical Specialists/Royal Dutch Medical Association			NLMA02/03	
20/04/2016/ 12/10/2016	face-to-face	General Practitioner	NLDR17			
18/03/2016/ 29/08/2016	face-to-face	Gynaecology	NLDR18			

Annex 3: Dutch Guideline for Severe Asthma, Dutch Association of Physicians for Lung Disease and Tuberculosis (NVALT), Flowchart for patients. (Full text upon request)



Annex 4: Dutch Association of Physicians for Lung Disease and Tuberculosis (NVALT) Disclosure Report 2014

Zoeken op KvK-nummer

U heeft gezocht op: Kvk-nummer "40477494", Jaar: "2014".

Zoekresultaat

Naam	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT)
Plaats	'S-HERTOGENBOSCH

Resultaten 1-23 van 23

1. Farma/MD: Astra-Zeneca
   Type: Sponsoring samenkomst
   Bedrag: € 10.500,00
2. Farma/MD: Astra-Zeneca
   Type: Sponsoring samenkomst
   Bedrag: € 650,00
3. Farma/MD: Astra-Zeneca
   Type: Sponsoring samenkomst
   Bedrag: € 8.600,00
4. Farma/MD: Boehringer Ingelheim BV
   Type: Sponsoring samenkomst
   Bedrag: € 27.500,00
5. Farma/MD: Chiesi Pharmaceuticals BV
   Type: Sponsoring samenkomst
   Bedrag: € 12.900,00
6. Farma/MD: Chiesi Pharmaceuticals BV
   Type: Sponsoring samenkomst
   Bedrag: € 7.000,00
7. Farma/MD: Eli Lilly and Company
   Type: Sponsoring samenkomst
   Bedrag: € 40.000,00
8. Farma/MD: Eli Lilly and Company
   Type: Sponsoring samenkomst
   Bedrag: € 650,00
9. Farma/MD: Eli Lilly and Company
   Type: Sponsoring samenkomst
   Bedrag: € 7.000,00
10. Farma/MD: Eli Lilly and Company
    Type: Sponsoring project
    Bedrag: € 7.022,00
11. Farma/MD: Eli Lilly and Company
    Type: Sponsoring samenkomst
    Bedrag: € 8.200,00
12. Farma/MD: Eli Lilly and Company
    Type: Sponsoring samenkomst
    Bedrag: € 8.600,00
13. Farma/MD: GlaxoSmithKline BV
    Type: Sponsoring samenkomst
    Bedrag: € 14.000,00
14. Farma/MD: Mundipharma Pharmaceuticals B.V.
    Type: Sponsoring samenkomst
    Bedrag: € 3.500,00
15. Farma/MD: Mundipharma Pharmaceuticals B.V.
    Type: Sponsoring samenkomst

Bedrag: € 4.300,00

16. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 1.750,00
17. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 1.750,00
18. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 10.500,00
19. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 12.900,00
20. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 4.300,00
21. Farma/MD: Roche Nederland B.V.
    Type: Sponsoring samenkomst
    Bedrag: € 750,00
22. Farma/MD: Takeda Nederland BV
    Type: Sponsoring samenkomst
    Bedrag: € 7.000,00
23. Farma/MD: Takeda Nederland BV
    Type: Sponsoring samenkomst
    Bedrag: € 8.600,00

Terug naar zoeken op kvk-nummer

Annex 4: Dutch Association of Physicians for Lung Disease and Tuberculosis (NVALT) Disclosure Report 2015

Zoeken op KvK-nummer

U heeft gezocht op: Kvk-nummer "40477494", Jaar: "2015".

Zoekresultaat

Naam	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT)
Plaats	'S-HERTOGENBOSCH

Resultaten 1-29 van 29

1. Farma/MD: Astra-Zeneca
   Type: Sponsoring samenkomst
   Bedrag: € 8.600,00
2. Farma/MD: Astra-Zeneca
   Type: Sponsoring samenkomst
   Bedrag: € 9.000,00
3. Farma/MD: Boehringer Ingelheim BV
   Type: Sponsoring samenkomst
   Bedrag: € 24.200,00
4. Farma/MD: Boehringer Ingelheim BV
   Type: Sponsoring project
   Bedrag: € 5.203,00
5. Farma/MD: Boehringer Ingelheim BV
   Type: Sponsoring samenkomst
   Bedrag: € 7.260,00
6. Farma/MD: Bristol-Myers Squibb
   Type: Sponsoring samenkomst
   Bedrag: € 12.000,00
7. Farma/MD: Eli Lilly and Company
   Type: Sponsoring samenkomst
   Bedrag: € 40.000,00
8. Farma/MD: Eli Lilly and Company
   Type: Sponsoring samenkomst
   Bedrag: € 40.000,00
9. Farma/MD: Eli Lilly and Company
   Type: Sponsoring samenkomst
   Bedrag: € 6.000,00
10. Farma/MD: Eli Lilly and Company
    Type: Sponsoring samenkomst
    Bedrag: € 8.600,00
11. Farma/MD: Gilead Sciences Netherlands B.V.
    Type: Sponsoring project
    Bedrag: € 2.618,00
12. Farma/MD: Gilead Sciences Netherlands B.V.
    Type: Sponsoring samenkomst
    Bedrag: € 5.203,00
13. Farma/MD: GlaxoSmithKline BV
    Type: Sponsoring samenkomst
    Bedrag: € 14.520,00
14. Farma/MD: Mundipharma Pharmaceuticals B.V.
    Type: Sponsoring samenkomst
    Bedrag: € 3.000,00
15. Farma/MD: Mundipharma Pharmaceuticals B.V.
    Type: Sponsoring samenkomst

Bedrag: € 4.300,00

16. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 10.000,00
17. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 2.150,00
18. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 2.150,00
19. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 4.300,00
20. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 6.000,00
21. Farma/MD: Pfizer BV
    Type: Sponsoring project
    Bedrag: € 10.000,00
22. Farma/MD: Pfizer BV
    Type: Sponsoring samenkomst
    Bedrag: € 3.000,00
23. Farma/MD: Roche Nederland B.V.
    Type: Sponsoring samenkomst
    Bedrag: € 1.750,00
24. Farma/MD: Roche Nederland B.V.
    Type: Sponsoring samenkomst
    Bedrag: € 12.000,00
25. Farma/MD: Roche Nederland B.V.
    Type: Sponsoring samenkomst
    Bedrag: € 20.000,00
26. Farma/MD: Roche Nederland B.V.
    Type: Sponsoring samenkomst
    Bedrag: € 4.300,00
27. Farma/MD: Sandoz
    Type: Sponsoring samenkomst
    Bedrag: € 3.630,00
28. Farma/MD: Takeda Nederland BV
    Type: Sponsoring samenkomst
    Bedrag: € 3.630,00
29. Farma/MD: Takeda Nederland BV
    Type: Sponsoring samenkomst
    Bedrag: € 5.203,00

Terug naar zoeken op kvk-nummer

Annex 4: Dutch Association of Physicians for Lung Disease and Tuberculosis (NVALT) Disclosure Report 2015

Zoeken op KvK-nummer

U heeft gezocht op: Kvk-nummer "40477494", Jaar: "2016".

Zoekresultaat

Naam	Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT)
Plaats	'S-HERTOGENBOSCH

Resultaten 1-24 van 24

1. Farma/MD: Astra-Zeneca
   Type: Sponsoring project
   Bedrag: € 10.889,00
2. Farma/MD: Astra-Zeneca
   Type: Sponsoring samenkomst
   Bedrag: € 10.890,00
3. Farma/MD: Astra-Zeneca
   Type: Sponsoring samenkomst
   Bedrag: € 24.200,00
4. Farma/MD: Boehringer Ingelheim BV
   Type: Sponsoring project
   Bedrag: € 1.210,00
5. Farma/MD: Boehringer Ingelheim BV
   Type: Sponsoring samenkomst
   Bedrag: € 14.520,00
6. Farma/MD: Boehringer Ingelheim BV
   Type: Sponsoring samenkomst
   Bedrag: € 24.200,00
7. Farma/MD: Bristol-Myers Squibb
   Type: Sponsoring samenkomst
   Bedrag: € 14.520,00
8. Farma/MD: Chiesi Pharmaceuticals BV
   Type: Sponsoring project
   Bedrag: € 18.567,00
9. Farma/MD: Chiesi Pharmaceuticals BV
   Type: Sponsoring samenkomst
   Bedrag: € 27.500,00
10. Farma/MD: Eli Lilly and Company
    Type: Sponsoring samenkomst
    Bedrag: € 20.000,00
11. Farma/MD: Eli Lilly and Company
    Type: Sponsoring samenkomst
    Bedrag: € 6.000,00
12. Farma/MD: GlaxoSmithKline BV
    Type: Sponsoring samenkomst
    Bedrag: € 14.520,00
13. Farma/MD: GlaxoSmithKline BV
    Type: Sponsoring samenkomst
    Bedrag: € 24.200,00
14. Farma/MD: GlaxoSmithKline BV
    Type: Sponsoring samenkomst
    Bedrag: € 5.203,00
15. Farma/MD: Mundipharma Pharmaceuticals B.V.
    Type: Sponsoring samenkomst

Bedrag: € 6.000,00

16. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 10.000,00
17. Farma/MD: Novartis Pharma BV
    Type: Sponsoring samenkomst
    Bedrag: € 20.000,00
18. Farma/MD: Pfizer BV
    Type: Sponsoring samenkomst
    Bedrag: € 10.000,00
19. Farma/MD: Pfizer BV
    Type: Sponsoring project
    Bedrag: € 20.000,00
20. Farma/MD: Pfizer BV
    Type: Sponsoring samenkomst
    Bedrag: € 3.000,00
21. Farma/MD: Pfizer BV
    Type: Sponsoring samenkomst
    Bedrag: € 3.000,00
22. Farma/MD: Roche Nederland B.V.
    Type: Sponsoring project
    Bedrag: € 20.000,00
23. Farma/MD: Roche Nederland B.V.
    Type: Sponsoring samenkomst
    Bedrag: € 20.000,00
24. Farma/MD: Sandoz
    Type: Sponsoring samenkomst
    Bedrag: € 3.630,00

Terug naar zoeken op kvk-nummer

Annex 5: Disclosure of Author Conflict of Interests Dutch Guideline for Severe Asthma

Werkgroeplid	Functie	Nevenfuncties	Persoonlijke financiële belangen	Persoonlijke relaties	Reputatie-management	Extern gefinancierd onderzoek	Kennis-valorisatie	Overig belang
Author 1	Longarts St. Franciscus Gasthuis Rotterdam	Nederlands Tijdschrift voor Allergie (lid/redactie, onbetaald) Merck Sharp & Dohme BV (lid/adviesraad, betaald). Mundipharma BV (lid/adviesraad, betaald) Novartis Pharma BV (lid/adviesraad, betaald)						
Author 2	Longarts Haga Ziekenhuis Den Haag (part-time). Als ZZP-er werkzaam in het kader van consultancy op het gebied van obstructieve longaandoeningen	In 2012 enkele maanden waarneming Nederlands Astmacentrum Davos ivm ziekte collega						
Author 3	Longarts, staflid. AMC, Amsterdam							
Author 4	Longarts, Medisch Centrum Leeuwarden							

Annex 5: Disclosure of Author Conflict of Interests Dutch Guideline for Severe Asthma

Werkgroeplid	Functie	Nevenfuncties	Persoon-lijke financiële belangen	Persoonlijke relaties	Reputatie-management	Extern gefinancierd onderzoek	Kennis-valorisatie	Overig belang
Author 5	Longarts in het Nederlands Astmacentrum Davos, Zwitserland Onderzoeker					Het Nederlands Astmacentrum Davos heft sponsoring gekregen van de Patiënten Vereniging Nederland Davos, om wetenschappelijk onderzoek naar het effect van Hooggebergte behandeling wetenschappelijk te evalueren.		
Author 6	Hoogleraar Afdeling-shoofd Longziekten, AMC Amsterdam				Vice-president European Respiratory Society (onbetaald). Lid. Wetenschappelijke commissie GINA (Global Initiative for Asthma) (onbetaald). Lid Richtlijn commissie Severe Asthma voor de American Thoracic Society/European Respiratory Society (onbetaald). Lid Wetenschappelijke redactie American Journal of Respiratory and Critical Care Medicine (onbetaald).	GlaxoSmithKline: deelname onderzoek naar effect Monoclonal antilichaam tegen IL-5 bij astma. GlaxoSmithKline: financiering onderzoek naar astma dat op oudere leeftijd ontstaat. Novartis: onderzoek naar prevalentie van ernstig astma in Nederland.		

Annex 6: Tables showing Hungarian Medical College members and corresponding position within Hungarian Medical Associations. (Original data)

College of Clinical Immunology and Allergology

College Chairmen	Medical Organization and Position
Member 1	Hungarian Allergology and Clinical Immunology Society: Member of the Board and Vice-Chairman
Member 2	No affiliations
Member 3	No affiliations

College of Anaesthesiology and Intensive Therapy

College Chairmen	Medical Organization and Position
Member 1	Hungarian Anaesthesiology and Intensive Therapy Society: Vice-Chairman of the Scientific Commission
Member 2	Hungarian Anaesthesiology and Intensive Therapy Society: Ex-Chairman
Member 3	Hungarian Anaesthesiology and Intensive Therapy Society: Vice-Chairman

College of Balneotherapy

College Chairmen	Medical Organization and Position
Member 1	Hungarian Balneology Society :Vice-Chairman
Member 2	Hungarian Balneology Society: Member of the Board
Member 3	Hungarian Rheumatologists Association: Vice-Chairman Hungarian Balneology Society: Member of the Board

College of Internal Medicine, Endocrinology, Diabetes, and Metabolic Diseases

College Chairmen	Medical Organization and Position
Member 1	Hungarian Internal Medicine Society: Member of the Board
Member 2	Hungarian Internal Medicine Society: Member of the Board Hungarian Endocrinology and Metabolism Society: Member of the Board

College of Dermatology and Sexually Transmitted Diseases

College Chairmen	Medical Organization and Position
Member 1	Hungarian Dermatology Society: Member of the Board
Member 2	Hungarian Dermatology Society: Member
Member 3	Hungarian Sexually Transmitted Infection Society: Member of the Board

College of Gastroenterology and Hepathology

College Chairmen	Medical Organization and Position
Member 1	Hungarian Gastroenterology: Society: ex-Member of the Board, currently Honorary Member
Member 2	Hungarian Gastroenterology Society: Member of the Board
Member 3	Hungarian Gastroenterology Society: Member of the Board

College of Transfusion and Haematology

College Chairmen	Medical Organization and Position
Member 1	Hungarian Haematology and Transfusion Society: Member of the Board
Member 2	Hungarian Haematology and Transfusion Society: Member
Member 3	Hungarian Haematology and Transfusion Society: Member of the Scientific Commission

College of Infectology

College Chairmen	Medical Organization and Position
Member 1	Hungarian Infectology and Clinical Microbiology Society: Member of the Board
Member 2	Hungarian Infectology and Clinical Microbiology Society: Secretary General
Member 3	Hungarian Infectology and Clinical Microbiology Society: Ex-Chairman

College of Cardiology

College Chairmen	Medical Organization and Position
Member 1	Hungarian Society of Cardiologists: Chairman of the Scientific Committee
Member 2	Hungarian Society of Cardiologists: Advisory Board Member
Member 3	Hungarian Society of Cardiologists: Advisory Board Member

College of Oncology and Radiation Therapy

College Chairmen	Medical Organization and Position
Member 1	Hungarian Society of Oncologists: Member of the Board Hungarian Radiotherapy Society: Member
Member 2	Hungarian Society of Oncologists: Member of the Board
Member 3	Hungarian Society of Clinical Oncologists: Honorary Chairman

College of Nephrology and Dialysis

College Chairmen	Medical Organization and Position
Member 1	Hungarian Nephrology Society: Member of the Board
Member 2	Hungarian Nephrology Society: Member of the Board
Member 3	Hungarian Nephrology Society: Chairman

College of Neurology

College Chairmen	Medical Organization and Position
Member 1	No affiliations
Member 2	Hungarian Neurology Society: Chaiman
Member 3	No affiliations

College of Obstetrics, Gynaecology, and Assisted Reproduction

College Chairmen	Medical Organization and Position
Member 1	Hungarian Gynaecological Society: Member of the Board
Member 2	Hungarian Gynaecological Society: Treasurer
Member 3	No affiliations

College of Orthopaedics

College Chairmen	Medical Organization and Position
Member 1	Hungarian Orthopaedic Society: Member of the Board
Member 2	Hungarian Orthopaedic Society: Member of the Board
Member 3	No affiliations

College of Psychiatry and Psychotherapy

College Chairmen	Medical Organization and Position
Member 1	Hungarian Psychiatric Association: Member of the Board
Member 2	Hungarian Psychiatric Association: Member of the Board
Member 3	Hungarian Society of Psychopharmacologists: Member of the Board

College of Rheumatology

College Chairmen	Medical Organization and Position
Member 1	Hungarian Rheumatologists Association: Member of the Board
Member 2	Hungarian Rheumatologists Association: Vice-Chairman
Member 3	Hungarian Rheumatologists Association: Member of the Board

College of Surgery

College Chairmen	Medical Organization and Position
Member 1	Hungarian Surgical Society: Member of the Board
Member 2	Hungarian Surgical Society: Member of the Board
Member 3	Hungarian Surgical Society: Chairman (stepping down)

College of Ophthalmology

College Chairmen	Medical Organization and Position
Member 1	Hungarian Ophthalmology Society: Chairman
Member 2	Hungarian Ophthalmology Society: Vice-Chairman
Member 3	Hungarian Ophthalmology Society: Member of the Board

College of Transplantation

College Chairmen	Medical Organization and Position
Member 1	Hungarian Transplantation Society: Member of the Board
Member 2	Hungarian Transplantation Society: Member of the Board
Member 3	Hungarian Transplantation Society: Member of the Board

College of Traumatology and Hand Surgery

College Chairmen	Medical Organization and Position
Member 1	Hungarian Traumatology Society: Member
Member 2	Hungarian Traumatology Society: Member of the Board
Member 3	Hungarian Traumatology Society: Member of the Board

College of Pulmonary Medicine

College Chairmen	Medical Organization and Position
Member 1	Hungarian Pneumatic Society: Chairman
Member 2	Hungarian Pneumatic Society: Member of the Board
Member 3	Hungarian Pneumatic Society: Member of the Board

College of Urology

College Chairmen	Medical Organization and Position
Member 1	Hungarian Society of Urologists: Member of the Board
Member 2	Hungarian Society of Urologists: Member of the Board
Member 3	Hungarian Society of Urologists: Secretary General