Continuous innovation in the drug life cycle

Joris Langedijk

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Continue innovatie in de levenscyclus van een geneesmiddel

(met een samenvatting in het Nederlands)

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Chapter 1

General introduction

INTRODUCTION

Drug regulation starts before but continues after initial market approval and throughout the entire drug life cycle.[1] Likewise innovation continues after the initial marketing authorisation such as the use for new therapeutic indications and the development of new dosage forms. Previously such innovation has been referred to as 'post-innovation innovation'.[1,2] Throughout the drug life cycle various factors affect the continuation of innovation. One such factor may be the introduction of a generic product version (Figure 1). The introduction of a generic product version of a medicinal product is a specific and important moment in a drug life cycle with several consequences for public health and further innovation. For a proper understanding of those consequences one needs to understand what generic products are and how the intellectual property prospects of a drug changes when it enters the post-generic phase of its life cycle, in that regard see Box 1.

POST-INNOVATION INNOVATION: MAJOR DISCOVERIES AND INCREMENTAL IMPROVEMENTS

Drug innovation encompasses both major discoveries and incremental improvements. Obviously the discovery of a new active substance is considered as a major discovery in drug innovation. In the post-innovation phase the discovery of a new therapeutic indication, as with drug repositioning, may also be considered a major discovery. Drug repositioning refers to the development of new therapeutic indications for existing drugs.[1–3] It is believed that drug repositioning offers great benefits over *de novo* drug discovery, the traditional way of drug discovery by searching for a new active substance. Drug repositioning should allow for a quicker and cheaper drug development by the utilisation of current knowledge of the drug, e.g. pharmacokinetic and safety data.[3] Moreover, in the post-generic phase the active substance is available at low costs. Already many potential new therapeutic indications for old drugs as well as methods to identify such uses have been proposed in literature.[4–7] For example, the cholesterol-lowering drugs simvastatin and fluvastatin have been suggested as candidates for further research into use for the treatment of prostate cancer.[8] From a public health perspective, it is important that such new indications are not only developed but also licensed. The licensing procedure allows for an in-depth benefit-risk assessment by the competent authorities. Moreover, after approval the new indications will be included in the official product information, e.g. the package leaflet. This provides physicians and patients with reliable information about the use of the product, including posology and potential side effects.

Box 1: Generic products and changes to the intellectual property prospect.

Generic products contain the same active substance and have (basically) the same dosage form as the innovator product, i.e. the original drug. For the substantiation of the efficacy and safety of a generic product, the marketing authorisation holder refers to the non-clinical and clinical data of the innovator product. In addition, the marketing authorisation holder of a generic product needs to show bioequivalence or therapeutic equivalence with the innovator product.[45]

Initially after the development of a new drug, generic product versions are prevented from entering the market by patents and/or regulatory protection. This results in a period of exclusivity, during which the innovator company is essentially the sole manufacturer of that specific product.[46] In short, and without legal particularities, in the EU patents provide the exclusive right to commercialize an invention for a period of twenty years starting upon the patent application.[47,48] Patents can be granted for 1) active substances (i.e. composition of matters patents), 2) the composition or the method of application of a drug (formulation patents), 3) methods to manufacture an active substance or dosage form (process patents), or 4) the use of a drug in a therapeutic indication (usage patents).[49] In addition to patent protection, there is regulatory protection such as data exclusivity. During the period of data exclusivity applicants of a generic marketing authorisation cannot refer to the non-clinical and clinical data in the dossier of the innovator product.[47,50] In the EU, data exclusivity lasts 8 years and is complemented by 2 years of market protection. During those 2 years generic product versions can be approved but cannot be placed on the market.[50,51] Finally, there is a possibility to obtain special market exclusivity for orphan medicinal products. This market exclusivity prevents other medicinal products for the same therapeutic indication to obtain market approval.[18] It should be noted that patents and regulatory protection are subject to strict conditions and limitations, which have been omitted here for the sake of clarity.

In general, pharmaceutical companies will use a combination of patents and regulatory protection to create a period of exclusivity.[47,49] That period allows the innovator company to increase the probability of a sufficient return on investment.[52] The exclusivity also provides an incentive for further innovation that enlarges the product's market, for example, by extensions of the therapeutic indication which subsequently enlarges the usage potential for their product.[53–55] In addition, patents ensure disclosure of innovations, which may facilitate further innovation by others. Once the initial patents and regulatory protection, e.g. the patent on the active substance, the data exclusivity and market protection, have expired generic product versions can enter the market.[47] Generic product versions tend to be much cheaper than the innovator product. Therefore, the market share of the innovator product plummets after the introduction of a generic product version.[56,57] Grabowski et al. have shown that in the US the market share of innovator products reduced on average to only 16% one year after generic introduction.[56]

However, in the post-innovation period also smaller incremental improvements to existing drugs occur such as the development of new dosages forms, target populations and improvements in drug formulation. Similarly, the development of generic product versions is a form of innovation that contributes to social prosperity. From a public health and cost-containment perspective the availability of cheaper alternatives for clinical usage is of great benefit.[9,10] One year after generic introduction price reductions have been reported to range from 16% (Italy) to 59% (Sweden).[11] Savings by generic medicinal products may provide necessary resources to reimburse newer and more expensive drugs.[12] The use of generic drugs may thus also increase access to medicines for society as a whole.

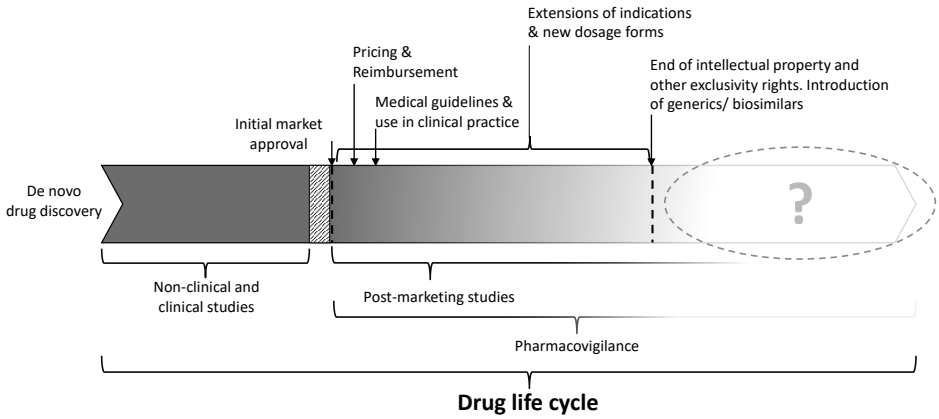
POST-INNOVATION INNOVATION IN THE DRUG REGULATORY SYSTEM

Drug innovation takes place within one of the most heavily regulated sectors. Legislation concerns virtually every aspect from drug development to drug use. In 1965, regulations on prior market approval have been established on a European level and ever since the European Union's (EU) legislation on medicinal products has expaneded.[13–18] Moreover, national laws of EU member states regulate pricing, reimbursement, prescribing and dispensing of medicines, which may have been subject to regular policy changes too. As a whole the drug regulatory system aims to provide patients with access to safe and effective medicines.

One of the major challenges faced by the regulatory system is to find the right balance between safeguarding public health and stimulation of innovation to address patient needs. Previous research has shown a licensing failure rate of approximately 34% to 40% for new drugs and 27.1% to 29% for all drugs approved through the EU centralised procedure.[19–22] Licensing failure means that a company has applied for a licence and the regulatory authorities have refused the application or the company has withdrawn the application. Both lead to waste of resources and less access to medicines. Knowledge about the reasons for licensing failure could help pharmaceutical companies to identify deficiencies in their applications and to improve their drug development programs. It may also assist regulatory authorities to remove unnecessary hurdles for market approval. Currently, however, little is known about the outcome of regulatory pathways such the EU Decentralised Procedure (DCP) and the EU Mutual Recognition Procedure (MRP) in which known active substances, such as generic products, account for the far majority of licensing applications.[23] Given the cost benefits of generic medicinal products the drug regulatory system should also function properly to obtain market approval for generic medicinal products.

Furthermore, very little is known about to what extent the drug regulatory system enhances or hampers post-innovation innovation specifically once a drug has entered the post-generic phase of its life cycle (Figure 1).[1] The drug life cycle may be more complex than the linear model in Figure 1 suggests. The introduction of generic competition may have major consequences for investments in further studying and regulatory processing of new, additional, indications. Pharmaceutical companies will benefit less from extensions of the indication after the approval of a generic product version than during the initial period of exclusivity. Their products may be substituted by generic product versions, even for new therapeutic indications. In addition, post-innovation innovation may be driven directly by the needs in clinical practice to treat patients with the medicines available. Consequently, new therapeutic uses may not be licensed first, but become common practice as off-label use or as the use of pharmacy prepared medicinal products. This raises questions about the alignment of patient needs in clinical practice and the purpose and scope of the marketing authorisation within the current drug regulatory system.

Figure 1: The drug life cycle.



DRUG REGULATORY SCIENCE

As outlined above, the regulatory system itself may play an important role in post-innovation innovation. The scientific discipline of drug regulatory science aims to assess the efficiency and effectiveness of the drug regulatory system and to develop tools to improve the regulatory process.[24,25] It provides data to the public debate on how the system performs. The knowledge gained on the functioning of the drug regulatory system also allows for better decision making by governmental organisations and other stakeholders such as pharmaceutical companies. In the Netherlands, the Escher project was one of the largest projects in its kind which initiated research projects that

aimed to identify, evaluate and remove regulatory bottlenecks in the process from drug development to patient access.[26] Additionally, the Dutch Medicines Evaluation Board has fostered regulatory science over time.[27] On a European level the Innovative Medicines Initiative (IMI) has launched several projects. The GETREAL project, for example, aims to develop new ways of incorporating real-life clinical data into drug development.[28]

Drug regulatory science relates to the regulatory process over the full scope of the drug life cycle. Previous research in the field of regulatory science has already covered a wide variety of topics. For instance, the drug life cycle itself has been used as a heuristic tool to analyse safety controversies to obtain a better understanding of the drug life cycle dynamics.[29] Furthermore, scientists and regulators have studied the value of animal studies,[30,31] regulatory challenges of clinical trial designs,[32,33] the decision making process for approval of new chemical entities,[19,34] the development of orphan drugs,[35] the approval of biosimilars,[36] pharmacovigilance measures,[37,38] and have proposed new regulatory approaches and tools.[39] The focus of drug regulatory science has thus frequently been on new chemical entities and biologicals and specific forms of innovation such as orphan medicinal products and biosimilars.[19,20,40–44] So far, however, little attention has been paid to the performance of the drug regulatory system in the late phase of the drug life cycle and the opportunities for further innovation during that phase.

THESIS AIM

The aim of this thesis is to provide insight in the performance of the drug regulatory system for medicines in the post-innovation phase, including the post-generic phase, of their life cycle from both a regulatory and a legal perspective. This insight may contribute to current debates within the pharmaceutical sector on hot topics such as regulatory reform, drug pricing and cost containment, pharmacy preparations and off-label use. First, we aim to study licensing failure in the DCP and MRP as those two procedures are frequently used to obtain approval for generic medicinal products. Subsequently, we aim to assess to what extent the drug regulatory system allowed for innovation in the post-innovation phase of the drug life cycle in the form of licensing new therapeutic indications and other uses. Finally, we intend to position such innovation within the legal context of the drug regulatory system.

THESIS OUTLINE

In **chapter 2** we focus on licensing failure. First, in **chapter 2.1,** we determine the frequency of and determinants for licensing failure of marketing authorisation applications submitted via the DCP. Next, **chapter 2.2** studies outcomes of marketing authorisation applications via the MRP and DCP and assesses determinants of licensing failure during CMDh referral procedures.[1]

Chapter 3 evaluates the development and licensing of new therapeutic indications in the post-innovation phase of the drug life cycle. In **chapter 3.1** we assess the quantity and nature of extensions of indication of small molecule medicinal products authorised through the European Medicines Agency throughout the drug product life cycle and the impact of the introduction of a first generic competitor on these measures. Subsequently, we examine in **chapter 3.2** whether the introduction of a generic product version is associated with changes in the number and funding source of clinical trials. **Chapter 3.3** characterises medicines used in clinical practice before 1 January 2000 that were approved for a new innovation, i.e. a new therapeutic indication or other innovation.

Subsequently, **chapter 4** provides a legal context to post-innovation innovation in clinical practice and highlights the need for clear terminology. **Chapter 4.1** focuses on the scope and purpose of the marketing authorisation, specifically on the legal space for off-label use and pharmacy prepared medicinal products. In **chapter 4.2** we explore the terminology and definitions used for the development of new uses of existing drugs such as drug repositioning.

In **chapter 5** we present the general discussion to place the results in a broader perspective. In this chapter we also provide recommendations for policy makers and drug developers and indicate areas for future research.

1 The Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh) coordinates marketing authorisation application that involve multiple member states and aims to resolve any disagreements among Member States.

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Chapter 2

Reasons for licensing failure

Chapter 2.1

Licensing failure in the European decentralised procedure

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ABSTRACT

The majority of the licensing applications in the European Union are submitted via the decentralised procedure. Little is known about licensing failure (i.e. refusal or withdrawal of a marketing authorisation application) in the EU decentralised procedure compared to the EU centralised procedure and the approval procedure in the United States. The study aim was to determine the frequency of and determinants for licensing failure of marketing authorisation applications submitted via this procedure. We assessed procedures that failed between 2008 and 2012 with The Netherlands as leading authority and assessed the remaining major objections. In total 492 procedures were completed, of which 48 (9.8%) failed: 8 refused, 40 withdrawn. A wide variety of major objections was identified and included both quality (48 major objections) and clinical (45 major objections) issues. The low failure rate may be related to the regular interaction between competent authorities and applicants during the procedure. Some degree of licensing failure may be inevitable, as it may also be affected by the financial feasibility or willingness to resolve major objections, as well as other reasons to withdraw an application besides the raised major objections.

INTRODUCTION

Regulation of pharmaceutical products essentially covers two main categories: medicinal products with a new active substance and products with a known active substance that is generally not no longer patent protected. So-called generic medicinal products represent the majority of this second category. Previous research on licensing failure, i.e. a company has applied for a licence and the regulatory authorities have refused the application or the sponsor has withdrawn the application, focused on the regulatory fate of new active substances in the United States (US) and in the European Union (EU) centralised procedure.[1–7] The latter procedure results in a single marketing authorisation for the entire EU. These studies indicate that approximately a fourth of the marketing authorisation applications fail. So far, however, little is known about the outcome of other regulatory pathways,[8] like the decentralised procedure (DCP) in Europe, which is most commonly used for the second category of medicinal products.[9]The DCP was introduced in 2005 and allows an applicant to file for a marketing authorisation in multiple, but not necessarily all, EU member states through a single procedure. The DCP accounted for the majority of applications for a marketing authorisation with 1052 procedures in 2013[9] compared to 80 procedures submitted through the centralised procedure.[10] Upon the application one member state acts as the Reference Member State and leads the procedure which includes performing the main benefitrisk assessment. For example, the Netherlands acted as the leading authority in over 25% of all finished DCP procedures in 2013.[9] In the assessment of the submitted dossier the member states may raise major objections, which, if unresolved, are cause for refusal of the marketing authorisation application.

Licensing failure can be seen as a signature of robust regulatory control and protection of public health by preventing unsafe or inefficacious medicines reaching the patient. On the other hand, considerable resources are spent by both companies and regulatory authorities in navigating a dossier through a myriad of procedural steps raising the question of regulatory efficiency and preventable failure. Knowledge about the reasons for licensing failure could help pharmaceutical companies to identify deficiencies in their applications and to improve their drug development programs. Also, it may assist regulatory authorities to remove unnecessary hurdles for market approval.

Our study aimed to determine the frequency of and determinants for licensing failure of marketing authorisation applications submitted via the DCP. We focussed our study on those applications where the Netherlands (i.e. the Dutch Medicines Evaluation Board) was the lead member state.

MATERIAL AND METHODS

Data source

All marketing authorisation applications submitted between 1 January 2008 and 31 December 2012 in the DCP for which the Netherlands acted as the leading authority were extracted from the EU Communication and Tracking System in January 2014. Applications for the same medicinal product, but with different strengths or different product names, by the same (group of) applicant(s) were grouped into a single procedure. Subsequently, we selected the procedures in which all applications were completed and determined their outcomes. Licensing failure was defined as refusal of all applications within a procedure or withdrawal of all applications within a procedure by the applicant.

Data collection

For all completed procedures the Anatomical Therapeutic Chemical (ATC) code of the medicinal products and the legal basis (e.g. generic, hybrid or full dossier application)[11] were extracted from the Dutch Medicines Evaluation Board's documentation system. Next, for the failed procedures with at least an initial assessment report we extracted the remaining major objections from the last available assessment report – assessment reports are compiled at day 70, 120, 180 or 210 of the assessment procedure – in each procedure as documented by the Dutch Medicines Evaluation Board. So, no major objections were analysed for invalid applications and applications withdrawn before day 70 of the assessment procedure. For the failed procedures we also noted whether scientific advice was provided prior to the application.

Major objections were grouped into domains and subdomains: (1) Quality — Drug products and Drug substance; (2) Non-clinical — Pharmacodynamics, Pharmacokinetics and Toxicology; and (3) Clinical — Benefit-Risk and Equivalence. Within the subdomains the major objections were grouped into issue categories and subsequently specific issues were identified.

Data analysis

The number of procedures and the number of major objections per domain, subdomain, issue category and specific issues were entered into a database. We used descriptive statistics to present characteristics of the completed procedures, licensing failure rates and frequencies of specific major objections. Risk ratios were calculated using MedCalc (www.medcalc.org/calc/relative_risk.ph). To assess potential differences in reasons for failure at different points in time during the procedure an additional analysis was performed comparing early termination of a procedure (latest report is from day 70 or day

120) with late termination (latest report is from day 180 or day 210) of a procedure using a chi-square test.

RESULTS

Characteristics of the analysed procedures and licensing failure rates

During the study period 2482 marketing authorisation applications were submitted that constituted a total of 519 procedures. Of these, 492 procedures including 188 active substances were completed by January 2014, of which 48 (9.8%) procedures including 40 active substances resulted in licensing failure: 8 (1.6%) by refusal and 40 (8.1%) by withdrawal.

Table 1 shows the general characteristics of all 492 completed procedures and the 48 failed procedures. The procedures were evenly distributed between 2008 and 2012. Generic and hybrid procedures accounted for the far majority of the procedures with 80.5% and 9.8% respectively. The procedures were about as often withdrawn or refused after day 70 (n = 12) as after day 120 (n = 7), 180 (n = 12) or 210 (n = 10). In 7 procedures the applications were withdrawn before the initial assessment was finalised (i.e. at day 70). The licensing failure rate was the highest in medicinal products acting on the alimentary tract and metabolism and especially low for medicinal products acting on the cardiovascular system (risk ratio 0.06 (95% confidence interval (CI) 0.00–0.49) compared to products acting on the alimentary tract and metabolism. Hybrid applications were twice as likely to fail as generic applications (risk ratio 2.18, 95% CI 1.12–4.24).

Number and nature of the major objections

For 7 procedures no day 70 assessment report was available, leaving 41 procedures for analysis of the major objections. The total number of major objections and the numbers per domain, subdomain and issue category are shown in Table 2. A total of 93 major objections were identified in 34 of the procedures (see supplementary table for a detailed description of the individual major objections). In 7 (17%) procedures the application for a marketing authorisation was withdrawn by the applicant despite the absence of any (remaining) major objection. In most procedures there were one (n = 9) or two (n = 9) remaining major objections at the time of refusal or withdrawal. The highest number of major objections in one procedure was eight. This concerned an inhalation combination product for the treatment of asthma. It had six major objections regarding methodology and design of the bioequivalence study and demonstration of therapeutic equivalence, e.g. choice of patient category and choice of endpoints, and one safety concern due to insufficient measurements of blood concentrations levels.

Table 1: Characteristics of all procedures and failed procedures.

	All 492 completed procedures	**Failed 48 procedures**		**Risk ratio (95% CI)**
Year of submission				
2008	81	5	(6.2%)	Ref
2009	89	8	(9.0%)	1.46 (0.50-4.27)
2010	93	11	(11.8%)	1.92 (0.69-5.28)
2011	124	17	(13.7%)	2.22 (0.85-5.78)
2012	105	7	(6.7%)	1.08 (0.36-3.28)
Most recent report available in the procedure				
Day 70	-	12	NA	NA
Day 120	-	7	NA	NA
Day 180	-	12	NA	NA
Day 210	-	10	NA	NA
No report	-	7	NA	NA
ATC code				
A/ Alimentary tract & metabolism	47	10	(21.3%)	Ref
C/ Cardiovascular system	73	1	(1.4%)	0.06 (0.00-0.49)
G/ Genito-urinary system and sex hormones	34	4	(11.8%)	0.54 (0.18-1.57)
J/ Antiinfectives for systemic use	51	3	(5.9%)	0.28 (0.08-0.94)
L/ Antineoplastic and antineoplastic and immunomodulating agents	77	7	(9.1%)	0.43 (0.17-1.06)
M/ Musculo-skeletal system	35	2	(5.7%)	0.27 (0.06-1.15)
N/ Nervous system	109	14	(12.8%)	0.60 (0.29-1.26)
R/ Respiratory system	25	4	(16.0%)	0.75 (0.26-2.16)
S/ Sensory organs	20	2	(10.0%)	0.47 (0.11-1.95)
Other	21	1	(4.8%)	0.22 (0.03-1.64)
Legal basis				
Generic application	396	34	(8.6%)	Ref
Hybrid application	48	9	(18.8%)	2.18 (1.12-4.27)
Full dossier application	12	1	(8.3%)	0.97 (1.14-6.51)
Well established use application	18	3	(16.7%)	1.94 (0.66-5.73)
Fixed dose combination application	4	0	(0.0%)	N/A
Other[A] and combinations[b]	14	1	(7.1%)	0.83 (0.12-5.65)
Scientific advice				
Yes	-	3	NA	NA
No	-	45	NA	NA

[a] *i.e. Informed consent.*

[b] *i.e. Generic and hybrid applications combined in one procedure or generic and an informed consent application combined in one procedure.*

Quality

The identified major objections were about equally distributed between quality and clinical concerns. No major objections with regard to the non-clinical aspects of the application dossier were identified. Quality major objections more often concerned the drug product than the drug substance (Table 2). The major objections concerning the drug product related to insufficient control of impurities, insufficient control of the manufacturing process, insufficient pharmaceutical development and insufficient pharmaceutical equivalence with the innovator product. The latter constituted quality major objections because quality data may need to be provided in support of bioequivalence or therapeutic equivalence studies or to substantiate a biowaiver (i.e. permission not to submit bioequivalence studies). This may include, for example, data to demonstrate similarity of dissolution profiles of the generic product and the innovator product. An example of a major objection on the insufficient control of impurities is the lack of a proper explanation for brown spots observed on the tablets. Therefore the shelf life of the tablets could not be guaranteed.

Table 2: Major objections and related procedures per domain, subdomain and specific issue.

	Major objections		**Procedures**	
Total	**93**	**100%**	**41**	**100%**
Quality	**42**	**52%**	**22**	**54%**
Drug product	**32**	***34%***	**17**	***42%***
Insufficient control of impurities	9		6	
Insufficient control of manufacturing process	4		4	
Insufficient pharmaceutical development	3		2	
Insufficient pharmaceutical equivalence with reference product	15		9	
Drug substance	**16**	***17%***	**7**	***17%***
Active substance master file	16		7	
Clinical	**45**	**48%**	**22**	**54%**
Benefit-Risk	**16**	***17%***	**8**	***20%***
Efficacy not demonstrated	12		6	
Safety concerns	4		3	
Equivalence with reference product	**29**	***31%***	**15**	***37%***
Bioequivalence not demonstrated	23		14	
Therapeutic equivalence not demonstrated	7		3	

**No major objections with regard to the non-clinical aspects of the application dossier were identified.*
The significance of bold indicate the main categories.

All major objections about the drug substances concerned the Active Substance Master File[1] (ASMF) (Table 2). In particular, the identified major objections concerned insufficient control of impurities, inadequate definition of starting material, concerns about the validation of analytical methods and a violation of Good Manufacturing Practice. For example, in one procedure the starting material of the active substance had an alkylating structure that could be genotoxic. Therefore the manufacturer had to demonstrate that the amount of this potential genotoxic impurity was within the acceptable limit. The applicant withdrew the application immediately after the major objection was raised in the day 70 assessment report.

Clinical

Clinical major objections related to the benefit-risk profile of the product and the equivalence of the product with the reference product (Table 2). In the benefit-risk subdomain 12 of the 16 major objections concerned the demonstration of efficacy, while only 4 major objections were raised on safety issues. The majority of the clinical major objections related to the demonstration of equivalence with an innovator product as part of the substantiation of its efficacy and safety. In more detail the major objections regarding equivalence related to a wide variety of specific issues (Supplementary Table).

Figure 1 compares the number of procedures with clinical or quality major objections and the number of clinical and quality major objections between early (after day 70 and day 120) terminated procedures and late (after day 180 or day 210) terminated procedures. A slight, but not significant, shift towards more clinical than quality major objections was observed for late versus early termination.

In 3 of the 48 (6%) procedures scientific advice was given. This concerned one full application for oral contraceptive pills and two hybrid applications for a combination inhalation product for the treatment of COPD and for a tablet for the treatment of colitis ulcerosa, respectively.

1 Note: The Active Substance Master File (ASMF) contains all information about the active substance to assess the quality of the active substance. It is submitted by the manufacturer of the active substance under confidentiality.

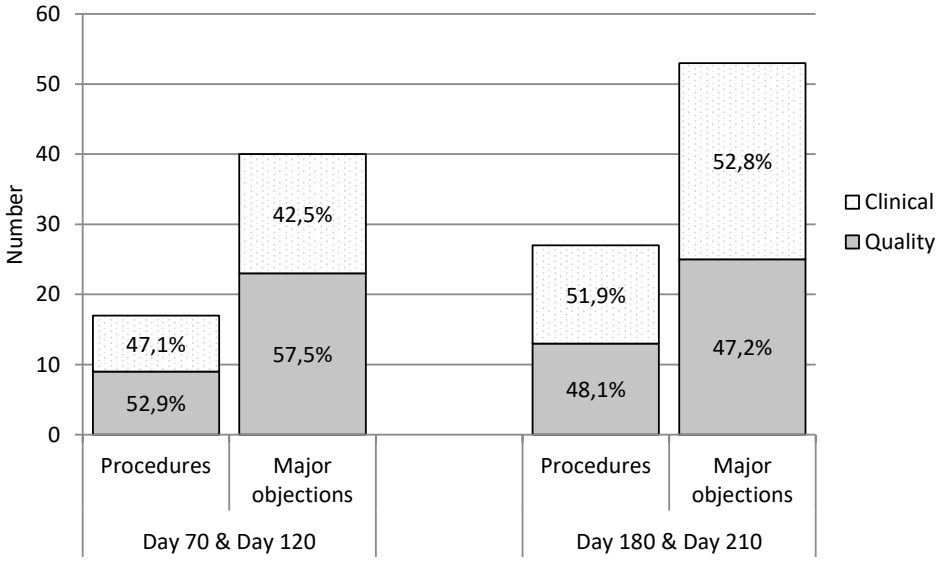

Figure 1: Comparison of the number of procedures with quality and/or clinical major objections and the nature of the major objections between early (latest report available day 70 or 120) and late (latest report available day 180 or 210) termination of the marketing authorisation application.

DISCUSSION

Of all the DCP procedures in the period 2008 to 2012 with the Netherlands as lead European authority, one out of 10 procedures failed. Important remaining deficiencies regarded both quality and clinical aspects. We observed a wide variety of specific deficiencies leading to refusal or withdrawal of applications. Clinical major objections mainly concerned the equivalence with the innovator product. Quality major objections concerned the medicinal products and the active substances, e.g. the amount of impurities. In addition, a substantial share of the quality major objections concerned substantiation of the equivalence to the innovator product by pharmaceutical characteristics.

The licensing failure rate of the procedures in our study (9.8%) is low when compared to the applications via the EU centralised procedure (27.1%)[4] and approval procedures for new molecular entities in the US (26.5%).[6] The lower failure rate may be attributed to the large proportion of generics and hybrid applications in our study, for which the development is relatively straightforward as the efficacy and safety of the active moiety is already known and not to be re-established. Interestingly, in our study hybrid applications failed twice as often as generic applications. Licensing applications for hybrid products

refer to efficacy and safety date of an innovator product, such as generic products. In contrast to generic applications, in hybrid applications equivalence to the innovator product cannot be determined by bioequivalence. For instance, locally applied and locally acting products, such as eye drops, to which blood levels are of no meaning, are authorised by hybrid applications. Moreover, the product in a hybrid application may differ essentially from the innovator product in terms of, for example, therapeutic indications or formulation. Therefore, hybrid applications may require more advanced tests or clinical studies to demonstrate equivalence with the innovator product than generic applications and as a result may fail more often.

The relative high approval rate may be the outcome of an interaction and learning-curve between the regulators and pharmaceutical companies. Early in the assessment more major objections may have been present than identified in our study in which we assessed major objections in the latest assessment report. Regulators assess the submitted data and point out the deficiencies at different points in time during the process, allowing the applicant to submit additional data and argumentation to resolve the raised objections. For that purpose a 'clockstop' period of up to six months is included after day 105 of the assessment. This allows the applicant to prepare its response to the major objections and, if necessary, to conduct additional studies.[12] Also after the distribution of the report at day 120 and 180 the applicants is provided with an opportunity to respond to the major objections.[12,13] At about 195 days after start of assessment a break-out session may take place in which the applicant can discuss the remaining major objections with the leading member state and the concerned member states.[13,14] So, at regular intervals the authorities and applicants interact in order to resolve major objections. The process of interaction and the accompanying relatively high approval rate should not be misunderstood for negligence of the regulatory authorities to thoroughly assess the applications or to make sound judgements. The assessment procedure in the DCP, including for generics and hybrids, is as rigorous as for new chemical entities in the EU centralised procedure.

In terms of the variety of specific deficiencies leading to refusal or withdrawal, our study results do not differ from previous studies on licensing failure in the US or the EU centralised procedure.[2,6,7] The considerable number of quality concerns, as well as concerns regarding equivalence, could have been expected considering the dominance of generic products in the DCP. Their established benefit-risk profile substantially eliminates efficacy and safety as points for concerns. In addition, a specific reason for the high number of quality issues might be related to the use of contract manufacturers by generic companies, for example, to manufacture active substances. Such manufacturers often produce the same active substance for multiple generic companies and might not be willing to resolve a specific issue for one generic company. Instead, innovative companies

often have full control over the manufacturing process, as they tend to manufacture their new chemical entity active substance themselves.

Several of the identified major objections in the DCP may have been resolvable, e.g. during the clock-stop, by submitting readily available or obtainable quality data or additional bioequivalence data. However, non-innovator pharmaceutical companies might be less willing, or able, to resolve deficiencies considering the investments at low profit margins. In some cases, companies may have tried to obtain approval with minimal investments while accepting a refusal. This may explain the minimal number of quality concerns in previous studies on licensing failure for new chemical entities and biologicals, since innovator companies might be more driven to resolve outstanding quality major objections during the assessment, given the prospect of substantial profits.[2,6]

We expected that quality related major objections would cause earlier termination of marketing authorisation applications, because quality issues might be more pronounced early in the assessment, while clinical issues could be more susceptible to debate with the regulators. However, only a slight shift in type of major objection between early and late termination of procedures was found, not constituting a clear difference.

Various major objections concerned deviations from scientific or regulatory guidelines, as can be observed in the Supplementary Table. Regulatory and scientific guidelines are intended to provide pharmaceutical companies with a clear course of the assessment procedure. Drug development in conformity with those guidelines may reduce the licensing failure rate. In case of doubts on the applicability or interpretation of guidelines, companies may apply for scientific and/or regulatory advice, preferably in an early stage of the development. In 6% of the failed procedures such advice was requested prior to the application. From internal Medicines Evaluation Board documents we know that scientific advice was given for 11% of the medicinal products approved between September 2011 and September 2013 through the DCP with the Netherlands as leading authority. Compliance with scientific advice has been associated with marketing approval in the centralised procedure.[4]

Furthermore, it should be noted that licensing failure may be due to other reasons than the major objections in the assessment procedure. In our study, 7 procedures were withdrawn without any major objections remaining. Some applicants explicitly mentioned such reasons, such as the withdrawal of an application because the company changed the development focus from generics to new medicinal products. Another applicant withdrew its application because of an overlap in product portfolio after a recent merger.

Our study has several limitations. First, we only included the remaining major objections of failed procedures. As mentioned before multiple major objections may have been resolved throughout the assessment. Future studies may assess in greater detail how initial major objections changed or are resolved throughout the assessment procedure. This may provide regulatory authorities insight in the major objections which initially constitute hurdles, but do not lead to refusal. It may also help pharmaceutical companies to submit better applications, which may save valuable time in the assessment procedure. Second, the present study only concerned procedures with the Netherlands as leading authority and EU member states may differ in their specialities and preferences regarding therapeutic areas, which may affect the licensing failure rate. However, as mentioned before the Netherlands acts as the leading authority for a substantial share of all application through the DCP.[9] In addition, the DCP is by nature a combination of assessments by multiple member states. Hence, we believe that our data may provide a comprehensive representation of major objections in the DCP in general. Finally, it should be noted that the major objections are often of a multidisciplinary nature. They may include aspects of multiple different, but related deficiencies. Therefore the assessment of the major objections is subject to interpretation of the researchers, although this has been prevented as much as possible by consultation of senior assessors and regulators of the Dutch Medicines Evaluation Board to determine the key point of the major objections.

CONCLUSIONS

In the best interest of public health, it is the regulators' task to prevent ineffective and unsafe medicines from entering the market, and to contribute to patients' access to beneficial medicines. Our study showed that approximately one out of 10 procedures in the DCP with the Netherlands as leading authority failed, which was due to a wide variety of determinants, both quality and clinical related. The low failure rate may be related to the regular interaction between authorities and pharmaceutical companies throughout the assessment. However, given the wide variety of major objections there might not be a magic button to prevent the deficiencies in the submitted dossiers. In addition, the success of an application may to some extent depend on the financial feasibility and willingness to resolve major objections, especially for off patent generic medicinal products. Besides, pharmaceutical companies may withdraw their marketing authorisation applications due to reasons other than the raised major objections. Overall, some degree of licensing failure may thus be inevitable.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary Table: Number of major objections per domains, subdomains, issue categories and specific issues.

	Major objections		Procedures	
Total	**93**	100.0%	**41**	100.0%
Quality	**48**	51.6%	**22**	53.7%
Drug product	**32**	34.4%	**17**	41.5%
Insufficient control of impurities	9	9.7%	6	14.6%
Insufficient demonstration product stability throughout the proposed shelf-life	6		5	
Photo stability test not performed concordant with guideline	1		1	
Impurities exceeding guideline limits	1		1	
Presence of potential genotoxic impurities	1		1	
Insufficient control of manufacturing process	4	4.3%	4	9.8%
Lack of adequate manufacturing process validation	4		4	
Insufficient pharmaceutical development	3	3.2%	2	4.9%
Sterilisation method not concordant with guideline	1		1	
Insufficient characterisation of the final product	2		1	
Insufficient pharmaceutical equivalence with reference product	16	17.2%	10	24.4%
Dissolution study not performed concordant with guideline	7		4	
Differences in dissolution profile between test and reference product	1		1	
Concern about the dissolution study design or selection of the innovator batch	1		1	
Dissolution limits cannot be finalised due to lack of bioequivalence	1		1	
In-vitro test methods not concordant with guideline	1		1	
Concerns about methodology to compare particle size	1		1	
Differences in qualitative and quantitative composition between test and reference product	1		1	
Unclear composition of the bioequivalence study product compared to final product	2		2	
Chosen reference product not concordant with regulations	1		1	
Drug substance	**16**	17.2%	**7**	17.1%
Active Substance Master File	16	17.2%	7	17.1%
Concerns about the validation of analytical methods	2		1	
Good manufacturing practice concerns	1		1	
Inadequate definition of starting material	5		4	
Insufficient control of impurities	8		4	

Supplementary Table: Number of major objections per domains, subdomains, issue categories and specific issues. (continued)

	Major objections		Procedures	
Clinical	**45**	48.4%	**22**	53.7%
Benefit-Risk	**16**	17.2%	**8**	19.5%
Efficacy not demonstrated	12	12.9%	6	14.6%
Literature data are insufficient to support efficacy	8		3	
Insufficient clinical relevance	1		1	
Lack of efficacy	1		1	
Not concordant with regulatory guideline on fixed dose combinations	1		1	
Study design concern	1		1	
Safety concerns	4	4.3%	3	7.3%
Inadequate description of the pharmacovigilance system	1		1	
Inferior safety profile	1		1	
Posology concern	1		1	
Study design concern	1		1	
Equivalence with reference product	**29**	31.2%	**15**	36.6%
Bioequivalence not demonstrated	22	23.7%	14	34.1%
Pharmacokinetic parameters are outside predefined borders	9		8	
Bioequivalence data not concordant with guidelines	3		2	
Good clinical practice concerns	3		2	
Literature data are insufficient to bridge to reference product	1		1	
Literature data are insufficient to support bioequivalence	2		2	
Concern about the extrapolation of the in vitro in vivo correlation to paediatrics	1		1	
Particle size range used in the bioequivalence study is not acceptable	1		1	
In vitro in vivo correlation between fine particle dose and absorption not demonstrated	1		1	
Insufficient substantiation for absence of a bioequivalence study	1		1	
Therapeutic equivalence not demonstrated	7	7.5%	3	7.3%
Study design concerns	7		3	

**No major objections with regard to the non-clinical aspects of the application dossier were identified.*

Chapter 2.2

An analysis of marketing authorisation applications via the mutual recognition and decentralised procedures in Europe

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ABSTRACT

Purpose: The aim of this study is to provide a comprehensive overview of the outcomes of marketing authorisation applications via the mutual recognition and decentralised procedures (MRP/DCP) and assess determinants of licensing failure during CMDh referral procedures.

Methods: All MRP/DCP procedures to the Co-ordination group for Mutual recognition and Decentralised procedures– human (CMDh) during the period from January 2006 to December 2013 were analysed. Reasons for starting referral procedures were scored. In addition, a survey under pharmaceutical companies was performed to estimate the frequency of licensing failure prior to CMDh referrals.

Results: During the study period, 10392 MRP/DCP procedures were finalised. Three hundred seventy-seven (3.6%) resulted in a referral procedure, of which 70 (19%) resulted in licensing failure, defined as refusal or withdrawal of the application. The frequency of CMDh referrals decreased from 14.5% in 2006 to 1.6% in 2013. Of all referrals, 272 (72%) were resolved through consensus within the CMDh, the remaining 105 (28%) were resolved at the level of the CHMP. Most referrals were started because of objections raised about the clinical development program. Study design issues and objections about the demonstration of equivalence were most likely to result in licensing failure. An estimated 11% of all MRP/DCP procedures resulted in licensing failure prior to CMDh referral.

Conclusion: Whereas the absolute number of MRP/DCP procedures resulting in a referral has reduced substantially over the past years, no specific time trend could be observed regarding the frequency of referrals resulting in licensing failure. Increased knowledge at the level of companies and regulators has reduced the frequency of late-stage failure of marketing applications via the MRP/DCP.

INTRODUCTION

Several regulatory pathways exist to authorise medicines in the European Union (EU). The centralised procedure was introduced in European legislation in 1993 and came into operation in 1995.[1,2] It results in a single marketing authorisation (MA) that is valid throughout the EU. The centralised procedure is mandatory for marketing authorisation applications (MAAs) of new active substances for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, all biologicals, advanced therapies, and orphan products. Applications for multiple Member States for products that do not fall within the mandatory scope of the centralised procedure must follow the mutual recognition procedure (MRP) or the decentralised procedure (DCP). In terms of volume, MRP and DCP procedures outnumber the centralised procedure and considerable resources are spent by both MA holders and national competent authorities on MAAs via the MRP/DCP procedures. When MAAs result in licensing failure—defined as those procedures that did not result in a MA—this leads to wasted resources, especially if this concerns preventable, late-stage failures. Whereas reasons for licensing failure for products authorised via the centralised procedure has received considerable attention, little is known about MAAs via the MRP/DCP procedure.[3,4]

Since January 1, 1998, the MRP is mandatory for any product that is to be marketed in multiple Member States, when a MA exists anywhere in the EU.[5] During the MRP, an applicant informs the Reference Member State (RMS) that it aims to market a product in multiple countries and requests these other countries, the so-called concerned member states (CMSs), to recognise the MA granted by the RMS. The RMS circulates the assessment report, including the approved summary of product characteristics (SmPC), labelling and package leaflet. If the CMSs agree with the assessment of the RMS, they should recognise the decision within 90 days after receipt of these documents by granting a national MA (Figure S1).[6]

The DCP was introduced into European legislation in 2004 and should be followed when a MA is applied for in multiple Member States at once.[7] Like the MRP, the DCP is also based on recognition of a first assessment performed by a RMS, but there is no preexisting MA. For both MRP and DCP procedures, a positive outcome will result in harmonised national MAs, granted by the respective national competent authorities. After a positive outcome of the MRP/DCP procedure (i.e. all CMSs agree to grant the MA), the procedure is closed and a national MA should be granted within 30 days, provided that well-translated documents are provided within 5 days after closing the procedure.

Member States can refuse to recognise the assessment of the RMS, but only on grounds of a 'potential serious risk to public health' (PSRPH). A PSRPH is defined as 'a situation where there is a significant probability that a serious hazard resulting from a human medicinal product in the context of its proposed use will affect public health'.[8] Despite the development of guidance, uncertainty remains about what qualifies as a PSRPH.[9] If disagreement on the PSRPH cannot be resolved by the RMS and the CMSs, the issue is referred to the Co-ordination group for mutual recognition and decentralised procedures–human (CMDh), through a so-called Article 29(1) procedure. The CMDh works by achieving consensus between the Member States. If it does not achieve consensus to approve or refuse the MAA within 60 days, the case is referred to the Committee for Medicinal Products for Human Use (CHMP) through an Article 29(4) procedure who will adopt an opinion that will result in a binding decision from the European Commission.[10]

Limited data are currently available on the outcomes of MAAs via the MRP/DCP procedure. Furthermore, data on licensing failure prior to MRP/DCP procedures are not available from publicly accessible sources. Therefore, the current study aims to assess the efficiency of the MRP/DCP procedure by providing a comprehensive overview of the outcomes with these regulatory pathways. To do so, we have investigated frequencies and determinants for CMDh referral procedures, as well as reasons for licensing failure during the MRP/DCP. Three objectives were formulated. The first objective was to determine the frequency of CMDh referrals. The second objective was to assess the association of objections raised as PSRPH and other determinants with licensing failure during CMDh referrals. The third objective of this study was to determine the frequency of licensing failure of MAAs via the MRP/DCP prior to the initiation of a CMDh referral procedure.

METHODS

Data were obtained from different sources. The total number of MRP/DCP procedures finalised between January 2006 to December 2013 and all data relating to Article 29(1) procedures, including procedure type (i.e. DCP or MRP), legal basis (see Table S1) and prescription status, were obtained from statistics and reports available from the CMDh website.[11] Additional data on individual products, including pharmaceutical form and legal status were retrieved from public assessment reports that were obtained via the Mutual Recognition Product Index.[12] Article 29(4) commission decision reports were obtained from the European Commission pharmaceuticals community register.[13] Our analysis was limited to initial MAAs; renewal procedures and type II variations were excluded.

A scoring system was developed to categorise objections raised during the CMDh procedure (see Table S2 of the Supplementary information). Two researchers (HE and JL) independently scored the objections; disagreement was resolved by consensus. Multiple objections were scored as 'Multiple objections from different categories', unless the issues concerned the same category. Licensing failure was defined as a MAA procedure that did not result in a MA and included negative results at the level of the CMDh, a negative European Commission decisions, or withdrawals by the applicant.

MAAs via the MRP/DCP may also result in licensing failure prior to the start of a CMDh referral. When an MAA is withdrawn before day 90 of the MRP (including the preexisting MAs) or day 120 of the DCP procedure, the information will not be reported on the CMDh website and was thus not available for our study. Therefore, a survey was conducted under 58 member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Association of the European Self- Medication Industry (AESGP) to estimate the frequency of licensing failure during the early phase of the MRP/DCP procedure. The European Generic Association (EGA) declined the invitation to participate in the survey. The survey also included questions on the consequences of PSRPHs raised during the MRP/DCP.

All data were entered into a database, and descriptive statistics were obtained using IBM SPSS statistics version 20.0.0 (IBM Corporation, 2011). Significance for numerical variables was tested using Mann-Whitney U test (two-sided $\alpha < 5\%$).

RESULTS

Frequency of referral procedures

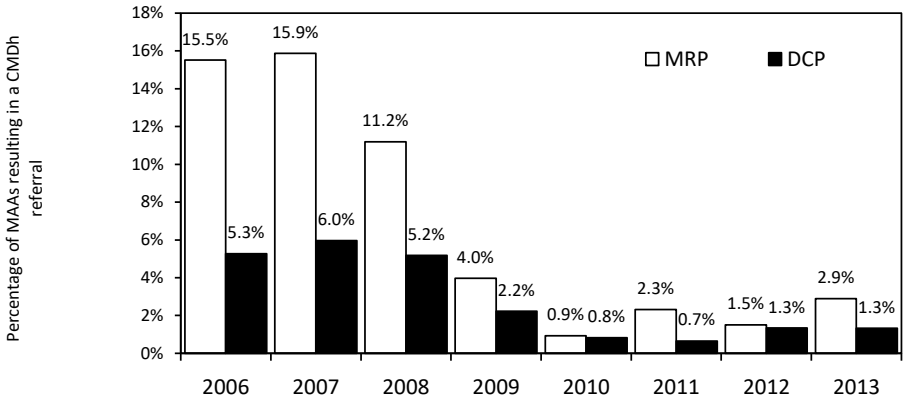
A total of 10,392 MRP/DCP procedures were finalised during the study period, 2822 MRP and 7570 DCP procedures (Table 1). Generic applications accounted for 78% of the procedures and hybrid procedures for 10%. Full dossiers were provided for 6% of the applications, bibliographic applications accounted for 4% and the remaining 2% concerned other applications (see Table S1). Most MAAs concerned products that were authorised as prescription-only in the RMS.

Table 1: Total number of marketing authorisation applications and CMDh referrals.

		Total, n	Referrals, n	%	Risk ratio (95% CI)
Procedure Type	DCP	7570	135	1.8%	Ref
	MRP	2822	242	8.6%	4.8 (3.9-5.9)
Period*	2010-2013	6140	70	1.1%	Ref
	2006-2009	4245	307	7.2%	6.3 (4.9-8.2)
Prescription status (in RMS)	Prescription only	9890	356	3.6%	Ref
	Non-prescription	502	21	4.2%	1.2 (0.8-1.8)
Legal basis*	Art. 10.1 - Generic	8120	248	3.1%	Ref
	Art. 10.3 - Hybrid	1010	29	2.9%	0.9 (0.6-1.4)
	Art. 8.3 - Full dossier	600	63	10.5%	3.4 (2.6-4.5)
	Art. 10a - Well-established use (Bibliographic)	439	29	6.6%	2.2 (1.5-3.1)
	Art 10b - Fixed combination	147	8	5.4%	1.8 (0.9-3.5)
	Other	56	0	0%	NA

**Total numbers differ from procedure type and prescription status categories due to missing data.*
DCP: Decentralised procedure, MRP: Mutual recognition procedure, RMS: Reference Member State.

While MRP procedures predominated in 2006 and 2007, from 2008, DCP procedures accounted for the majority of the MAAs. During the study period, 377 (3.6%) CMDh referral procedures were started. During the first years after the introduction of the DCP, more procedures resulted in a referral, compared to more recent years (Figure 1). For the combined MRP/DCP procedures, the frequency of CMDh referrals declined from 14.5% in 2006 to 1.6% in 2013. MRP procedures were nearly five times more likely to result in a referral than DCP procedures (Table 1). MAAs based on a full dossier and on bibliographic data were more likely to result in a referral compared to generic applications. No difference in the frequency of CMDh referrals was observed for prescription versus nonprescription medicines.



Total number of MAAs per year

	2006	2007	2008	2009	2010	2011	2012	2013
MRP	535	441	411	378	325	259	266	207
DCP	57	386	733	1304	1452	1381	1198	1052

Figure 1: Percentage of procedures resulting in CMDh referral per year.

Assessment of determinants of licensing failure during the CMDh referrals

Of the 377 CMDh referrals, consensus was found within the CMDh for 272 (72%) referrals, leading to a positive opinion for 239 (63%) MAAs and licensing failure for 33 (9%) MAAs. Article 29(4) procedures (CHMP arbitrations) were started for 105 (28%) MAAs. Of these, 37 (10%) ended in a refusal and 68 (18%) resulted in a positive recommendation from the CHMP. So, overall, 70 (19%) MAAs resulted in a licensing failure. Two illustrative cases that were referred to the CMDh are presented in supplementary Box 1. The majority of PSRPH leading to a CMDh referral procedure were related to the clinical phase (Table 2). PSRPHs concerning the main category benefit-risk concerns accounted for most CMDh referrals. PSRPHs related to the design of the clinical studies and the demonstration of therapeutic equivalence and bioequivalence were more likely to result in a licensing

failure during the referral procedure, than referrals started because of benefit/risk concerns, quality or regulatory/procedural objections. For 88 referrals, multiple objections from different categories were raised (see Table S4 for more detailed information on the combinations). The number of CMDh referrals was small, especially in the second half of the study period. No time trends could be observed in terms of relative frequency of the categories of PSRPH leading to CMDh referral (Figure 2 and supplementary Table S3).

Table 2: Categories of 'potential serious risk to public health' objections raised leading to CMDh referrals and licensing failure during CMDh referrals.

Main Category - Sub Categories*	**Total, n**	**Licensing failure, n**	**%**	**Risk ratio (95% CI)**
Clinical (study design issues)	64	21	33%	Ref
Clinical (equivalence)	64	21	33%	1.0 (0.6-1.6)
Bioequivalence/therapeutic equivalence *not demonstrated*	39	15	38%	1.2 (0.7-2.0)
Bioequivalence/therapeutic equivalence *not investigated in sub group*	25	6	24%	0.7 (0.3-1.6)
Clinical (benefit risk concerns)	83	8	10%	0.3 (0.1-0.6)
Insufficient data to support B/R in claimed indications	34	7	21%	0.6 (0.3-1.3)
Safety concerns	19	0	0%	NA
Overall Benefit/Risk negative	18	1	6%	0.2 (0.0-1.1)
Posology concerns	12	0	0%	NA
Quality	38	3	8%	0.2 (0.1-0.8)
Concerns on quality or manufacturing parameters	35	3	9%	0.3 (0.1-0.8)
packaging concerns/medication errors	3	0	0%	NA
Regulatory/procedural	40	2	5%	0.2 (0.0-0.6)
Concerns about SmPC wording	30	1	3%	0.1 (0.0-0.7)
Administrative concerns (incl. Patient Leaflet / SmPC issues)	10	1	10%	0.3(0.0-2.0)
Multiple objections from different categories	88	15	17%	0.5 (0.3-0.9)
Overall	377	70	19%	

**For a detailed description of the categories, see Supplemental information Table S2.*

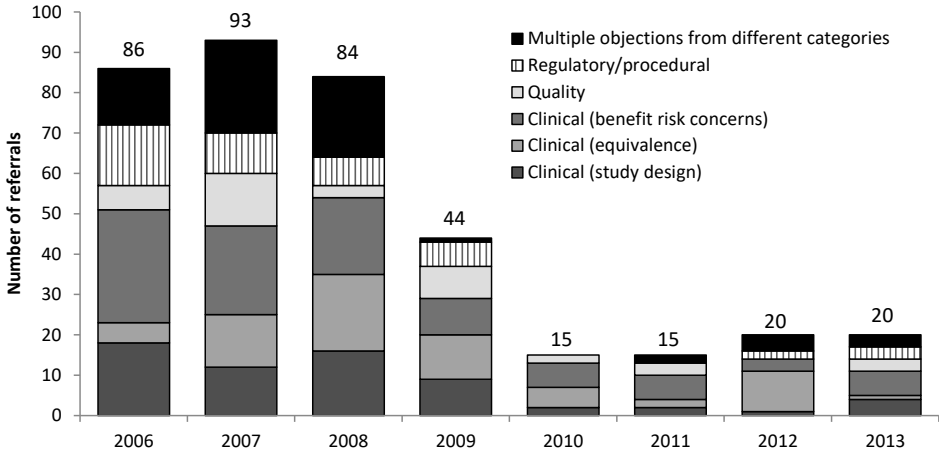


Figure 2: Main categories of 'potential serious risk to public health' objections per year. A detailed overview of the category of objection by subcategory and licensing outcome is provided in supplementary Table S3.

No association was observed between licensing failure and active substance type, administration route, prescription status or MRP vs. DCP application during the referral procedure (Table 3). Referrals of MAAs based on a full dossier (Article 8.3) were less likely to result in licensing failure. Cardiovascular products and nervous system products were the two product classes most frequently included in CMDh referrals. Antineoplastic and immunomodulating agents and genitourinary system and sex hormones were less likely to result in licensing failure when compared to cardiovascular agents. The Netherlands, Germany, Denmark, the UK and Sweden together acted as RMS for 78% of all referrals. Procedures in which the Netherlands or Sweden were RMS, were less likely to result in licensing failure, whereas procedures where Denmark was the RMS more often resulted in licensing failure, when compared to all other Member States. Per procedure, a median of 8 (IQR 4–12) CMSs were involved. Procedures that resulted in licensing failure involved fewer CMSs (5.5; IQR 1– 9) than procedures with a positive outcome (8; IQR 4–23; $p<0.001$). This difference remained when we limited our analysis to only MRP, or only DCP procedures. No specific time trends were observed for the frequency of licensing failure.

Table 3: Other determinants of licensing failure during CMDh procedures.

Category	Subcategory	Total	Licensing failure	%	Risk ratio (95% CI)
Procedure Type	DCP	135	29	21.5%	Ref
	MRP	242	41	16.9%	0.8 (0.5-1.2)
Period	2006	86	14	16.3%	Ref
	2007	93	23	24.7%	1.6 (0.9-2.8)
	2008	84	11	13.1%	0.8 (0.4-1.7)
	2009	44	5	11.4%	0.7 (0.3-1.8)
	2010	15	5	33.3%	2.1 (0.9-4.9)
	2011	15	4	26.7%	1.7 (0.6-4.4)
	2012	20	2	10.0%	0.6 (0.2-2.5)
	2013	20	6	30.0%	1.9 (0.8-4.2)
Prescription status (in RMS)	Prescription only	356	65	18.3%	Ref
	Non-prescription	21	5	23.8%	1.3 (0.6-2.9)
Legal basis	Art 10.1 - Generic	248	50	20.2%	Ref
	Art 8.3 - Full dossier	63	4	6.3%	0.3 (0.1-0.8)
	Art 10.3 - Hybrid	29	8	27.6%	1.4 (0.7-2.6)
	Art 10a - Well established use (Bibliographic)	29	8	27.6%	1.4 (0.7-2.6)
	Art 10b - Fixed combination	8	0	0.0%	NA
Active substance type	Small molecules	361	68	18.8%	Ref
	Biologicals*	16	2	12.5%	0.7 (0.2-2.5)
Route of administration	Oral	264	48	18.2%	Ref
	Injectables	40	4	10.0%	0.6 (0.2-1.4)
	Other systemic	30	6	20.0%	1.8 (0.8-3.7)
	Inhaled	16	5	31.3%	1.7 (0.8-3.7)
	Topical	16	3	18.8%	1.0 (0.4-2.0)
	Other	11	4	36.4%	2.0 (0.9-4.6)

Table 3: Other determinants of licensing failure during CMDh procedures. (continued)

Category	Subcategory	Total	Licensing failure	%	Risk ratio (95% CI)
ATC level	C - Cardiovascular system	88	23	26.1%	Ref
	N - Nervous system	76	17	22.4%	0.9 (0.5-1.5)
	J - Anti-infectives for systemic use	38	4	10.5%	0.4 (0.1-1.1)
	A - Alimentary tract and metabolism	34	4	11.8%	0.5 (0.2-1.2)
	L - Antineoplastic & immunomodulating agents	30	1	3.3%	0.1 (0.0-0.9)
	R - Respiratory system	30	9	30.0%	1.1 (0.6-2.2)
	G - Genitourinary system and sex hormones	29	1	3.4%	0.1 (0.0-0.9)
	M - Musculoskeletal system	21	3	14.3%	0.5 (0.2-1.7)
	Other	28	5	17.9%	0.7 (0.3-1.6)
	Unknown†	3	3	100%	
RMS	Other	86	22	25.6%	Ref
	The Netherlands	81	4	4.9%	0.2 (0.1-0.5)
	Germany	68	9	13.2%	0.5 (0.3-1.1)
	Denmark	54	29	53.7%	2.1 (1.4-3.2)
	United Kingdom	51	6	11.8%	0.5 (0.2-1.1)
	Sweden	37	0	0.0%	NA

**Teicoplanin included in the biologics group.*
† All Article 8.3 procedures ('full dossiers') that did not receive marketing authorisation (excluded from analysis).
DCP: Decentralised procedure, MRP: Mutual recognition procedure, RMS: Reference Member State.

Licensing failure prior to initiating a CMDh referral

In total, 16 of the 58 (28%) invited companies returned the survey. Of these, four companies provided two surveys from different departments within the same company, e.g., consumer health care and innovative medicines, or consumer health care and generics. This resulted in 20 completed individual surveys, reporting a total of 208 MRP/DCP procedures (Table 4). Out of all MRP/DCP procedures, 174 (84%) ended in a MA, whereas 11% resulted in licensing failure at the level

of the RMS (i.e., were refused or withdrawn) prior to CMDh referral, and 10 (5%) procedures were referred to the CMDh. For 20 (10%) of the procedures, the applicant withdrew the application in one or more Member States. The majority of the withdrawals

were reported to occur for reasons other than safety concerns. Five respondents (25%) indicated that their company had withdrawn MAAs (and MAs) in response to safety concerns at least once. Of all the respondents, 21% reported that their company had decided not to market a product in one or more Member States because of restrictions on the use of the product introduced during the MRP/DCP procedure at least once.

Table 4: Survey results on marketing authorisation applications using MRP/DCP.

	Total	Procedures resulting in a MA	Procedures resulting in licensing failure	CMDh referral
Completed in all Member States	174 (84%)	156 (75%)	9 (4%)	9 (4%)
Withdrawn ≥1 Member States†	20 (10%)	19 (9%)	0	1 (<1%)
Withdrawn in all Member States prior to CMDh referral*	14 (7%)	0	14 (7%)	0
Total number of procedures	208 (100%)	175 (84%)	23 (11%)	10 (5%)

† Outcome in remaining Member States.
** Including the existing marketing authorisation in the RMS.*
MA: marketing authorisation.

DISCUSSION

We have provided a comprehensive overview of MAAs via the MRP/DCP. We found that only a limited number of applications are referred to CMDh, and the majority of these referrals resulted in a MA. PSRPH objections that related to the design of the clinical studies and the demonstration of therapeutic equivalence and bioequivalence were most likely to result in a licensing failure, whereas discussion on quality or regulatory concerns rarely resulted in a licensing failure during the procedure. Some factors, including procedure type, legal basis and timing of the procedure were associated with the frequency of triggering a CMDh referral, but not with a higher rate of negative outcomes once the referral was initiated. Overall, these data show that the frequency of late-stage licensing failure of MRP/DCP procedures, i.e., licensing failure after referral, has decreased substantially.

Care must be taken when interpreting outcomes of regulatory procedures. We defined licensing failure as a withdrawal or refusal, but this does not mean that the procedure failed. On the contrary, it may imply that the DCP/MRP functions as expected and prevented (potential) untoward outcomes resulting from subpar products reaching patients. Moreover, our study focused on overall licensing failure, meaning that we did not take into account that for some products, the authorised indications and/or

patient populations may have been restricted at the end of the MRP/DCP procedure. Respondents to the survey reported that this had on occasion resulted in decisions not to market a product. However, we did not systematically investigate the underlying reasons for those restrictions. This may be a topic for further study.

The frequency of MAAs that resulted in a CMDh referral decreased substantially over the years, indicating that regulatory learning takes place. Increased experience in the use of this pathway may have resulted in improved MAAs filed by companies, but also in earlier withdrawal of applications that are likely to result in a referral. Companies may also adapt their filing strategies to anticipate regulatory concerns and file in selected Member States. For regulators, regulatory learning means that they may have become better in finding consensus about MAAs in earlier phases of the application, but also the development of guidance on what are considered PSRPHs may reduce disagreements between different Member States.[9] Furthermore, an ever-increasing body of information about outcomes of referral and arbitration procedures will provide more clarity on the interpretation of PSRPHs and prevent referrals. Work within the CMDh is ongoing to improve the harmonised interpretation of existing guidance.[14] Moreover, ongoing harmonisation efforts of SmPCs of products for which Member States have adopted different decisions over the years (resulting in different authorised indications, contraindications or posology) will continue to reduce sources of disagreement.[15]

Our data clearly show that MRP procedures result in CMDh referrals more frequently than DCP procedures. A possible explanation for this finding is that the RMS is more reluctant to accept changes to the existing SmPC, than in the situation of a DCP, where there is no preexisting MA. Moreover, given the fact that DCPs do not have preexisting MAs, companies may withdraw an MAA more easily in response to objections raised during the assessment procedure, in order to resubmit with different claims, or in different member states.

Objections raised on the design and outcome of clinical studies were most likely to lead to licensing failure. Often, these objections related to bioequivalence parameters that were outside predefined borders, even when the studies were adequately designed. These cases may be the result of unforeseen differences in the product characteristics or due to chance findings, which may be challenging to prevent. On the other hand, a considerable amount of referrals were due to causes that may have been prevented by the applicant through early communication with the competent authorities, such as the choice of reference product or dosage strength. Consequently, careful planning of clinical studies and consideration of existing guidelines could further reduce the frequency of referrals.

We found that procedures resulting in licensing failure involved fewer CMSs than those that resulted in a MA. This seems counterintuitive, as more CMSs would give rise to more opportunity for disagreement. A possible explanation may be that applicants anticipate objections and file in strategically selected Member States. For example, it has been recognised that the MRP/DCP is underutilised by the non-prescription sector, because of different approaches towards self-medication in the member states.[16] While we did not observe a higher frequency of licensing failure for non-prescription medicines compared to prescription medicines, companies may anticipate concerns during the procedure and run multiple procedures for the same product, leading to fewer referrals. We found that five RMSs accounted for 78% of all referrals. However, these five countries also acted as RMSs for 69% of all existing MAs included in the Mutual Recognition Product Index (Table S4).[12] ATC classes of authorised products were also distributed unevenly over the RMSs (data not shown), which may also account for some of the observed variation in the licensing failure frequency seen in our study. It may be of interest to further investigate the underlying reasons for the observed differences in frequency of licensing failures between RMSs.

Data from our survey suggest that 16% of all MAAs via the MRP/DCP procedures were withdrawn in one or all Member States at some point. This suggests that companies anticipate that objections will be raised and take mitigating measures.

STRENGTHS AND LIMITATIONS

Our study was the first to provide a comprehensive overview of MAAs via the mutual recognition and decentralised procedures. An important limitation of our study is that for the MAAs which did not result in a referral various attributes were only available on an aggregated level, such as legal basis, prescription status and procedure. While these did not show major differences over the years, we were unable to perform multivariate analyses to identify explanatory variables for changes in the frequency of referrals over time. Other variables, including RMS, ATC class, and route of administration, were unavailable altogether.

Multiple data sources were required to obtain a full picture on the outcomes of MRP/DCP procedures. While it may be preferable to use a single data source, the use of multiple data sources allowed us to validate our findings. For example, it may not be possible to extrapolate our survey results to all users of the MRP/DCP procedures, as our sample included only a few generic companies. Nevertheless, in our survey, 10 out of 208 procedures (4.8%) resulted in a CMDh referral. This is comparable to the

number of referrals included in the CMDh database (377/10,392=3.6%), providing some reassurance with respect to the representativeness of the survey sample. The data of the current study are also in accordance with data from another study that investigated licensing failure of DCP applications filed in the Netherlands and found that 9.8% resulted in licensing failure (Langedijk et al., manuscript in preparation). This is in the same range as the 7.9% observed in our survey (where 7% of the applications were withdrawn prior to CMDh referral and an estimated 0.9% failed during CMDh referral).

CONCLUSION

A limited number of MRP/DCP procedures in our study ended in a CMDh referral, and the frequency of referrals has decreased substantially in recent years, indicating that companies and regulators have learnt to prevent late-stage failures of MAAs via the MRP/DCP. Ever-increasing experience in using the MRP/DCP results in a growing body of information about past referral outcomes that may facilitate the development of strategies to prevent licensing failure late in the procedure. Ongoing harmonisation activities on the side of regulatory authorities will likely lead to a further reduction of licensing failure during the MRP/DCP procedure.

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SUPPLEMENTARY INFORMATION

Figure 1: Flowchart of MRP/DCP procedures.
Both procedures can be closed if the RMS and CMS reach consensus to approve or refuse the marketing authorisation application. Of note, only procedures that have been positively assessed by the RMS may be referred to the CMDh. Referrals cannot be initiated for applications that are negatively assessed by the RMS, even though one or more CMSs are of the opinion that a MA may be granted. RMS: Reference Member State, CMS: Concerned Member State.

Supplementary Box 1: Examples of referrals

Referral that resulted in licensing failure

The procedures have been referred to the CMD(h) based on a question regarding the requirements to show bioequivalence. The disagreement was regarding whether bioequivalence should be shown for the parent compound losartan or for the active metabolite. The 90% confidence interval for Cmax is within 80-125% for the metabolite (94.8-114.74%), but outside the normal acceptance range for the parent compound losartan (91.26-133.64%). The extraordinarily wide acceptance range for Cmax %CI (70–143%) for the parent compound losartan was not considered acceptable by CMS. An agreement could not be reached and the marketing authorisation applications were withdrawn in RMS and CMS before the CMD(h) meeting.
Score: Bioequivalence/therapeutic equivalence not demonstrated.

Referral that resulted in a marketing authorisation

There were concerns with regard to the following issues:
1. Bioequivalence was demonstrated on the basis of the metabolite data, and not on the basis of the parent.
2. The pictogram and text in the SmPC and Package Leaflet give the impression that there is a dose recommendation for half a tablet, but there is no such recommendation. This may confuse prescribing physicians and patients.
At the CMD(h) meeting the RMS presented its view and the applicant's written response was dis-cussed. There was a discussion on whether bioequivalence should be demonstrated only on the active metabolite enalaprilat data, or whether bioequivalence should also be demonstrated on the parent compound enalapril. The applicant made a post-approval commitment to perform an additional single dose fasten bioequivalence study on the parent compound. The SmPC and Package Leaflet were adapted regarding information about the score line. Agreement reached.
Score: Combinations of 1. Concerns about the quality of the studies and 2. Administrative concerns (including concerns involving the PL /SmPC).

Table S1: Legal basis.

Legal basis		
Article 8.3	Full dossier	**1. Stand-alone application** An application for marketing authorisation based on: – pharmaceutical (physico-chemical, biological or microbiological) tests, – preclinical (toxicological and pharmacological) tests, – clinical trials. For such applications, the relevant published literature also has to be submitted and these scientific publications can be used as supportive data. Mostly used for new active substances. **2. "Mixed application"** Applications for marketing authorisation consisting of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references.
Article 10.1	Generic	According to Article 10.1 of Directive 2001/83/EC the applicant is not required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product which has been authorised not less than 8 years in a Member State or in the Union. A generic medicinal product is defined as a medicinal product that has: – the same qualitative and quantitative composition in active substance(s) as the reference product, – the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.
Article 10.3	Hybrid medicinal product	Hybrid applications differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary in the following three circumstances: 1. where the strict definition of a 'generic medicinal product' is not met; 2. where the bioavailability studies cannot be used to demonstrate bioequivalence; 3. where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product. In such cases the results of tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC. These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data. Some guidance on the appropriate additional studies required is indicated in Annex IV of the Chapter 1 of the Notice to Applicants. The type of applications mentioned above refer to information that is contained in the dossier of the authorisation of the reference medicinal product, for which a marketing authorisation has been granted in the Union.

Table S1: Legal basis. (continued)

Legal basis		
Article 10a	Well-established medicinal use supported by bibliographic literature	For medicinal products the active substance(s) of which has/have a 'well-established medicinal use', with recognised efficacy and an acceptable level of safety, the applicant is not required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I, part II of Directive 2001/83/EC. In that event, the test and trial results shall be replaced by appropriate scientific literature.
Article 10b	Fixed combination of active substances in a medicinal product	Applications based upon Article 10b shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.

Table S2: Scoring categories of reported reasons for CMDh referral.

Main category	Subcategories	Description
Clinical (equivalence)	Bioequivalence/ therapeutic equivalence *not demonstrated*	BE parameter outside predefined border, endpoint not met for BE/TE studies, post hoc widening of acceptance criteria, exclusion of outliers not supported.
	Bioequivalence/ therapeutic equivalence *not investigated in sub group*	Including dose, fasting/fed condition group, or patient category. Discussions on the acceptability of biowaivers of studies, extrapolation of different dose strengths included in the BE studies.
Clinical (study design)	Concerns about the quality of the studies	Study design issues, choice of comparator, choice of test product, GCP compliance, choice of (predefined) endpoints, predefined widening of 90% CI.
Clinical (benefit risk concerns)	Insufficient data to support B/R in claimed indications	Including insufficient bibliographic data presented, bibliographic data not enough to support B/R in indications, requests for clinical efficacy studies / therapeutic equivalence studies, claim of well-established use questioned.
	Safety concerns	Concerns raised about adverse events, safety of the product, discussions around the addition/removal of contraindications, special safety warnings and drug interactions.
	Posology concerns	Concerns about posology, including differences in approved posology in different member states, duration of treatment, concomitant therapy, posology in different patient categories.
	Overall B/R negative	Concerns about the overall Benefit/Risk of the product (including cases where claimed efficacy is not sufficiently demonstrated in one or more indications). Including cases where B/R is considered negative.
Quality	Concerns on quality or manufacturing parameters	Including stability and safety of excipients, formulation concerns, GMP issues, concerns about the quality/ size of the biobatch, impurities, residuals, related substances, etc.
	Packaging concerns / medication errors	Child-resistant packaging, device concerns, device storage orientation, complexity of dispenser, potential for medication errors.
Regulatory/ procedural	Concerns about SmPC wording	Including differences in approved (contra)indications in different member states for the reference product.
	Administrative concerns (incl. concerns involving the PL /SmPC)	Objections because a product has a different legal status in member states, unclear patient leaflet, unclear SmPC, different SmPCs for different strengths, movement of data to another section of SmPC, providing an RMP, updating patient leaflet, discussions about the legal basis of the application, discussions of acceptability of reference product when the original products was no longer on the market, redefinition of starting material.

BE: Bioequivalence, GCP: Good clinical practice, GMP: Good Manufacturing Practices.

Table S3: Reasons for referral per year and licensing failure.

Main category	Sub category	2006		2007		2008		2009		2010		2011		2012		2013	
		MA	LF	MA	LF	MA	LF	MA	LF	MA	LF	MA	LF	MA	LF	MA	LF
Clinical (study design)	Concerns about the quality of the studies	8	10	6	6	13	3	9	0	2	0	1	1	1	0	3	1
Clinical (equivalence)	Bioequivalence/therapeutic equivalence not demonstrated	2	2	4	2	8	6	6	3	1	2	1	0	1	0	1	0
	Bioequivalence/therapeutic equivalence not investigated in sub group	1	0	3	4	5	0	2	0	0	2	1	0	7	0	0	0
Clinical (benefit risk concerns)	Insufficient data to support B/R in claimed indications	10	1	6	0	5	1	2	1	2	1	2	1	0	0	0	2
	Safety concerns	1	0	7	0	5	0	2	0	1	0	1	0	1	0	1	0
	Posology concerns	7	0	3	0	0	0	1	0	0	0	0	0	1	0	0	0
	Overall B/R negative	2	0	1	0	8	0	2	0	0	0	2	0	0	1	2	0
Quality	Concerns on quality or manufacturing parameters	6	0	12	0	2	0	8	0	2	0	2	1	0	0	1	2
	packaging concerns/medication errors	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Regulatory/ procedural	Concerns about SmPC wording	11	1	4	0	6	0	6	0	0	0	0	0	2	0	0	0
	Administrative concerns (incl concerns involving the PL /SmPC)	3	0	2	1	1	0	0	0	0	0	0	0	0	0	3	0
Combinations of multiple concerns	NA	21	0	21	10	19	1	1	1	2	0	1	1	5	1	3	1
Total		**72**	**14**	**70**	**23**	**73**	**11**	**39**	**5**	**10**	**5**	**11**	**4**	**18**	**2**	**14**	**6**

MA: procedures ending marketing authorisation, LF: procedures ending in licensing failure.

Table S4: Combinations containing at least one of the following.

Category	**n**	**%**
Concerns about the quality of the studies	26	30%
Bioequivalence/therapeutic equivalence *not demonstrated*	13	15%
Bioequivalence/therapeutic equivalence *not investigated in sub group*	17	19%
Insufficient data to support B/R in claimed indications	23	26%
Safety concerns	15	17%
Posology concerns	29	33%
Overall B/R negative	8	9%
Concerns on quality or manufacturing parameters	17	19%
packaging concerns/medication errors	9	10%
Concerns about SmPC wording	19	22%
Administrative concerns (incl. concerns involving the PL /SmPC)	24	27%
Total number of combinations	88	100%

B/R: Benefit/risk, PL: package leaflet, SmPC: Summary of Product Characteristics.

Table S5: Authorised* products via DCP/MRP available in the Mutual Recognition Product Index by Reference Member State.

Country	n	%
Denmark	1954	17.55%
Germany	1816	16.31%
United Kingdom	1643	14.76%
The Netherlands	1263	11.35%
Finland	1177	10.57%
Sweden	956	8.59%
Portugal	526	4.73%
France	291	2.61%
Poland	212	1.90%
Czech Republic	186	1.67%
Austria	168	1.51%
Italy	157	1.41%
Ireland	156	1.40%
Spain	117	1.05%
Hungary	117	1.05%
Belgium	89	0.80%
Norway	73	0.66%
Estonia	67	0.60%
Greece	42	0.38%
Slovakia	38	0.34%
Malta	22	0.20%
Slovenia	18	0.16%
Romania	16	0.14%
Latvia	11	0.10%
Iceland	9	0.08%
Bulgaria	3	0.03%
Lithuania	2	0.02%
Luxemburg	2	0.02%
Grand Total	**11132**	**100.00%**

**This concerns also products approved prior to 2006 via the MRP.*

Chapter 3

Post-innovation innovation: the current situation

Chapter 3.1

Extensions of indication throughout the drug product lifecycle: a quantitative analysis

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ABSTRACT

The marketing authorisation of the first generic product version is an important moment in a drug product lifecycle. The subsequently changed intellectual property protection prospects could affect the incentives for further drug development. We assessed the quantity and nature of extensions of indication of small molecule medicinal products authorised through the European Medicines Agency throughout the drug product lifecycle with special attention for the impact of the introduction of a first generic competitor. The majority (92.5%) of the extensions of indication was approved during the exclusivity period of the innovator product. Regulatory rethinking might be needed for a sustainable stimulation of extensions of indications in the post-generic period of a drug product lifecycle.

PROBLEM STATEMENT

A crucial issue of drug development strategies is the time horizon for innovator pharmaceutical companies to recoup their investments. To increase the probability of a sufficient return on investment, innovations can be protected from competitors by patents and other exclusivity rights (e.g. data exclusivity).[1] This creates a period of market exclusivity, during which pharmaceutical companies are essentially the sole manufacturer of a product.[2]

During the period of market exclusivity, pharmaceutical companies can increase the usage potential of their products, and thereby return on investment, by extending the therapeutic indication of their products.[3] Once the drug product is proven to be effective and safe for the new indication, it can be included in the marketing authorisation (i.e. the label) of the drug. More indications in the label enlarge the patient population that could use the drug; which in turn increases sales. Moreover, the market exclusivity period can be extended if a new indication is added to the label. For example, in the European Union (EU) an additional year of data exclusivity can be awarded if a drug is approved for one or more new therapeutic indications that bring a significant clinical benefit in comparison with existing therapies.[4]

Previously, Grabowski et al. showed that in the USA innovator products have on average a period of market exclusivity of 12.9 years.[5] During the market exclusivity period it is common practice for pharmaceutical companies to continue clinical trials in search for marketing authorisation, and to add new indications.[6,7] DiMasi demonstrated that 982 new use approvals were authorised between 1998 and 2011 for drugs authorised in the USA, including new indications and new populations.[8] In the EU the number of applications for extensions of indication is about the same as the number of applications for new medicinal products.[9] Overall, the development of new indications accounts for a substantial share of pharmaceutical innovation.Upon expiration of patents and other exclusivity rights of the innovator product, generic products enter the market. Consequently, the market share of the innovator product plummets.[5,10] From the perspective of public health and cost-containment cheaper alternatives become available for clinical use.[11,12] However, patent expiration and generic competition can have major consequences for investments in further studying and regulatory processing of new, additional indications. Innovator companies will benefit less from extensions of the indication after the approval of a generic competitor than during the initial market exclusivity period. Although new patents and regulatory protection can be obtained for an extension of indication, current clinical practice shows frequent prescribing of generic medicinal products for the extended indications, even though the generic product versions are not authorised for these new therapeutic indications. Moreover, once a patent

has been obtained it can be challenged by other pharmaceutical companies – with an uncertain outcome. Likewise, generic companies can study and apply for extensions of indication for their products, but they face the same problem regarding lack of incentives as innovator companies. All this sounds logical but so far the issue: to what extent new indications are developed once generic products are approved, has been poorly studied.

In this analysis, we determined the quantity and nature of extensions of indication of small molecule medicinal products authorised through the European Medicines Agency (EMA). Subsequently, we compared the frequency of extensions of indication throughout the drug product lifecycle with special attention for the impact of the authorisation of the first generic product per active substance. We hypothesised that neither indications of innovator products nor generic products were extended around the time of introduction of the first generic product version.

APPROACH

A list of small molecule medicinal products authorised since the beginning of the EU centralised procedure, or authorised and later withdrawn, up to 31 August 2013 was obtained from the EMA website (http://www.ema.europa.eu/ema/). Subsequently, the medicinal products with active substances first authorised in the EU through the EMA were selected. These were grouped by active substance in which different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives were considered as the same active substances. Combination products constituted their own ‘active substance’. The active substances were our unit of analysis.

For each active substance, the duration of the ‘innovator period’ and the ‘generic period’ was calculated. The innovator period was defined as the time between the marketing authorisation of the first innovator product and the first generic product. The approval of the first generic product marks the expiration of patents and other exclusivity rights on the active substance. The generic period comprised the time between the marketing authorisation of the first generic product and 31 August 2013; the date on which data collection started. Active substances were eligible for analysis, if the generic period lasted at least one year, because it was assumed that these needed at least this period of time to obtain approval for a new indication.

Subsequently, the European Public Assessment Report (EPAR) of each medicinal product was collected from the EMA website. This document contains references to changes of the marketing authorisation (e.g. extensions of indication). In addition, the initial Summary

of Product Characteristics (SmPCs) and its subsequent versions were collected from the Pharmaceuticals Community Register of the European Commission (http://ec.europa.eu/health/documents/community-register/) if the SmPCs were necessary to characterise the nature of the extensions of indication.

Per active substance, the EPARs were screened for references to 'extensions of indication'. The approval dates of the extensions of indication were extracted from the EPARs. In addition, initial indications of subsequent products per active substance were considered as extension of indication. For instance, the approval of Aclasta® (zoledronic acid) for the treatment of Paget's disease was regarded an extension of indication, because Zometa® (also zoledronic acid) was only authorised for prevention of skeletal related events and the treatment of tumour-induced hypercalcaemia.[13,14] Extensions of indication were only counted the first time an indication was approved per active substance.

The active substances, medicinal products, marketing authorisation dates and extensions of indication – including the approval dates – were entered into a database. The number of extensions of indication per year was plotted with a distinction between the innovator period and the generic period (Figure 1). In this graph t = 0 is the marketing authorisation date of the first generic product per active substance. The rate of extensions of indication in the innovator period and generic period were calculated.

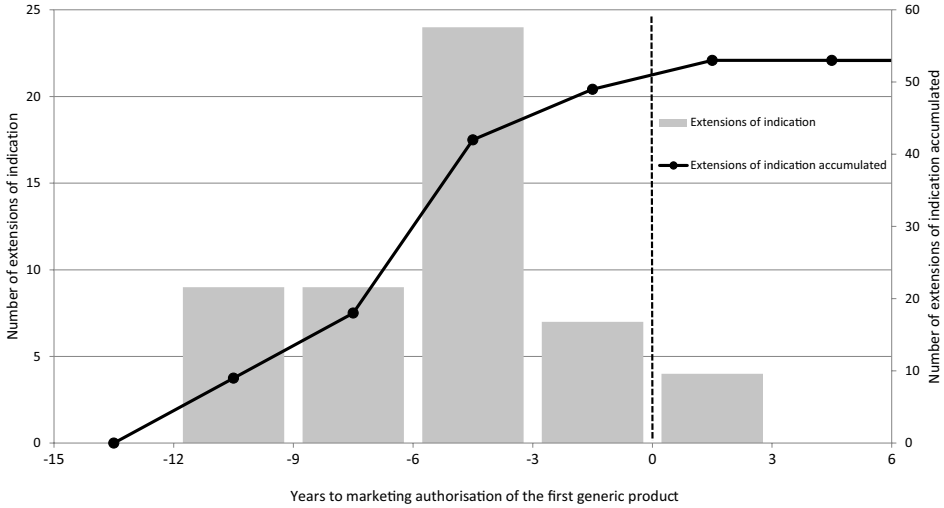

Figure 1: Number of extensions of indication synchronised by the marketing authorisation of the first generic product per active substance. Bars indicate the absolute number of extensions of indication (left y axis) relative to the entry of the first generic product version for each active substance, denoted as t = 0. The line represents the cumulative number of extensions of indications during the analysis period (right y axis).

NEW INDICATIONS

In total, we identified 557 small molecule medicinal products that were approved in the EU through the centralised procedure and that were authorised or withdrawn up to 31 August 2013. The medicinal products included 297 different active substances or combinations of active substances. Of these, 26 met the subsequent selection criteria of approval of one or more generic products with a follow-up period of at least one year. These 26 active substances comprised 186 products: 65 innovator products and 121 generic products (Table 1). The innovator products were first authorised between 1995 and 2001. The generic products were authorised between 2007 and 2012. The median number of innovator and generic products per active substance was 2 [interquartile range (IQR) 2–4] and 4 (IQR 2–6), respectively. The median length of the innovator period was 11.2 years (IQR 11.0–12.3 years), whereas it was 3.6 years (IQR 2.5–4.1 years) for the generic period.

In the analysis of the 26 active substances, we identified 53 extensions of indication, of which two concerned changes to the posology (i.e. paediatric posology). These all applied to innovator products. Figure 1 displays the number of extensions of indication per time interval of 3 years before and after the approval of the first generic product. It shows that the vast majority of extensions of indication (n = 49; 92.5%) were authorised in the innovator period. The first was authorised on average 5.2 years [standard deviation (Sd) 3.3 years] after approval of the first innovator product and 6.5 years (Sd 3.3 years) before the approval of the first generic product. The incidence of extensions of indications was 49/304.6 years during the innovator period and 4/88.3 years during the generic period. Figure 1 also displays how the number of extensions of indication accumulates each year. It increases steadily until 3 years before the approval of the first generic product (t = 0) when it starts to level off. Subsequently, 2 years after approval of the first generic product version no extensions of indication were identified during the study period.

In more detail, Figure 2 depicts the number of extensions of indication per active substance. On average 2.0 (Sd 2.1) extensions of indication were approved per active substance. However, the active substances varied considerably in the number of extensions of indication. Docetaxel had the most extensions of indication (n = 9), whereas six active substances had none. The four extensions of indication in the generic period related to four individual active substances.

Table 1: Active substances included in the analysis of extensions of indication.

Active substance	Innovator[a]							Generic[b]		
	ATC group	Brand name	Company	Approval date[c]	Products[d]	Years[e]	Initial scope[f]	Approval date[g]	Years[h]	Products[i]
Pioglitazone	A10BG03	Glustin / Actos	Takeda	11-10-2000	2	11.4	Type 2 diabetes	9-3-2012	1.5	8
Repaglinide	A10BX02	NovoNorm / Prandin	Novo Nordisk	17-8-1998	2	10.9	Type 2 diabetes	29-6-2009	4.2	4
Clopidogrel	B01AC04	Clopidogrel BMS / Plavix / Iscover / Clopidogrel Zentiva / Grepid	Bristol-Myers Squibb / Sanofi / Sanofi-aventis / Pharmathen	15-7-1998	4	11.0	Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes)	21-7-2009	4.1	23
Irbesartan	C09CA04	Irbesartan BMS / Aprovel / Karvea / Irbesartan Zentiva	Bristol-Myers Squibb / Sanofi / Sanofi-aventis	27-8-1997	4	11.3	Essential hypertension	1-12-2008	4.8	3
Irbesartan / hydrochlorothiazide	C09DA04	Irbesartan Hydrochlorothiazide BMS / CoAprovel / Karvezide / Irbesartan Hydrochlorothiazide Zentiva	Bristol-Myers Squibb / Sanofi / Sanofi-aventis	15-10-1998	4	11.0	Essential hypertension	23-10-2009	3.9	2
Telmisartan	C09CA07	Pritor / Kinzalmono / Micardis	Bayer / Boehringer Ingelheim	11-12-1998	3	11.1	Essential hypertension	26-1-2010	3.6	4
Raloxifene	G03XC01	Evista / Optruma	Daiichi Sankyo / Eli Lilly	5-8-1998	2	11.7	Non traumatic vertebral fractures in postmenopausal women	29-4-2010	3.3	1
Sildenafil	G04BE03	Viagra / Patrex / Revatio	Pfizer	14-9-1998	3	11.0	Erectile dysfunction	21-9-2009	3.9	4
Efavirenz	J05AG03	Stocrin / Sustiva	MSD / Bristol-Myers Squibb	28-5-1999	2	12.6	HIV	9-1-2012	1.6	1

Table 1: Active substances included in the analysis of extensions of indication. (continued)

Active substance	Innovator[a]							Generic[b]		
	ATC group	Brand name	Company	Approval date[c]	Products[d]	Years[e]	Initial scope[f]	Approval date[g]	Years[h]	Products[i]
Lamivudine	J05AF05	Epivir / Zeffix	ViiV Healthcare / Glaxo Group	8-8-1996	2	13.2	HIV	23-10-2009	3.9	2
Lamivudine / zidovudine	J05AR01	Combivir	ViiV Healthcare	18-3-1998	1	13.0	HIV	28-2-2011	2.5	1
Nevirapine	J05AG01	Viramune	Boehringer Ingelheim	5-2-1998	1	11.8	HIV	30-11-2009	3.8	1
Capecitabine	L01BC06	Xeloda	Roche	2-2-2001	1	11.2	Metastatic colorectal cancer	20-4-2012	1.4	5
Docetaxel	L01CD02	Taxotere / Docetaxel Winthrop	Aventis	27-11-1995	2	14.2	Metastatic breast cancer	26-1-2010	3.6	6
Leflunomide	L04AA13	Arava / Leflunomide Winthrop	Sanofi-Aventis	2-9-1999	2	10.9	Active rheumatoid arthritis	27-7-2010	3.1	4
Mycophenolate mofetil	L04AA06	CellCept	Roche	14-2-1996	1	12.0	Prophylaxis of acute transplant rejection	21-2-2008	5.5	3
Temozolomide	L01AX03	Temodal	MSD	26-1-1999	1	11.0	Glioblastoma multiforme	25-1-2010	3.6	6
Topotecan	L01XX17	Hycamtin / Evotopin	SmithKline Beecham / Beecham Group	12-11-1996	2	12.7	Metastatic carcinoma of the ovary	24-7-2009	4.1	5
Ibandronic acid	M05BA06	Bondronat / Destara / Bondenza / Bonviva	Roche	25-6-1996	4	14.2	Tumour-induced hypercalcaemia	17-9-2010	3.0	4
Zoledronic acid	M05BA08	Zometa / Aclasta	Novartis	20-3-2001	2	11.1	Tumour-induced hypercalcaemia	20-4-2012	1.4	6
Entacapone	N04BX02	Comtess / Comtan / Entacapone Orion	Orion Corporation / Novartis	16-9-1998	3	12.4	Parkinson's disease	18-2-2011	2.5	1
Levetiracetam	N03AX14	Keppra	UCB Pharma SA	29-9-2000	1	10.9	Epilepsy.	26-8-2011	2.0	7

Table 1: Active substances included in the analysis of extensions of indication. (continued)

Active substance	Innovator[a]							Generic[b]		
	ATC group	Brand name	Company	Approval date[c]	Products[d]	Years[e]	Initial scope[f]	Approval date[g]	Years[h]	Products[i]
Olanzapine	N05AH03	Zyprexa / Olansek / Zyprexa Velotab / Zypadhera	Eli Lilly	27-9-1996	4	11.0	Schizophrenia	27-9-2007	5.9	9
Pramipexole	N04BC05	Sifrol / Daquiran / Mirapexin	Boehringer Ingelheim / Dr. Karl Thomae	14-10-1997	3	10.9	Idiopathic Parkinson's disease	12-9-2008	5.0	3
Rivastigmine	N06DA03	Exelon / Prometax / Rivastigmine Hexal / Rivastigmine Sandoz	Novartis / Hexal / Sandoz	12-5-1998	4	10.9	Alzheimer's dementia	17-4-2009	4.4	4
Desloratadine	R06AX27	Aerius / Allex / Azomyr / Neoclarityn / Opulis	MSD / Schering-Plough	15-1-2001	5	10.9	Seasonal allergic rhinitis	24-11-2011	1.8	4

[a] The innovator products were defined as the medicinal product that was approved first and all other medicinal products with the same active substance manufactured by the same company, or group of companies, e.g. in a joint marketing or licensing agreement.
[b] Generic product were all products not designated as innovator products.
[c] Marketing authorisation date of the first innovator product.
[d] Number of products considered as innovator products.
[e] Length of the innovator period in years.
[f] Scope of the indication of the first innovator product, [g] Marketing authorisation date of the first generic product.
[h] Length of the generic period in years, [i] Number of products considered as generic products.

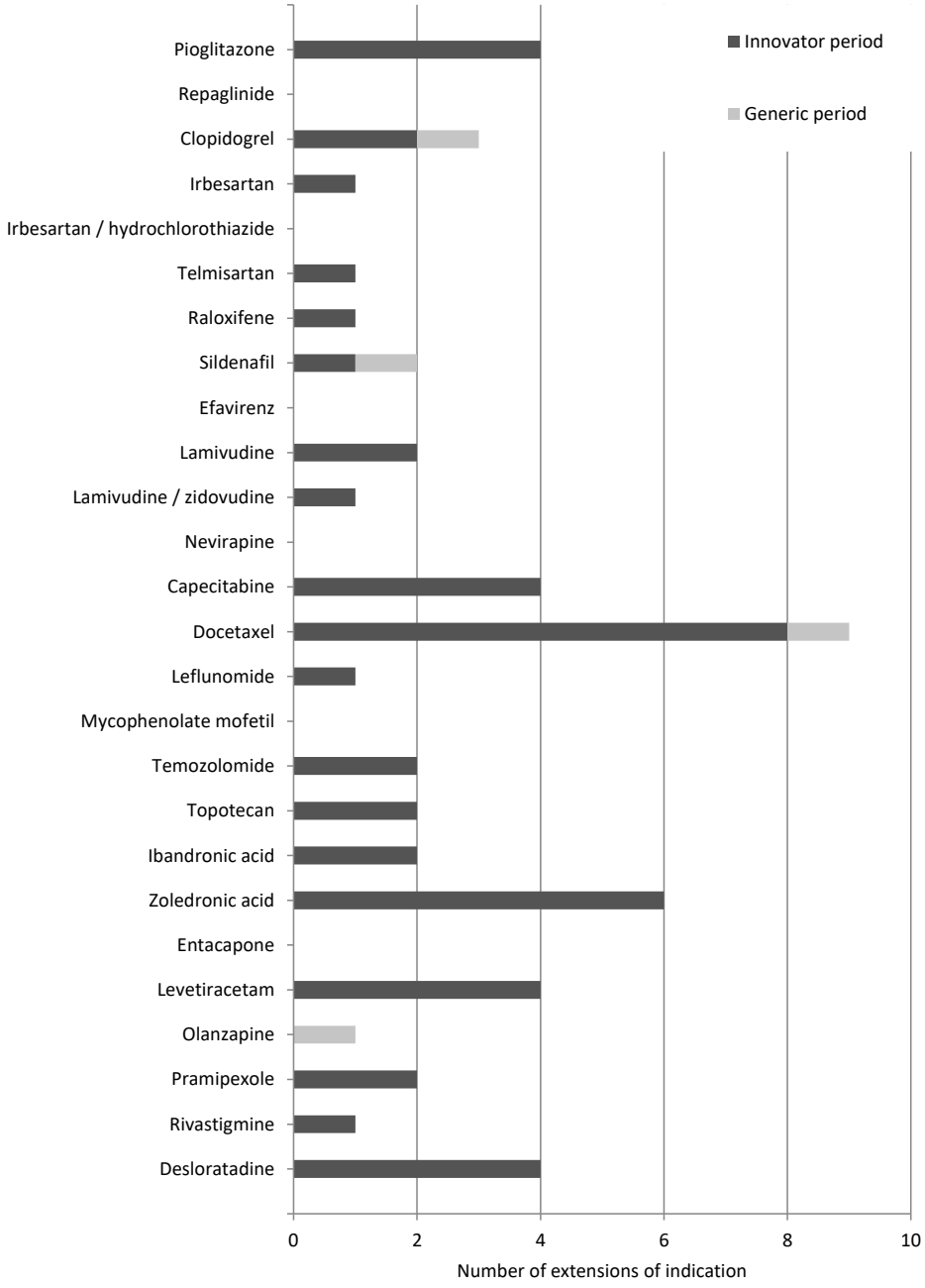

Figure 2: Total number of extensions of indication per active substance. Dark bars represent extensions of indication during the innovator period and light bars represent extensions of indication during the generic period.

DYNAMICS OF EXTENSIONS OF INDICATIONS

In this analysis, we observed the following dynamics of the extensions of indication in the drug product lifecycle: an upsurge after the initial marketing authorisation, a peak 6 to 3 years before generic introduction and a decline starting 3 years before generic introduction, and no new extensions of indications were observed 2 years thereafter. During the study period extensions of indication were only approved for innovator products and mainly during the innovator period; only shortly after the start of generic competition was a limited number of extensions of indication approved. These results are in line with our hypothesis that the number of extensions of indication ceases around the time a generic product version is approved.

The upsurge and subsequent peak could be the result of pharmaceutical companies seeking to enlarge their market, and it could also provide them with an extension of their market exclusivity period. The incline in extensions of indication started a few years after initial authorisation of the innovator products, which could be explained by the fact that companies would have needed time to complete clinical studies in support of the new indication. Anticipating the introduction of generic competitors, the innovator companies might have ceased the development of additional indications years earlier to that moment. The extensions of indication after generic introduction could generally be explained by a delay in the drug development, for example prolonged clinical development.

In addition, two of the four extensions of indication in the generic period seem to be explainable by the ongoing specific intellectual property protection. Zypadhera® (olanzapine) was authorised as a prolonged-release dosage form for maintenance treatment in schizophrenia therapy. In contrast to Zyprexa® (olanzapine), Zypadhera® contains olanzapine pamoate, which is still under patent protection.[15] For Revatio® (sildenafil) a paediatric indication for the treatment of pulmonary arterial hypertension was approved. Revatio®, but not Viagra®, which has the same active substance, still benefits from 10 years of marketing exclusivity as an orphan drug. The other two extensions of indication in the generic period were for clopidogrel (Plavix®, Iscover®, Clopidogrel Zentiva®) in atrial fibrillation and docetaxel (Taxotere®, Docetaxel Winthrop®) in the treatment of node-negative breast cancer. The clinical trials supporting these extensions of indication might have been performed during the innovator period, whereas the inclusion in the label might have been delayed.

The incidence of extensions of indication has received little attention in literature. In 2006, Berndt et al. studied the number of supplemental indications of angiotensin-converting enzyme inhibitors, proton-pump inhibitors/H2-antagonists and selective serotonin

reuptake inhibitors/serotonin–norepinephrine reuptake inhibitors between 1984 and 2004.[3] For all three groups they found a considerable number of extensions of indication, which seemed to have been approved mainly during the 12 years after approval of the initial indication. However, they did not relate the extensions of the indication to the approval of generic versions of the products. DiMasi demonstrated a fluctuation in the number of supplemental indications per year between 1999 and 2011 in the USA without exhibiting a marked trend.[8]

LENGTH OF EXCLUSIVITY PERIOD AND SCOPE OF THE NEW INDICATIONS

Our identified 11.2 years of innovator period approximates the average length of the market exclusivity period identified in previous studies.[5,16] However, these periods are noticeably shorter than the 15 years of exclusivity the EU legislator deemed necessary to cover for the investments in drug development when it established the EU Supplementary Protection Certificate (SPC).[17] The SPC prolongs the basic patent as compensation for the time between the filing of the patent and the initial marketing authorisation with a maximum of 5 years.[18] The SPC in the EU is similar to the patent term restoration in the USA.[2] The short market exclusivity period could be explained by the soaring drug development time over the years up to 14.2 years for drugs approved in the USA between 1990 and 1999.[19] More-recent data show that clinical development and regulatory approval ranged from 5.8 years for AIDS antiviral drugs to 8.7 years for antineoplastic drugs approved by the FDA in the period 2003–2007.[20] This excludes the time involved in discovery and preclinical testing of the drug. The remaining period of patent protection cannot be extended with the SPC to the aforementioned 15 years.

We noticed that the extensions of indication differed in their respective scopes. Some extensions of indication seemed to be within the scope of the original indication. For instance, the therapeutic indication of pioglitazone, an antidiabetic drug, has been extended with variations to the treatment of type 2 diabetes mellitus.[21] Other drugs have been extended with indications outside the scope of their original use. A prime example is sildenafil, which is used for the treatment of erectile dysfunction (Viagra®),[22] and afterwards was authorised for pulmonary hypertension (Revatio®).[23]

IMPLICATIONS FOR PUBLIC HEALTH

From a public health perspective, it is important that new indications are developed and the results are included in a marketing authorisation and product information. The application for authorisation enables an in-depth benefit:risk assessment by the competent authorities. Moreover, after approval the new indications will be included in the official product information (e.g. the package leaflet). This provides physicians and patients with reliable information about the use of the product, including posology and potential side effects.

A substantial share of the authorised drugs has subsequent indications that are not included in a marketing authorisation, as the commonness of off-label use indicates.[24–27] Radley et al. estimated that 21% of the overall medication use is off-label, whereas 73% of those uses were supported by little or no scientific evidence.[28] In addition, many potentially new indications for approved drugs have been suggested based on in vitro and in silico techniques used for drug repositioning.[29] The fact that our analysis showed that approval of extensions of indication by a regulatory authority mainly occurred during the pre-generic period is of concern from this point of view. The relative absence of extensions of indication in the generic period, despite the presence of potential new indications, could question the capability of the regulatory system to facilitate continuous innovation in the form of extensions of indication. Regulatory rethinking might be needed to overcome some of the obstacles faced in this respect.

In future research it would be interesting to determine whether the decrease in extensions of indication correlates with a reduction in clinical research. Because clinical trials are needed to confirm the efficacy and safety of a drug in new indications, a decrease in clinical trials might precede a reduction in extensions of indication. We focused on the influence of generic competition on the rate of extensions of indication. Another interesting question for future research is how this rate is affected by the authorisation of me-too products (subsequent products within a therapeutic class), because they also pose competition.

LIMITATIONS OF THE ANALYSIS

Several limitations to our analysis should be noted. Firstly, we assessed the first cohort of medicinal products with generic competitors authorised in the European centralised procedure, which has only been in place since 1995. For most of the 297 active substances no generic products are yet authorised. This explains the rather small sample

size. Secondly, the centralised procedure is only one of the regulatory routes to obtain a marketing authorisation in the EU. Extensions of indication could be included in marketing authorisations granted through the decentralised procedure or the national procedure. Lastly, we did not have the same follow-up time for each active substance. This differed particularly for the generic period. However, the decline in and subsequent absence of extensions of indication after generic introduction might only be partially attributed to differences in follow-up time of active substances in the generic period. Three, four and five years into the generic period, we had data on 20, 17 and eight active substances, respectively, and no extensions of indication were approved during those years.

CONCLUDING REMARKS

During the study period innovator products were approved for new indications during their lifecycle, whereas generic products were not. Extensions of indication were mainly authorised a few years before approval of the first generic product version. Regulatory rethinking might be needed for a sustainable stimulation of extensions of indications in the post-generic period of the drug product lifecycle, especially for the sake of public health.

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Chapter 3.2

Effect of generic introduction on clinical trial activities

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Submitted

ABSTRACT

The introduction of a generic product version is an important moment in a drug life cycle. We examined whether that occurrence was associated with changes in the number and funding source of clinical trials (CTs). Clinicaltrials.gov was searched for CTs conducted with drugs of the first cohort of small molecule medicinal products authorised through the European Medicines Agency with a generic product version. Within four years before and four years after generic approval 2689 and 2069 CTs were identified for 24 drugs, respectively. The median number of CTs per drug was 73 (IQR 30-144) pre-generic and 41 (IQR 21-102) post-generic. After correction for the increase in clinical trial registration over time the median ratio post:pre-generic was 0.6 (IQR 0.4-0.7). The median ratio was similar for industry and non-industry funded CTs: 0.5 (IQR 0.4-0.8) and 0.6 (IQR 0.5-0.8), respectively, indicating that the number of CTs decreased regardless of the funding source.

INTRODUCTION

The introduction of a generic product version of a medicinal product is an important moment in a drug life cycle. Innovator companies obtain an exclusivity period through patents and other exclusivity rights such as data protection, during which generic products cannot enter the market. That exclusivity period offers the innovator company an incentive to continue clinical research in order to extend their product's therapeutic indications. Extensions of indication allow the medicinal product to be used for the treatment of a larger patient population and consequently may generate an increase in revenue.[1–3] However, the introduction of a first generic product version changes the ability to recoup investments such as costs for clinical trials, because thereafter the market has to be shared with a frequently cheaper product. Moreover, generic products will generally also be prescribed "off-label" for future extensions of indication of the innovator company's product, even if the new indication is still under patent protection. Previous research has shown that as a result, the market share of innovator company's products tends to decrease substantially.[4,5]

In a previous study, we assessed the quantity and nature of extensions of indication before and after the approval of a first generic product version.[2] That study used the first cohort of small molecule medicinal products with at least one generic product version authorised through the European Union (EU) centralised procedure since 1995, which are assessed through the European Medicines Agency. In summary, the results showed that the majority (92.5%) of the extensions of indication were approved during the exclusivity period of the innovator product. It is, however, unclear whether this effect can be attributed to a reduction in the number of conducted trials after entry of a generic product version or to a general disincentive to apply for an extension of indication even when clinical trials have been conducted.

In 2011, Luijn et al. demonstrated that during 10 years after approval of the biological drug etanercept a substantial number of clinical studies was still conducted (n=84). About half of these studies focused on new indications and were funded by independent sponsors.[1] However, their study did not cover the period during which a generic (biosimilar) version of etanercept was available on the market. More recently, Borg et al. assessed the number of high impact publications on four drugs (olanzapine, atovaquone, reviparin and glimepride) and suggested that the crest in knowledge base is reached two to three years prior to generic introduction.[6] However, previous research did not study the effect of generic approval on the number of conducted clinical trials.

Post-approval clinical research is important to deepen the knowledge of medicinal products and to assess efficacy and safety.[7,8] This is especially important as it has been suggested that innovative drugs are approved quicker and additional testing is shifted to the post-approval phase.[9,10] Moreover, continuous clinical research is of interest in relation to drug repositioning: a trending drug development strategy that aims to develop new therapeutic uses for existing active substances.[11]

The purpose of the present study is therefore to examine whether the introduction of generic product versions of a drug in Europe is associated with changes in the number and funding source of clinical trials. We expected a reduction in the number of clinical trials after the approval of a first generic product version due to a reduced incentive for pharmaceutical companies to continue investments in clinical research. Conversely, independent sponsors may continue clinical research to deepen the knowledge of medicinal products.

We used clinicaltrials.gov to search for all clinical trials on 24 drugs of the first cohort of small molecule medicinal products authorised through the European Medicines Agency with a generic product version as identified in our previous study.[2] We included all trials that started within the four years before or the four years after the approval of the first generic product version. Ratios of the number of clinical trials post:pre-generic product approval were calculated per drug with a differentiation by funding source. The ratio per drug was corrected for the increase in clinical trial registration over time due to reforms of clinical trial registration requirements.[12–14]

RESULTS

In total, 4758 clinical trials were extracted from clinicaltrials.gov covering the eight-year study period of each of the 24 drugs. Of these, 2689 started in the pre-generic and 2069 in the post-generic period. The median number of clinical trial per drug was 73 pre-generic (interquartile range (IQR), 30-144) and 41 post-generic (IQR: 21-102) (Table 1). The median ratio of the number of clinical trials post:pre-generic was 0.7 (IQR: 0.6-0.9). The correction for the increase in number of registered clinical trials over time resulted in a median ratio of 0.6 (IQR: 0.4-0.7).

There were 2287 industry funded clinical trials (48.07% of all trials): 1403 (29.49%) pre-generic and 884 (18.58%) post-generic. Consequently, 2469 clinical trials (51.89%) were non-industry funded: 1284 (26.99%) pre-generic and 1185 (24.91%) post-generic. The post:pre-generic ratios were 0.6 (IQR: 0.5-0.9) for industry funded clinical trials and 0.9

Table 1: Overview of active substances and the number of clinical trials registered in the pre- and post-generic period.

	ATC group	Intial scope**	Approval date of the first generic product version	Number of clinical trials pre-generic	Number of clinical trials post-generic
Pioglitazone*	A10BG03	Type 2 diabetes	9-3-2012	147	47
Repaglinide	A10BX02	Type 2 diabetes	29-6-2009	14	10
Clopidogrel	B01AC04	Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes)	21-7-2009	189	263
Irbesartan	C09CA04	Essential hypertension	1-12-2008	37	19
Telmisartan	C09CA07	Essential hypertension	26-1-2010	84	47
Raloxifene	G03XC01	Non traumatic vertebral fractures in postmenopausal women	29-4-2010	15	10
Sildenafil	G04BE03	Erectile dysfunction	21-9-2009	94	91
Efavirenz*	J05AG03	HIV	9-1-2012	117	83
Lamivudine	J05AF05	HIV	23-10-2009	120	112
Nevirapine	J05AG01	HIV	30-11-2009	61	33
Capecitabine*	L01BC06	Metastatic colorectal cancer	20-4-2012	311	262
Docetaxel	L01CD02	Metastatic breast cancer	26-1-2010	526	412
Leflunomide	L04AA13	Active rheumatoid arthritis	27-7-2010	12	22
Mycophenolate mofetil	L04AA06	Prophylaxis of acute transplant rejection	21-2-2008	291	219
Temozolomide	L01AX03	Glioblastoma multiforme	25-1-2010	209	154
Topotecan	L01XX17	Metastatic carcinoma of the ovary	24-7-2009	89	43
Ibandronic acid	M05BA06	Tumour-induced hypercalcaemia	17-9-2010	31	8
Zoledronic acid*	M05BA08	Tumour-induced hypercalcaemia	20-4-2012	57	34
Entacapone	N04BX02	Parkinson's disease	18-2-2011	12	8

Table 1: Overview of active substances and the number of clinical trials registered in the pre- and post-generic period. (continued)

	ATC group	Intial scope**	Approval date of the first generic product version	Number of clinical trials pre-generic	Number of clinical trials post-generic
Levetiracetam	N03AX14	Epilepsy.	26-8-2011	41	38
Olanzapine	N05AH03	Schizophrenia	27-9-2007	141	83
Pramipexole	N04BC05	Idiopathic Parkinson's disease	12-9-2008	54	37
Rivastigmine	N06DA03	Alzheimer's dementia	17-4-2009	29	25
Desloratadine*	R06AX27	Seasonal allergic rhinitis	24-11-2011	8	9
Median				73	41
Interquartile range				30-144	21-102

** The length of the pre-generic period was adjusted to compensate for a shorter post-generic period.*

*** Scope of the indication of the first innovator product.*

(IQR: 0.6-1.2) for non-industry funded clinical trials. However, after correction for the increase in clinical trial registration over time the difference in decline between industry and non-industry funded trials largely disappeared. The ratio for industry funded clinical trials became 0.5 (IQR: 0.4-0.8) and for non-industry funded it became 0.6 (IQR: 0.5-0.8).

We observed a wide variety in the total number of clinical trials registered per drug as well as in their post:pre-generic ratios. For instance, capecitabine and docetaxel had 311 and 526 clinical trials registrations pre-generic, while only fifteen or less clinical trials were registered pre-generic for repaglinide, raloxifene, leflunomide, entacapone and desloratadine. Similar differences in number of clinical trial registrations were found in the number of clinical trials post-generic (Table 1). Figure 1 depicts how the overall ratios varied among the drugs. Some drugs show a strong reduction in the number of clinical trials post-generic, e.g. ibandronic acid (ratio 0.3, [corrected 0.2]), whereas there seems to be no change or a slight increase in other cases: clopidogrel (ratio1.4 [1.0]), leflunomide (ratio 1.8 [1.5]) and desloratadine (ratio 1.1 [1.0]).

Observed changes per funding source also varied extensively (Figure 1). For most drugs both industry and non-industry funded research decreased or increased about evenly. For irbesartan, raloxifene and levetiracetam, however, the number of industry funded clinical trials reduced strongly, while the number of non-industry funded trials did only change marginally. Conversely, for desloratadine industry funded research increased after approval of the first generic product version (corrected ratio 1.4), whereas non-industry funded research decreased (corrected ratio 0.5).

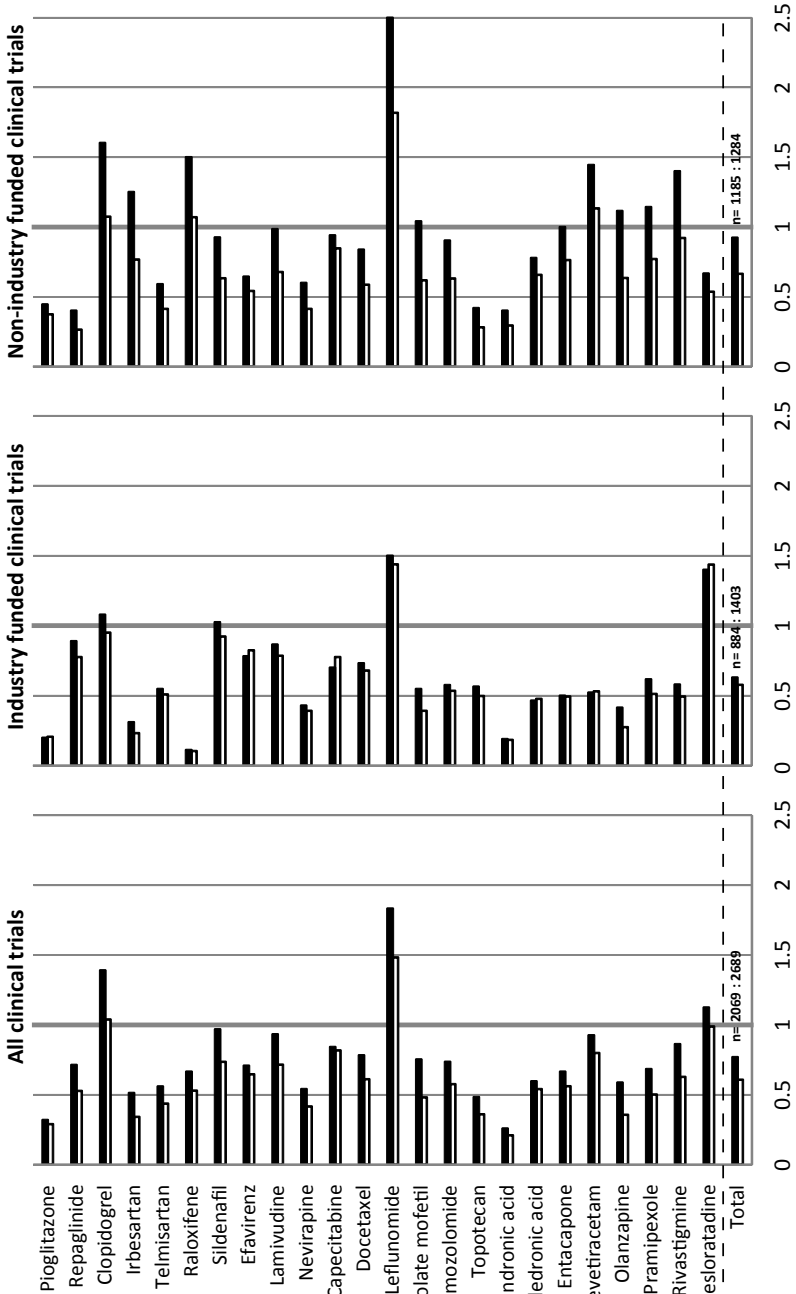

Figure 1: Ratio of the number of registered clinical trials in the post:pre-generic period per active substance overall (left), industry funded clinical trials (middle) and non-industry funded clinical trials (right). The blank bars represent the ratios corrected for the increase in clinical trial registrations over time.

DISCUSSION

The aim of the present study was to examine whether in the first cohort of small molecule medicinal products authorised through the European Medicines Agency the introduction of generic product versions of a drug in Europe was associated with changes in the number and funding source of clinical trials. The results show an overall decrease in clinical trials after the approval of a first generic product version, although still a considerable number of clinical trials were started after this point in the drug life cycle. The decrease was observed in the absolute number of clinical trials and consequently also in the post:pre-generic ratio. This result was even more pronounced after correction for the increase in clinical trial registration over time. Contrary to our expectations, the reduction in clinical trials registrations occurred both in industry funded and in non-industry funded clinical trials.

There are four general factors that are likely to contribute to the observed change in the number of clinical trials. These are (1) changed industry incentives to conduct clinical trials after generic product approval, (2) changed incentives for investigator-initiated studies by (academic) researchers and clinical practitioners to conduct clinical trials after generic product approval, (3) general trends in the number of conducted clinical trials during a particular drug life cycle and (4) general trends in the conduct of clinical trials over time.

After approval of a first generic product version in the EU there might be a reduced incentive to develop new therapeutic indications by the pharmaceutical industry. Therefore, pharmaceutical industry may cease the start of clinical trials on a particular drug. This would be in line with the virtual absence of extensions of indication after the approval of a first generic product version.[2] Another factor that may contribute to a decrease in industry funded clinical trials may be the seizure of phase IV clinical trials after generic product introduction. Phase IV clinical trials are post-approval studies to assess the efficacy and safety of a medicinal product after it has been placed on the market. The pharmaceutical industry, however, has used phase IV clinical trials as an effective marketing tool.[15–17] This marketing strategy may be of less benefit to a pharmaceutical company to increase their sales volume once a generic product version has been approved.

From an academic or clinical practice perspective there may be other incentives to conduct clinical trials on a drug. Firstly, after the introduction of a generic product version it may be easier for academia to carry out clinical trials independently from the pharmaceutical company, especially in case of expensive drugs that would constitute a larger proportion of academic research budgets. The introduction of generally cheaper generic product

versions may provide independent research institutions with new opportunities. Secondly, medicinal products may be used as an active comparator, or in a combination therapy in clinical trials on new chemical entities. For instance, clopidogrel (in combination with aspirin) has been considered as the standard of care in antiplatelet therapy for patients with acute coronary syndromes.[18,19] Therefore, clopidogrel might have been used often as active comparator in clinical trials to study the efficacy and safety of new antiplatelet therapies such as prasugrel and ticagrelor. Such research may also generate a vast amount of new data on older medicinal products although the main focus of the clinical trials is on another drug. The data in our study did not allow for a differentiation between the use of the medicinal product in the experimental arm or the control arm of the clinical trials, nor the extent to which the drugs were used in a combination therapy. In either case the medicinal product was registered as intervention therapy in clinicaltrials.gov.

Next, every drug may experience certain trends in the amount of research throughout its life cycle. After approval pharmaceutical companies may still have to conduct clinical trials in the context of pharmacovigilance and obligations towards the competent authorities.[20] A drug may also be at the centre of attention of the scientific community in its early years, while thereafter researchers may simply lose interest in conducting new clinical trials.[1] Initial knowledge gaps may be filled by previous research and the use of the drug in clinical practice. As a result, at the moment of the introduction of the first generic product version independent sponsors may have redirected their research efforts towards newer medicinal products, while pharmaceutical companies may have fulfilled their regulatory obligations. Furthermore, throughout the life cycle other methods to study the efficacy and safety of a medicinal product may be used. For instance, observational studies may gain importance once the drug is used on a large scale in daily clinical practice. Observational studies allow for a relative cheap and quick assessment of the effectiveness and safety of medicinal products based on real world data.[21]

Finally, there may also be a number of general time trends that may explain changes in the number of clinical trial registrations. Firstly, there seems to be an increase in compliance with the clinical registration requirements. The study of Gill showed a strong increase in non-industry funded clinical trials registrations since 2005, at which time the Committee of Medical Journal Editors established its requirement of clinical trial registration as condition for publication.[12,14] Differences in registration rates between industry and non-industry funded clinical trials may be related to the highly scrutinised and regulated research environment of pharmaceutical companies.[12,22] Gill suggested that non-compliance with clinical trial registration requirements may have financial consequences for pharmaceutical companies, while the industry may also be better equipped financially to comply with the regulations. This may explain why the pharmaceutical industry initially

had a higher registration rate. In our study we have corrected the ratios for an increase in registrations of clinical trials over time. This correction sorted a larger effect on the ratios of non-industry funded clinical trials compared to industry funded clinical trials. Secondly, research institutions cope with limited research budgets which need to be allocated to an ever increasing number of drugs.[23,24] Consequently, the number of clinical trials per drug may decrease over time. Conversely, over the last decade clinical trials conducted by emerging markets may have boosted clinical research. Drain et al. reported an annual growth in clinical trials of almost 30% in Asia and about 33% in lower-middle-income countries between 2005 and 2012.[25,26]

In the present study, we focused on the approval date of the first generic product version, but this approach has limitations. Even when the decrease in number of clinical trials is attributed to the introduction of a generic product version, the expected change is likely to be more gradual than the binary moment when a first generic product version is introduced in Europe. Firstly, the approval date of the first generic product version may be considered only a rough estimate of the expiration of the exclusivity period. In the EU, the application for a generic product version may be approved during the last two years of data exclusivity. Moreover, medicinal products may still have benefitted from some exclusivity rights after approval of the first generic product version, such as patents for a method to manufacture the drug. These exclusivity rights may prevent a generic product to be marketed and therefore may provide an incentive for further clinical research by the marketing authorisation holder. Secondly, pharmaceutical companies may plan their drug development strategies on a global level and take into account their market position and exclusivity prospects in multiple countries. Differences among countries may affect decisions to conduct clinical trials. For instance, a substantial differences exist between therapeutic indications of anticancer drugs authorised the United States and the EU.[27] Also the expirations of patents and other exclusivity rights may differ substantially among countries. In the US, for example, the first generic product version of leflunomide was approved almost five years earlier than in the EU.[28,29]

For each of the studied drugs it is likely that a mix of factors applies which can explain the large variation in the post:pre-generic ratios among the drugs observed in our study. Some medicinal products may still have good prospects for exclusivity after introduction of a first generic product version. For instance, in our cohort Revatio (sildenafil) had been granted an orphan designation for the treatment of pulmonary arterial hypertension, which provided 10 years of market exclusivity that extended beyond the approval date of the first generic product version of Viagra (sildenafil, used for erectile dysfunction).[30] Our data show that industry funded clinical trials only slightly decreased for sildenafil (ratio 1.0 [0.7]). Other drugs may be better suited for extensions of indication which may be

an important reason to conduct clinical trials. For instance, docetaxel, had obtained nine extensions of indications of which three extensions were approved within the four years prior to the introduction of a first generic product version and one extension one year thereafter.[2] As observed in our study, docetaxel was used in a high number of clinical trials. Some medicinal products may be used more often as an active comparator than others, such as in the example of clopidogrel provided above. How the factors interact may change over the years causing an increase or decrease in clinical research on a specific drug. The complexity and magnitude of the factors involved makes it difficult to predict to what extent a medicinal product will be involved in clinical trials after it has been marketed.

In conclusion, the overall number of clinical trials decreased after approval of the first generic products version in the EU. Even after a decrease a considerable amount of clinical research often remained. The extent to which clinical research is reduced differs extensively between medicines and for individual medicines clinical research may even increase. These findings indicate that multiple factors besides the introduction of a first generic product version in the EU may be of influence which may be specific for individual drugs. To what extent the clinical trials focus on new therapeutic purposes warrants further research.

METHODS

Data selection

We used the cohort of small molecule medicinal products and the approval dates of the first generic product version identified in our previous study.[2] These were medicinal products with active substances first authorised in the EU through the European Medicines Agency since the beginning of the EU centralised procedure, or authorised and later withdrawn, up to 31 August 2013, with at least one authorised generic product version for over a year. The medicinal products were grouped by active substance in which different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives were considered as the same active substance. For each active substance we selected the approval date of the fist generic product version. All those data were retrieved from www.ema.europa.eu. In the present study, we excluded combination products as individual units of analysis.

Subsequently, the clinical trials with one of the active substances as intervention therapy were obtained from clinicaltrials.gov. For each active substance we selected the clinical trials with a start date four years before and four years after the approval date of the first generic product version. The length of the pre-generic period was adjusted to the length

of the post-generic period in case the post-generic period lasted less than four years (i.e. pioglitazone, efavirez, capecitabine, zoledronic acid, desloratadine). In case a clinical trial included more than one of the active substances, we included the clinical trial for each active substance separately. This was the case for 180 clinical trials.

Data analysis

For each clinical trial the title, unique trial number, start date and type of funding source were entered into a database. We used the funding sources as categorised by clinicaltrials.gov. Industry funded relates to any industry funding and may be co-funded by an independent sponsor. Non-industry funded excludes any industry funding.

Per active substance we calculated the ratio of the number of clinical trials started before and after approval of the first generic product version with a differentiation by the funding source. Correction factors were calculated per active substance to compensate for the increase in clinical trial over time. Therefore we extracted all clinical trials registered at clinicaltrials.gov. The correction factor per active substance constituted of the ratio of all clinical trials started in the four years before and after approval of the first generic product version.

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Chapter 3.3

Challenges in innovations with well-known drugs: a quantitative and qualitative analysis

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ABSTRACT

Current leads for new innovations for well-known drugs may not always result in an authorised drug therapy. In order to exploit such leads it is important to learn from drugs which made it to an official marketing authorisation. We assessed well-known drugs (used before 1 January 2000) approved through the European Medicines Agency in 2014 and 2015 for new innovations, i.e. a new therapeutic indication or other innovation, and assessed three of the drug repositioning cases in greater detail. In total, 11 of the 121 drugs were approved for a new therapeutic indication and 5 drugs for another new innovation. The viability of the business case for the development of such products may depend on a specific window of opportunities within a therapeutic area and the possibility to establish a relative exclusivity. New strategies and opportunities may be needed to ensure the development and licensing of new innovations for well-known drugs and the optimal use of existing knowledge.

INTRODUCTION

In recent years, there has been an increasing interest in the development of new uses for known drugs.[1] Drug repositioning (also known as drug repurposing) may benefit from the use of existing knowledge on the pharmacology, pharmacokinetics, safety, and potentially even efficacy of already marketed drugs.[2,3] Numerous researchers have reported potential new therapeutic indications for existing drugs.[4–6] A recent example is prochlorperazine, an antiemetic drug known since the 1950's.[7] Prochlorperazine may be effective against dengue virus infection, which is a life-threatening infection that affects millions of people per year.[7] A wide variety of methods have been identified to discover new therapeutic indications for existing drugs which include various computational methods as well as in vitro screening models.[8–10] However, the leads for new therapeutic indications from such methods may not result in authorised drug therapies due to a variety of factors. In a previous project commissioned by the Netherlands Organisation for Health Research and Development (ZonMw) we identified key aspects of potential obstacles for drug repositioning.[11] These included obstacles in the marketing authorisation procedure, the lack of possibilities to establish a period of relative exclusivity, and pricing and reimbursement issues. In order to exploit the leads for drug repositioning suggested in literature, it is important to learn from successful cases of drug repositioning, i.e. well-known drugs that obtained approval for new therapeutic indications. In addition, also other innovations to well-known drugs may provide significant patient benefit. For example, tobramycin was recently licensed as Vantobra.[12] Its new technology allows cystic fibrosis patients with a chronic pulmonary infection to inhale their medicine in a shorter time than other tobramycin nebulisers but in similar time compared with dry powder inhalers. Vantobra may therefore improve the user convenience and therefore therapy adherence.

Despite the wealth of literature on drug repositioning, little is known on how many innovations to well-known drugs finally reach the market. In the present study, we aim to characterise well-known drugs approved for new innovations: a new therapeutic indications or other innovation. We focused on drugs that were already used in clinical practice before 1 January 2000. We also examined in more detail the challenges posed by regulatory constraints and the opportunities for a viable business case in a number of the drugs approved for a new therapeutic indication. This additional analysis aims to provide insight in (regulatory) hurdles and opportunities for drug repositioning and may inspire and assist others to develop new therapeutic indications for well-known drugs.

METHODS

From the European Medicines Agency's (EMA) website (www.ema.europa.eu) we extracted all drugs licensed in 2014 and 2015. We excluded drugs approved as true generic, biosimilar and informed consent based on articles 10.1, 10.4 and 10c of Directive 2001/83/EC, respectively. We identified drugs used in clinical practice before 1 January 2000 based on literature identified through PubMed. For combination products both drugs needed to be in use in clinical practice before that date. Subsequently, we determined whether the drugs were authorised for a new therapeutic indication, i.e. a therapeutic indication for which the drug was not previously authorised in the EU, or another new innovation, such as improved safety profile or compliance due to reformulation for the drug. The initial assessment of the drugs was performed by three regulatory experts including authors JL and HGML based on their knowledge, and additional information which was obtained from the drugs's European Public Assessment Report or literature identified through PubMed.

From the EPAR and the EMA website we also extracted information on the request of scientific advice, the ATC classification, the orphan designation status, conditional approval status and approval under exceptional circumstances. We defined company size in line with previous studies as small, medium, and large, based on ranking by total revenue as reported in Scrip's Pharmaceutical Company League Tables 2014 (www.scrip100.com/scrip100.html).[13,14] Companies were defined as large if ranked 1–20, medium if ranked 21–150, and small if the company was below 150. Drugs licensed as a co-production were ranged as developed by the largest company. Subsidiaries were ranked as their parent company. For companies not in the table we examined their revenues in 2014 in their annual report or on their website and ranked it in accordance with the Scrip table. If no revenue could be identified the company was ranked as small.

An in-depth analysis was conducted among three of the first drug repositioning cases approved after 1 January 2014. The cases were assessed along the previously identified key aspects of potential obstacles for drug repositioning to determine regulatory constraints in their development as well as their opportunities for value creation and a viable business case.[11] We used literature available from PubMed and Google Scholar, as well as information available through the websites of drug regulatory agencies, the European Union and pharmaceutical companies.

RESULTS

Between 1 January 2014 and 31 December 2015 a total of 121 drugs were licensed through the EMA based on applications other than true generic, biosimilar or informed consent (Table 1). Of these 121 drugs, 26 were well-known drugs used in clinical practice before 1 January 2000. We found that 16 (13%) of those drugs were approved for a new innovation: 11 drugs for a new therapeutic indication and 5 drugs for another innovation.

Table 1: Characteristics of the medicines approved through the EMA in 2014 and 2015.

	All (n=121)		**Well-known active substance < year 2000 (n=26)**		**Well-known active substance with a new innovation (indication or other) (n=16)**	
Year of approval						
2014	58	47,9%	13	50%	6	38%
2015	63	52,1%	13	50%	10	63%
Application type (legal basis)						
8.3 – Full-dossier	97	80,2%	12	46%	9	56%
10a – Well-established use	3	2,5%	2	8%	2	13%
10b – Fixed dose combination	12	9,9%	3	12%	2	13%
10.3 – Hybrid	9	7,4%	9	35%	3	19%
Company size						
Small	18	14,9%	8	31%	8	50%
Medium	40	33,1%	11	42%	7	44%
Large	63	52,1%	7	27%	1	6%
Scientific advice						
Yes	93	76,9%	15	58%	7	44%
No	28	23,1%	11	42%	9	56%
Orphan designation						
Yes	28	23,1%	4	15%	4	25%
No	93	76,9%	22	85%	12	75%
Approval under exceptional circumstances						
Yes	4	3,3%	1	4%	1	6%
No	117	96,7%	25	96%	15	94%
Conditional approval						
Yes	7	5,8%	0	0%	0	0%
No	114	94,2%	26	100%	16	100%

Table 1: Characteristics of the medicines approved through the EMA in 2014 and 2015. (continued)

	All (n=121)		**Well-known active substance < year 2000 (n=26)**		**Well-known active substance with a new innovation (indication or other) (n=16)**	
ATC-code						
A/ Alimentary tract & Metabolism	17	14,0%	2	8%	2	13%
B/ Blood & Blood forming organs	10	8,3%	3	12%	1	6%
C/ Cadiovascular system	7	5,8%	2	8%	2	13%
D/ Dermatologicals	2	1,7%	1	4%	1	6%
G/ Genito-Urinary system & Sex hormones	2	1,7%				
H/ Systemic hormonal prep, excl. sex hormones & insulins						
J/ Antiifectives	24	19,8%	4	15%	4	25%
L/ Antineoplastic and immunomodulating agents	26	21,5%	1	4%		
M/ Musculo-skeletal system	1	0,8%				
N/ Nervous system	8	6,6%	5	19%	3	19%
R/ Respiratory system	12	9,9%	5	19%		
S/ Sensory organs	5	4,1%	3	12%	3	19%
V/ Various	7	5,8%				

Half of the 16 well-known drugs with a new innovation were licensed by small-sized pharmaceutical companies, 7 drugs by a medium-sized company and 1 drug by a large-sized company. Scientific advice was provided to 93 (76.9%) of all drugs in our cohort, whereas scientific advice was provided to 7 (44%) of the well-known drugs approved for a new innovation. The extent to which scientific advice was applied for differed substantially between large and small-sized companies. Overall, small-sized companies applied for scientific advice for 50% of all their drugs approved in 2014-2015 whereas large companies did so for 89% of their drugs. For well-known drugs with a new innovation small-sized companies obtained scientific advice in 38% of the cases.

The majority of the drugs in our cohort was approved based on a full-dossier marketing authorisation application: 97 (80.2%) of all approvals and 9 (56%) of the well-known drugs. The other well-known drugs with a new innovation were approved based on well-established use applications (n=2, 13%), fixed-dose combination applications (n=2, 13%) and hybrid application (n=3, 19%). An orphan designation was granted to 4 of the 16 well-known drugs approved for a new innovation. A total of 26 (21,5%) of all drugs were classified as antineoplastic or immunomodulating agent (e.g. anticancer drugs), whereas no new innovations for well-known drugs were approved within that class. Table

2 provides more detailed information about the 16 well-known drugs approved for a new therapeutic indication or other innovation and the 10 other well-known drugs for which no real innovation occurred.

In the next sections, the cases of Ketoconazole HRA (ketoconazole), Tecfidera (dimethyl fumarate) and Hemangiol (propranolol) are assessed in greater detail.

Ketoconazole HRA - Cushing's syndrome

In 2014, Laboratoire HRA Pharma's Ketoconazole HRA obtained approval for the treatment of Cushing´s syndrome which consists of a collection of signs and symptoms, e.g. abdominal obesity, purple striae, diabetes, osteoporosis and psychiatric disorders, due to an excessive production of the hormone cortisol.[15,16] It is an orphan disease that affects approximately 0.9 in 10,000 people in the EU.[15] Ketoconazole inhibits the cortisol synthesis and can therefore be used in the treatment Cushing´s syndrome.[15] Originally, ketoconazole was licensed by Janssen-Cilag as Nizoral tablets for the treatment of fungal infections, but it has been used off-label for the treatment of Cushing's syndrome since the 1980's.[15,17]

The France authorities suspended the marketing authorisation of Nizoral in 2011 upon concerns about its hepatotoxicity.[18] An European Union (EU) referral procedure followed.[18] Aware of the potential consequence for the Cushing's syndrome treatment, the national and EU competent authorities searched for options to maintain patient access to ketoconazole tablets.[19] The Dutch Medicines Evaluation Board, for example, suggested that Janssen-Cilag could apply for a license of Nizoral for the treatment of Cushing's syndrome.[20] By the end of 2013 the European Commission decided that all marketing authorisations of oral ketoconazole drugs should be suspended.[21,22] Subsequently, Janssen-Cilag withdrew its drug from the market.[23]

Meanwhile both Laboratoire HRA Pharma and Agenzia Industrie Difesa-Stabilimento Chimico Farmaceutico Militare (AID-SCFM) had been granted an orphan designation for the use of ketoconazole in treatment of Cushing´s syndrome, because it was believed to offer significant benefit for patients with Cushing's syndrome due to its different mechanism of action over existing therapies.[24,25] Both companies submitted a well-established use marketing authorisation application for ketoconazole in the treatment of Cushing's syndrome. AID-SCFM withdrew its application after a negative opinion by the CHMP due to serious concerns about product quality and lack of adequate bridging data to literature in support of the effectiveness and safety of the drug.[26,27]

Table 2: Drugs approved in 2014-2015 through the EMA that were used in clinical practice before 1 January 2000.

Brand name	Drug	Company	Therapeutic indication (Current or previous**)	Innovation	Year	ATC	Company size	Scientific advice	Legal basis
Well-known active substances with a new therapeutic indication									
Tecfidera*	dimethyl fumarate	Biogen	Psoriasis	Indication: Multiple sclerosis	2014	N	Medium	No	8.3
Mirvaso*	brimonidine	Galderma	Open-angle glaucoma or ocular hypertension	Indication: Facial erythema of rosacea	2014	D	Medium	No	8.3
Hemangiol*	propranolol	Pierre Fabre Dermatologie	Various: e.g. cardiovascular diseases, migraine, tremor, thyrotoxicosis and hyperthyroidism	Indication: Proliferating infantile haemangioma	2014	C	Medium	Yes	8.3
Ketoconazole HRA*	ketoconazole	Laboratoire HRA Pharma	Fungal infections	Indication: Endogenous Cushing's syndrome	2014	J	Small	No	10a
Ikervis	ciclosporin	Santen Oy	graft rejection, endogene uveitis, nephrotic syndrome, Rheumatoid arthritis, psoriasis and atopic dermatitis	Indication: Severe keratitis in adult patients with dry eye disease	2015	S	Medium	Yes	8.3
Mysimba	naltrexone / bupropion	Orexigen Therapeutics	Naltrexone: alcohol dependence and opioid dependence. bupropion: depression	Indication: Adjunct to a reduced-calorie diet and increased physical activity for obesity	2015	A	Small	No	10b
Quinsair	levofloxacin	Regintel	Various infections	Indication: Chronic pulmonary infections due to Pseudomonas aeruginosa	2015	J	Small	Yes	8.3

Table 2: Drugs approved in 2014-2015 through the EMA that were used in clinical practice before 1 January 2000. (continued)

Brand name	Drug	Company	Therapeutic indication (Current or previous**)	Innovation	Year	ATC	Company size	Scientific advice	Legal basis
Omidria	phenylephrine / ketorolac	Omeros	Phenylephrine: various e.g. decongestant, mydriaticum and hypotension. Ketorolac: prophylaxis and reduction of inflammation and associated symptoms following ocular surgery	Indication: Maintenance of intraoperative mydriasis, prevention of intraoperative miosis and reduction of acute postoperative ocular pain in intraocular lens replacement surgery	2015	S	Small	No	8.3
Raxone	idebenone	Santhera Pharmaceuticals	Cognitive and behavioural deficits due to cerebral pathologies of vascular or degenerative origin	Indication: Visual impairment in adolescent and adult patients with Lebers Hereditary Optic Neuropathy (LHON).	2015	N	Small	Yes	10.3
Intuniv	guanfacine	Shire	Hypertension	Indication: Attention deficit hyperactivity disorder (ADHD)	2015	C	Medium	No	8.3
Kolbam	cholic acid	Retrophin	(Previously used as pharmacy prepared medicine)	Indication: Inborn errors of primary bile acid synthesis	2015	A	Small	No	8.3
Well-known active substances with another new innovation									
Granupas	para-aminosalicylic acid	Lucane Pharma	Tuberculosis	Other: Improved safety profile due to the new dosage form	2014	J	Small	No	10a
Simbrinza	brinzolamide / brimonidine tartrate	Alcon	Open-angle glaucoma or ocular hypertension	Other: Fixed dose combination	2014	S	Large	Yes	10b

Table 2: Drugs approved in 2014-2015 through the EMA that were used in clinical practice before 1 January 2000. (continued)

Brand name	Drug	Company	Therapeutic indication (Current or previous**)	Innovation	Year	ATC	Company size	Scientific advice	Legal basis
Vantobra	tobramycin	Pari Pharma	Chronic pulmonary infection in cystic fibrosis	Other: Shorter inhalation time	2015	J	Small	Yes	10.3
Raplixa	human fibrinogen / human thrombin	ProFibrix	Supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis	Other: Easier use and storage due to new formulation	2015	B	Medium	Yes	8.3
Zalviso	sufentanil	Grunenthal	Severe post-operative pain	Other: More patient friendly dosage form	2015	N	Medium	No	10.3
Well-known active substances without a new innovation									
BiResp Spiromax	budesonide / formoterol	Teva	Asthma / COPD	NA	2014	R	Large	Yes	10.3
DuoResp Spiromax	budesonide / formoterol	Teva	Asthma / COPD	NA	2014	R	Large	Yes	10.3
Envarsus	tacrolimus	Chiesi	Graft Rejection	NA	2014	L	Medium	Yes	10.3
Clopidogrel/ Acetylsalicylic acid Teva	clopidogrel / acetylsalicylic acid	Teva	Acute Coronary Syndrome / Myocardial Infarction	NA	2014	B	Large	No	10b
Budesonide/ Formoterol Teva Pharma B.V.	budesonide / formoterol fumarate dihydrate	Teva	Asthma	NA	2014	R	Large	Yes	10.3
Budesonide/ Formoterol Teva	budesonide / formoterol	Teva	Asthma / COPD	NA	2014	R	Large	Yes	10.3
Vylaer Spiromax	budesonide / formoterol	Teva	Asthma / COPD	NA	2014	R	Large	Yes	10.3
Respreeza	human alpha1-proteinase inhibitor	CSL Behring	Alpha1-proteinase inhibitor deficiency	NA	2015	B	Medium	No	8.3

Table 2: Drugs approved in 2014-2015 through the EMA that were used in clinical practice before 1 January 2000. (continued)

Brand name	Drug	Company	Therapeutic indication (Current or previous**)	Innovation	Year	ATC	Company size	Scientific advice	Legal basis
Ionsys	fentanyl	Incline Therapeutics	Pain	NA	2015	N	Medium	Yes	8.3
Numient	levodopa / carbidopa	Impax	Parkinson Disease	NA	2015	N	Medium	Yes	8.3

** Included in the in-depth analysis.*

*** For medicine with a new therapeutic indication the column shows the previously approved therapeutic indication(s) for the medicine. For the others the column shows the current indication(s).*

Laboratoire HRA Pharma has specialised in endocrinology and has held already marketing authorisations for two other steroidogenesis inhibitors metyrapone (e.g. Metopiron, 1979) and mitotane (Lysodren, 2004) used (off-label) in the treatment of Cushing's syndrome,[17,28] as well as an orphan designation for mifepristone in the treatment of Cushing's syndrome since 2005.[29] Ketoconazole seems to have fitted right in its product portfolio. Laboratoire HRA Pharma provided adequate literature in support of the efficacy and safety of ketoconazole in the treatment of Cushing's syndrome.[15] The CHMP considered the hepatotoxicity manageable and reversible upon treatment interruption. It also considered the need for ketoconazole in the treatment of Cushing's syndrome in clinical practice and the off-label use over 30-years. Ketoconazole HRA was approved with the requirement for a Post Authorisation Safety Study (PASS) to assess drug utilization patterns, to document the safety and effectiveness of ketoconazole and to distribute a Dear Health Care professional Letter regarding the hepatic safety profile of ketoconazole.

In the present case, the safety concern in the case of Nizoral actually may have contributed to the viability of the business case of Ketoconazole HRA. The hepatotoxicity caused Nizoral and other generic ketoconazole tablets to be withdrawn from the market and discouraged others to license oral ketoconazole-containing drugs as an antifungal treatment, because they would have to resolve this safety concern. The orphan designation in the treatment of Cushing syndrome prevents in principle other drugs to be approved for the treatment of Cushing's syndrome within the EU.[30] These circumstances added to the opportunity to make a sufficient return on investment. Currently, Ketoconazole HRA is marketed and reimbursed in the Netherlands at a price of 318 euro per 30 tablets; a tenfold of the price of the original Nizoral tablets.[31–33]

Tecfidera - multiple sclerosis

Tecfidera (dimethyl fumarate, DMF) has been licensed since 30 January 2014 for the treatment of adult patients with relapsing-remitting multiple sclerosis (MS).[34] MS is a chronic inflammatory demyelinating central nervous system disease that causes a variety of symptoms depending on the affected nerves, such as muscle weakness, loss of sensitivity or visual problems.[35] Typically the disease begins at the age of 20 to 50 years and affects approximately 30 per 100,000 people. The precise mechanism of action of DMF in the treatment of MS is unknown, but it is claimed to reduce the inflammatory response in order to prevent nerve cell damage.[35]

DMF is the dimethyl ester of fumaric acid. Fumaric acid esters have been used in the treatment of psoriasis since 1959. The Swiss company Fumapharm obtained approval for this indication in Germany in 1994 under the brand name Fumaderm, which contains

a mixture of DMF and three salts of mono-ethyl furmarate (MEF).[35–38] In other countries pharmacy preparations of DMF are used for that purpose.[37] In 2003, Biogen and Fumapharm announced their collaboration in the development of the second-generation fumarate derivate DMF, or BG-12, for the treatment of psoriasis.[39] Therefore, Biogen licensed the exclusive right for the development and marketing of that drug.

The immunomodulatory potential of fumaric acid esters prompted research for their potential in the treatment of MS and in 2000 Fumapharm had already filed a patent in the United States for the use of DMF in the treatment of MS.[36,40,41] In 2006, an exploratory, prospective, open-label study of the treatment of 10 MS patients with Fumaderm sponsored by Fumapharm was published.[40] The results on MS treatment were positive and warranted further research. Subsequently Biogen acquired Fumapharm and continued the development of DMF for the treatment of MS.[42] It also continued the marketing of Fumaderm for the treatment of psoriasis. A phase II study funded by Biogen which included 257 MS patients was published in 2008, and also suggested the efficacy of fumarate in the treatment of MS.[43] Subsequently, Biogen initiated two large multi-centre phase III clinical trials to study the efficacy and safety of DMF in the treatment of MS which included 1,234 and 1,417 patients.[44,45] Based on those two pivotal studies Tecfidera was approved in the EU upon Biogen's full-dossier marketing authorisation application.[35] Nowadays Tecfidera is part of the first-line treatment options in the treatment of MS. The choice of a drug depends on the efficacy and side effects in each individual patient, as well as personal patient choices, e.g. preferences for dosage form or dosing regimen.[46]

During the development phase Biogen may have benefitted from its experience in the therapeutic area of MS. When Biogen obtained approval for Tecfidera it already marketed three other drugs for the treatment of MS (Avonex 1997, Tysabri 2006, Fampyra 2011), would later obtain approval for Plegridy (2014) and Zinbryta (2016) and has three other treatments for MS in its clinical program.[47,48]

The intellectual property prospects of Tecfidera are of a specific nature. In general, a marketing authorisation holder can only obtain 8-years data exclusivity and 2-years of market protection per drug once and regardless of the dosage form, brand name etc., which is known as the notion of the global marketing authorisation.[30] This is important because Tecfidera and Fumaderm belong to the same marketing authorisation holder and DMF is part of the composition of Fumaderm. However, the Committee for Medicinal Products for Human Use (CHMP) of the EMA concluded that DMF and the MEF in Fumaderm are both biologically active, but "are not the same active substance since they do not share the same therapeutic moiety."[35] Therefore the DMF in Tecfidera is considered to be different from the esters in Fumaderm.[35] Consequently, Tecfidera and Fumaderm

are not considered to belong to the same global marketing authorisation, and as a result Tecfidera benefits from a new 10-year period of regulatory protection from generic product introduction.[30,35] In addition, Tecfidera benefits from a number of patents including a usage-patent for its use in the treatment of MS, although the latter patent was recently revoked by the European Patent Office and is currently under dispute.[49] Furthermore, based on the CHMP's decision about the differences between DMF and MEF the Dutch competent authority has refused a well-established use licensing application for DMF in the treatment of psoriasis, because the submitted literature data on Fumaderm was deemed inadmissible and could be bridged to the solely DMF containing drug under assessment.[50,51] That decision withholds a generic version of Fumaderm intended for treatment of psoriasis from the market that otherwise might have been used off-label in the treatment of MS.

The absence of generic product versions allows Biogen set a similar price for Tecfidera as competing drugs for MS treatment of approximately 1000 euro a month.[31,52] Nevertheless, in the Netherlands Biogen faces political protest about Tecfidera's price.[53,54] In the Netherlands Health insurance companies have even advocated to treat MS with of a cheaper pharmacy preparation of DMF which is intended for the treatment of psoriasis and costs approximately 130 euro a month.[55]

Hemangiol - proliferating infantile haemangioma

Hemangiol (an oral solution of propranolol) has been licensed since 23 April 2014 for treatment of proliferating infantile haemangioma. This is a benign vascular tumours of childhood, characterised by endothelial cell proliferation, that occurs in 3 to 10% of the population.[56] Propranolol is a well-known drug that has been used since the 1960's in the treatment of cardiovascular diseases, but also in the prophylaxis of migraine and management of essential tremor.[56,57] Previously an oral solution of propranolol (Syprol) was licensed in the United Kingdom.[56]

Hemangiols development started after a serendipitous discovery by the French physician Léauté-Labrèze.[58] In 2007, in a French hospital an infant suffered from a haemangioma in his nose.[59] The haemangioma of this infant was stabilized by the treatment with prednisolone, which was the golden standard at that time.[58,60] At four months of age the boy developed an obstructive hypertrophic myocardiopathy for which propranolol was administered. As a great surprise within days the haemangioma started to change colour and improved. After fourteen months of treatment the haemangioma had almost vanished. A second infant of two months of age that suffered from a massive haemangioma over the right side of his face and eye, was treated with propranolol for a heart condition. Seven days after the start of the treatment the haemangioma had shrunk to the extent that the

child could open his eye. After seven months of treatment the haemangioma had almost disappeared. Another 11 infants were treated with propranolol for their haemangioma with beneficial results. A follow-up study was conducted that confirmed the beneficial results of the propranolol treatment.[61] Soon propranolol became an off-label therapy, or therapy based on pharmacy compounded drugs, for the treatment of infantile haemangioma, despite the high risk of inappropriate dosing in infants.[57,62–64]

In 2009, Pierre Fabre Dermatologie obtained scientific advice from the EMA with regard to the non-clinical and clinical requirements for the development of Hemangiol. For the clinical part they conducted three studies: two phase I pharmacokinetic studies (one in 12 adults and one in 23 children) and one phase II/III randomised placebo controlled clinical trial with 456 children. The studies confirmed the effectiveness and safety of the propranolol treatment and were complemented by literature data and data from compassionate use programs in France and Switzerland, which included severe cases of infantile haemangioma that were not eligible for inclusion in the clinical trial.[56] Nowadays propranolol has become the first choice therapy for infantile haemangioma.[57]

Pierre Fabre Dermatologie was granted a so-called paediatric-use marketing authorisation (PUMA).[65] A PUMA can be obtained for drugs which are already licensed, but that are no longer under patent protection and are intended exclusively for use in a paediatric population.[66] It provides the marketing authorisation holder with as number of benefits including access to the European centralised marketing authorisation, a partial exemption from regulatory fees, and an 8-years of data exclusivity and 2-years of market protection even if the product would belong to an existing global marketing authorisation. The latter benefit seems of minor importance in the present case since the full-dossier marketing authorisation provides identical privileges that prevent generic product versions to be placed on the market. Besides, the PUMA does not prevent other companies to conduct similar clinical trials with propranolol and apply for market approval in the treatment of infantile haemangioma. Moreover, it has been suggested that other beta blockers, such as timolol and atenolol, and topical treatment with beta blockers may also be effective in treatment of infantile haemangioma.[57,67]
A summary of the three cases can be found in Table 3.

DISCUSSION

In a previous study we found that extensions of indication in the post-generic phase of the drug cycle were almost absent.[68] In contrast, one of the main findings of the present study was that a considerable number of well-known drugs were licensed for a new

Table 3: Summary of the three drug repositioning cases.

	Ketoconazole HRA (ketoconazole)	**Tecfidera** (dimethyl fumarate)	**Hemangiol** (propranolol)
Discovery	Long term off-label use with a high medical need	Mechanism of action	Serendipity
Application type (legal basis)	Well-established use (art. 10a Directive 2001/83/EC)	Full-dossier (art. 8.3 Directive 2001/83/EC)	Full-dossier (art. 8.3 Directive 2001/83/EC)
Data	Literature data	Own clinical trial programme	Own clinical trial, literature data and data from a compassionate use program
Company size	Small	Medium	Medium
Marketing authorisation holder's product portfolio	Specialised in endocrinology, one medicine licensed for Cushing's syndrome therapy and one medicine used off-label in Cushing's syndrome therapy	Multiple licensed medicines for the treatment of MS	Various products for skin conditions
Exclusivity	10-years of market exclusivity as an orphan drug Combined with the withdrawal of previously licensed ketoconazole tablets due to a safety concern	8-years of data exclusivity and 2-years of market protection for the start of a new global marketing authorisation of dimethyl fumarate Several patents	8-years of data exclusivity and 2-years of market protection for a paediatric use market authorisation (PUMA) Combined with the need for a specific dosage form for children not yet available
Value creation for clinical practice	High medical need	First-line oral therapy	First choice therapy
Other		Similar medicine available as pharmacy compounded medicinal product in principle for a different therapeutic indication (psoriasis)	After the discovery of the new therapeutic indication and before licensing of Hemangiol, propranolol was used off-label or as pharmacy compounded drug in the treatment of infantile haemangioma

innovation. In total 16 drugs of the 121 drugs approved through the EMA in 2014 and 2015 were drugs used in clinical practice before 1 January 2000 and were licensed for a new innovation: 11 drugs for a new therapeutic indication and 5 drugs for another new innovation. The qualitative analysis provided some insight in the development program and regulatory characteristics of three of the drugs licensed for a new therapeutic indication (Table 3). Main commonalities in these cases were the presence of a window of opportunity. The possibilities to benefit from data or market exclusivity as well as the market circumstances within a therapeutic area provided opportunities to establish of a viable business case.

Well-known drugs that were approved for a new innovation were predominantly developed by small and medium-sized companies. Of the 18 drugs licensed by small-sized companies 8 approvals concerned a well-known drug which were all licensed for a new innovation (Table 1). It has been suggested that small and medium-sized enterprises, as well as not-for-profit organizations, are best suited for drug repositioning because of their narrow disease area or specific techniques on which they build their intellectual property.[10] Moreover, since drug repositioning is believed to be relatively inexpensive it provides opportunities to smaller companies.[69]

Interestingly, the application of scientific advice was less common for well-known drugs approved for a new innovation than for all drugs. We noticed that especially small-sized companies did frequently not issue scientific advice, which was consistent with the outcome of a study by Regnstrom et al. in 2010.[70] In more detail, a study of Putzeist et al. showed that small-sized companies asked significantly fewer questions per scientific advice and their questions also concerned more frequently new applications for existing drugs compared to large pharmaceutical companies.[13] Previous studies have shown that compliance with scientific advice was significantly associated with approval of a licensing application.[70,71] Therefore, small-sized companies are encouraged to use the opportunities that the EMA as well as national competent authorities have established, such as scientific advice procedures especially for small-sized companies, often at a reduced fee.[72,73]

The fact that no drug repositioning cases were found within the class of anticancer drugs is remarkable. In that class a number of well-known drugs have been identified as potential candidates for the treatment of various cancers.[74] The Belgium Anticancer Fund has even established a research programme that focusses specifically on the development of anticancer therapies based on existing off-patent drugs: the Repurposing Drugs in Oncology (ReDO) project.[75]

Most of the well-known drugs were approved based on a full-dossier marketing authorisation application (i.e. art. 8.3 of Directive 2001/83/EC) which includes new studies conducted by the applicant whether or not combined with literature data. For the well-known drugs with a new innovation one might have expected more well-established use (art. 10a) or hybrid applications (art. 10.3), since those are basically designed to make use of existing knowledge on drugs.[30] Apparently the applicants deemed it more convenient to submit a full-dossier marketing authorisation. These results are in line with research by Papakrivos in 2011 on licensing of new uses for known drugs through the Decentralised Procedure and Mutual Recognition Procedure.[76] In the case of Tecfidera and Hemangiol the pharmaceutical company needed to submitted new clinical data on the efficacy and safety of their product. In addition, for Tecfidera a new product was needed that only contained DMF and for Hemangiol a new product with a new pharmaceutical form was developed. A full-dossier licensing application allowed them to submit such new data and to license new dosage forms.

The choice for full-dossier applications may also be (partly) related to the regulatory protection that such an application provides to withhold generic product versions from the market. By those means both Tecfidera and Hemangiol were able to establish a relative exclusivity. In contrast, a marketing authorisation through a hybrid application (art. 10.3) does not start of a new global marketing authorisation, and therefore does not provide data exclusivity and market protection. The well-established use application (art. 10a) as used for Ketoconazole HRA is in fact also a full-dossier application and may start a new global marketing authorisation, albeit it basically includes data from scientific literature.[30] Consequently, any other pharmaceutical company could collect the same literature data and apply for a licence. However, in general it may be considered a waste of resources to collect, submit and assess, for instance, non-clinical data about drugs of which the pharmacology, pharmacokinetics and toxicology are well known, if that only serves the purpose to benefit from data exclusivity and market protection. A new marketing authorisation application type may be preferable to ensure effective regulatory protection and the optimal use of existing knowledge.

The incentives to develop and license a new innovation for a well-known drug may also depend on the specific market circumstances for a drug. The orphan drug designation has probably been of specific importance for the development of Ketoconazole HRA, because it forbids in principle the approval of any other drug for the treatment of Cushing's syndrome. The market protection of orphan drugs is deemed useful to overcome challenges from expired intellectual property.[77] Interestingly, only 4 of the 16 well-known drugs approved for a new use were orphan drugs. Apparently the other 12 innovations not targeting an orphan disease benefited from sufficient other incentives for

pharmaceutical companies to invest in their development. In the case of Ketoconazole HRA, the fact that ketoconazole containing tablets licensed for the treatment of fungal infections were withdrawn from the market due to a safety concern seems to have substantially contributed to the creation of a viable business case for its development. Their withdrawal prevented the off-label use of other ketoconazole containing tablets in the treatment of Cushing's syndrome.[78]

Similarly, Tecfidera and Hemangiol may face competition from unlicensed pharmacy compounded drugs.[53–55] The use of such pharmacy compounded drugs could weaken the viability of the business case to develop and to obtain an official market approval for new innovations to well-known drugs. To ensure a viable business case is in place to develop innovations and to obtain an official market approval for new innovations to well-known drugs within the current drug regulatory framework, it is important that the use of licensed drugs is not circumvented by the use of pharmacy compounded drugs.

The EU legislation on drugs provides a rather limited incentive to a marketing authorisation holder to develop and license a new therapeutic indication for a well-known drug if the pharmaceutical company has already licensed a drug with that active substances and therefore has started a global marketing authorisation. In that cases, the pharmaceutical company would only obtain 1-year of data exclusivity based on article 10.5 of Directive 2001/83/EC provided that significant pre-clinical or clinical studies were carried out. If an identical application would be made by a company that has not previously licensed a drug with the concerned active substance it could still benefit from 10-years of regulatory protection. For instance, if Biogen would not have acquired Fumapharm then they may have benefitted the regulatory protection whether or not DMF was considered the same as Fumaderm. Furthermore, a PUMA provides 8-years of data exclusivity and 2-years of market protection regardless of a previous start of a global marketing authorisation, but only applies to drugs developed specifically for a paediatric therapeutic indication with a new formulation.[66]

It has been posed by Smith that from an intellectual property perspective the most attractive strategy for drug repositioning is to combine a new therapeutic indication with a new formulation, which may be patent protected.[78] This approach may prevent the off-label use of drugs with the same active substance and dosage form. However, the need to develop a new formulation to establish a viable business case would be unfortunate since an extension of indication would probably require less resources than the licensing of a complete medicinal product. Eventually, Pharmaceutical companies should consider the opportunities for regulatory protection carefully and early in the drug development program.[78]

In the present study we considered the licensing of a new innovation as a success. For a company, however, market approval is not the only hurdle towards a successful drug repositioning case. That also requires a reasonable price and reimbursement in order to make a sufficient return on investment. It was observed that for Ketoconazole HRA and Tecfidera their marketing authorisation holders set prices similar to drugs within their therapeutic area, which are substantially higher than the previously licensed drug or pharmacy compounded drugs, respectively. Companies may benefit from the opportunities to obtain scientific advice of the competent authorities in parallel with HTA bodies to increase their chances of a positive reimbursement decision.[72,79]

Especially small and medium-sized enterprises (SMEs) may benefit from several incentives offered by competent authorities. Our definition of small and medium-sized companies differed from the EMA's definition of SMEs, which is limited to an annual turnover of 50 million euro. We ranked a company as small that was in Scrip's Pharmaceutical Company League Tables 2014 below ranking 150, which correlates with a revenue of less than 332 million dollars. Nevertheless, the companies that licensed a new innovation and that we ranked as small would (probably) be categorized as SMEs according to the EMA criteria except for Mysimba (naltrexone / bupropion).

The more detailed assessment of the three drug repositioning cases may have been limited by the use of publicly available information. Some of the hurdles that the pharmaceutical company experienced in the drug development may have not been documented in the public domain. For example, deficiencies in the submitted data on the efficacy and safety may have been resolved during the licensing procedure as a result of the interaction between the pharmaceutical company and the regulators.

Finally, in the present study we focused on the licensing of new innovations through the centralised procedure. Further research could determine to what extent new innovations are licensed through the Decentralised Procedure or national procedure.

CONCLUSION

The findings of this study show that a considerable number of well-known drugs have been developed and licensed for new innovations, such as new therapeutic indications and other innovations that provide significant patient benefits. The EU centralised procedure appeared to be a feasible route to obtain market approval for such innovations. The positive benefit-risk assessment of the identified drugs was based on new clinical trial data, literature data or a combination of both. The viability of a business case to develop and

license new innovations for well-known drugs seems to require a window of opportunities regarding a medical need and the intellectual property prospects. Regulatory reform may be needed to ensure the development and licensing of new innovations for such drugs and the optimal use of existing knowledge. Moreover, pharmaceutical companies should carefully consider their opportunities within the current drug regulatory system and are advised to make full use of the opportunities to obtain scientific advice from the regulators. Especially small-sized companies may benefit from scientific advice and the dedicated scientific advice procedures of competent authorities.

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Chapter 4

Post-innovation innovation: legal context and terminology

Chapter 4.1

Patient needs and the marketing authorisation for medicinal products: an analysis of EU law

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ABSTRACT

EU law requires a marketing authorisation before a medicinal product is placed on the market. A marketing authorisation is granted after competent authorities have established the efficacy, safety and quality of a medicine in the treatment of a specific disease. Yet, off-label use and the use of unlicensed medicinal products are common to satisfy patient needs in a changing clinical practice. After the assessment of EU law and case-law over the past fifty years, the present study concludes that the EU legislator and the Court of Justice have established a strict marketing authorisation requirement with the purpose to safeguard public health. The EU may provide guidance on the legal options the position of unlicensed medicinal products and off-label use in order to enhance a right balance between a strict marketing authorisation requirement and patient needs in clinical practice.

1. INTRODUCTION

1.1 Synopsis

The use of medicinal products constitutes a common part of clinical practice. The law should allow patients access to appropriate medicines. Over the past fifty years European Union (EU) legislation has expanded massively. It requires that medicinal products obtain a marketing authorisation before being placed on the market. In the best interest of public health a marketing authorisation is granted after competent authorities have established a positive assessment of the efficacy, safety and quality of a medicine in the treatment of a specific disease. Nevertheless, physicians frequently prescribe medicinal products for unauthorised therapeutic uses (i.e. off-label) as well as the use of unlicensed pharmacy prepared medicinal products in order to satisfy their patients' needs. To provide a better understanding to what extent the need for a marketing authorisation aligns with patient needs the present study aims to examine the purpose and scope of the EU marketing authorisation requirement. We also provide recommendations for regulatory reform to serve the needs in daily medical practice.

1.2 Patient needs for medicinal products in clinical practice

In some cases patients can only be treated satisfactorily with the use of an unlicensed products, or with a licensed medicinal products for an unauthorised therapeutic indication. The latter is known as off-label use.[1] Both the use of unlicensed medicinal products and off-label use deviate from regular medicine use, i.e. the use of licensed medicinal products in accordance with its marketing authorisation. Reasons for such a deviation include the absence of appropriate licensed medicinal products with the needed active substance or dose, and shortages of authorised medicinal products. The latter has become a more prevalent reason for the use of unlicensed medicinal products over the past decade.[2],[3] Unlicensed medicinal products can be imported from other EU member states or can be specially prepared.

1 The definition of off-label use is topic of much debate. (A. Neubert, I.C.K. Wong, A. Bonifazi, M. Catapano, M. Felisi, P. Baiardi, et al., 'Defining off-label and unlicensed use of medicines for children: results of a Delphi survey*', Pharmacological research: the official journal of the Italian Pharmacological Society*, 58(5–6) (2008) 316–322. DOI: 10.1016/j.phrs.2008.09.007) It may, for example also include the use of a medicinal product of other patient populations then included in the marketing authorization. For the present article it suffices to consider off-label use the use of a medicinal product for the treatment of a disease of condition not included in the marketing authorisation.

2 E. Bos, ´Daling aantal bereiders zet door. Inspectie confronteert individuele apotheken met GMP-eisen´ - ENG: 'Reduction in number compounding pharmacies. Healthcare inspectorate confronts pharamcies with GMP requirements', *PW* 2013.

3 H. Jenzer and V. Fenton-May, 'Availability of Medicines', *Practical Pharmaceutics. Cham: Springer International Publishing*, (2015)25–49. DOI 10.1007/978-3-319-15814-3_3.

Pharmacies prepare a substantial number of unlicensed medicinal products.[4,5] In the Netherlands over 5 million pharmacy compounded medicinal products were dispensed in 2015.[6] The products are prepared either after the receipt of a prescription for an individual patient (i.e. magistral formula) or in advance and kept on stock for supply after receipt of a prescription (i.e. officinal formula). The landscape of pharmacy preparations is changing all over Europe. Medicinal products are increasingly prepared by so-called compounding centres, i.e. specialised pharmacies that prepare medicinal products on a larger scale and supply the medicinal products to other (local) pharmacies that dispense them to the patient.[7,8,9] More and more local pharmacies cease to prepare medicinal products and their patients depend on compounding centres for essential medicines.[10] These changes in clinical practice need to take place within a highly regulated environment and pose challenges to the legislation.

Off-label use concerns a substantial share of the prescriptions for licensed medicinal products and is frequently due to the lack of an adequate licensed treatment option.[11,12] Radley et al. reported that 21% of the overall medication use was off-label, while among some drug class, such in as cardiac medications, off-label use prevalence was as high as 46%.[13] Medical associations may recommend off-label uses in their treatment guidelines as the standard therapy based on evidence in medical literature.[14] One should understand that competent governmental authorities have not been involved in the assessment of the benefit-risk balance of the product for the off-label use and the package information leaflet

4 P. Minghetti, D. Pantano, C.G. Gennari, A. Casiraghi, 'Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe', *Health Policy* 117(3) (2014) 328-333. DOI: 10.1016/j.healthpol.2014.07.010.

5 H. Buurma, P.A. de Smet, O.P. van den Hoff, H. Sysling, M. Storimans, A.C. Egberts, 'Frequency, nature and determinants of pharmacy compounded medicines in Dutch community pharmacies' *Pharm World Sci.* 25(6) (2003) 280-287.

6 SFK, 'Kwart miljoen magistrale bereidingen in 2015', *Pharmaceutisch Weekblad*, 151(17) 28 april 2016 http://www.sfk.nl/nieuws-publicaties/PW/2016/kwart-miljoen-magistrale-bereidingen-in-2015 (Last accessed 26 September 2016) ENG: Quater of a million formulea magistralis in 2015.

7 Minghetti 2014 *supra* note 4.

8 Bos 2013 *supra* note 2.

9 H.P.A. Scheepers, G. Busch, E. Hofbauer, J. Huse, C. Kalcher, C. Landgraf, V. Neerup Handlos, S. Walser, 'Abridged survey report on quality and safety assurance standards for the preparation of medicinal products in pharmacies', *Pharmeuropa* 22(4) (2010) 405-413.

10 Bos, 2013 *supra* note 2.

11 M. Weda, J. Hoebert, M. Vervloet, C. Moltó Puigmarti, S.M. Nikky Damen, J. Langedijk, J. Lisman, L. van Dijk, 'Study on off-label use of medicinal products in the European Union (Nivel, National Institute for Public Health and the Environment, and European public health alliance)', 2016. (In press)

12 D.C. Radley, S.N. Finkelstein and R.S. Stafford, 'Off-label prescribing among office-based physicians', *Archives of internal medicine* 166(9) (2006) 1021–1026.

13 *Ibid.*

14 The Dutch College of General Practitioners (NHG), 'NHG standpunt - Off label voorschrijven van geneesmiddelen', 2007: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/ standpunt_aanbevelingen_voor_het_off_label_voorschrijven_van_geneesmiddelen.pdf (Last accessed 21 August 2015).

therefore lacks adequate information about the off-label uses.[15,16] In recent years, cost benefits have become a reason for off-label use. For instance, Avastin (bevacizumab), a drug authorised for cancer treatment, is regularly used off-label in several EU Member States for the treatment of the serious eye condition macular degeneration, because it is much cheaper than the authorised product for the treatment of macular degeneration Lucentis (ranibizumab). Such off-label use also poses challenges to the legal system.

1.3 Establishment of a legal framework

At the end of the 19th century and beginning of the 20th century, national governments started to regulate medicinal products mainly as a response to an increase in pharmaceutical innovation and to prevent quackery.[17,18] Since the well-known Softenon tragedy of 1962, medicinal products became regulated at a European-wide level through Directive 65/65/EEC. It became prohibited to place medicinal products on the market without a marketing authorisation; a marketing authorisation requirement was established.[19] Pharmaceutical companies have to apply for a marketing authorisation to the competent authorities, such as the Dutch Medicines Evaluation Board or the European Medicines Agency. Applicants submit data, e.g. the outcomes of clinical trials, to substantiate the efficacy, safety and quality of their medicinal product with regard to the treatment of a specific disease or condition. A marketing authorisation is granted if the benefit-risk balance is considered favourable and quality requirements are satisfied.

The EU legislation on medicinal products has expanded massively since its institution. In 1965, Directive 65/65/EEC was fairly basic and contained limited requirements for a marketing authorisation.[20] Nowadays, the EU legislation on medicinal products contains detailed requirements on efficacy, safety and quality of the products. In addition, requirements on the Summary of the Product Characteristics, patient information leaflet and pharmacovigilance have been established and specified over time. The legislation aims to control the entire distribution chain of medicinal product from manufacturing to

15 R. Gijsen, H. Jochemsen, L. van Dijk and P. Caspers, 'Frequency of ill-founded off-label prescribing in Dutch general practice', *Pharmacoepidemiology and drug safety* 18(1) (2009) 84–91.

16 J.M. Raine, 'Off-label use of medicines: legal aspects', in H. S. Thomsen and J. A. W. Webb (eds), *Contrast Media Safety Issues and ESUR Guidelines*. Berlin, Heidelberg: Springer Berlin Heidelberg, (2014), 17–21.

17 S. Anderson, *Making medicines. A brief history of pharmacy and pharmaceuticals* (London: Pharmaceutical Press, 2005) p. 155-168, p. 244-253.

18 Dutch Parliamentary Papers II 1951-1952, 2479, nr. 3, p. 9 (Explanatory memorandum Medicines Act – 'Wet op de Geneesmiddelenvoorziening').

19 Art. 3, Council Directive 65/65/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, OJ 1965 22/369.

20 *Ibid., a*rt. 8 (3).

the supply to patients.[21] Amendments incorporated scientific progress and experience with the legislation on medicinal products in the legal framework in order to ensure improved quality and greater safety and efficacy.[22,23] Currently, the legislation on medicinal products is mainly laid down in Directive 2001/83/EC. This directive codified a patchwork of Community legislation on medicinal products instituted between 1965 and 2001.[24] Specific topics such as a centralised marketing authorisation procedure[25] and incentives for the development of orphan medicinal products[26] are regulated in EU regulations in addition to Directive 2001/83/EC.

1.4 Study aim and methods

Patient needs for medicinal products in clinical practice and the requirement for a marketing authorisation by EU legislation should be in balance. The marketing authorisation requirement should protect patients from ineffective and unsafe medicinal products of poor quality, while patients may need access to medicinal products that may be unlicensed or used off-label. In order to provide a better understanding to what extent the marketing authorisation requirement aligns with patient needs – taking into account the current changes in clinical practice - the present study aims to examine the purpose and scope of the EU marketing authorisation requirement for medicinal products from a legal perspective with specific focus on pharmacy preparations and off-label use. Subsequently, we provide recommendations for regulatory reform to resolve bottlenecks in the legislation that may compromise patient needs.

The research method consisted of a two-step approach. First, provisions and preambles in EU directives and regulations on human medicinal products since 1965 were assessed with special attention for the provisions regarding the scope of the legislation, the prohibition of placing medicinal products on the market without a marketing authorisation and exemptions from these two items. Amendments to the legislation provide an understanding of the meaning of the legislation and the intention of the legislator. Next,

21 Recital 35 of preambles to Directive 2001/83/EC of the European Parliament and the Council on the Community Code relating to medicinal products for human use, OJ 2001 L311/67.

22 Recital 7 of preamble to Directive 2004/27/EC of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ 2004 L136/34.

23 Preambles to Council Directive 89/341/EEC amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, OJ 1989 L142/11.

24 J.A. Lisman and J.F.J Lekkerkerker, 'Four decades of European medicines regulation: What have they brought us?', *International Journal of Risk and Safety in Medicine* 17(1) (2005) 73–79.

25 Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ 2004 L136/1.

26 Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, OJ 2000 L18/1.

case-law of the Court of Justice of the EU, i.e. the Court of Justice and the General Court,[27] regarding medicinal products and relevant EU directives and EU regulations on medicinal products was systematically searched for in the database *'Curia'*.[28,29]

This article consists of nine sections. Section 2 describes the purpose of the EU legislation on medicinal products; Section 3 section focuses on the scope of the legislation. The legislation includes a number of exemptions to Directive 2008/83/EC. These exemptions are examined in section 4 pharmacy preparations; section 5 named patient supply; and section 6 compassionate use. Section 7 outlines case-law on the requirement for a marketing authorisation as a general rule. Section 8 focuses on off-label use. Section 9 discusses implications and challenges. Section 10 draws conclusions.

2. PURPOSE OF THE EU LEGISLATION ON MEDICINAL PRODUCTS

The preamble of the original Directive 65/65/EC stated its primary purpose as to safeguard public health, while not to hinder the development of the pharmaceutical industry or trade in medicinal products.[30]

> *"Whereas the primary purpose of any rules concerning the production and distribution of proprietary medicinal products must be to safeguard public health;*
>
> *Whereas, however, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community;"* (Preambles to Directive 65/65/EEC)

This bipartite aim has been consistently repeated in the preambles of subsequent directives on medicinal products, including the current Directive 2001/83/EC.[31]

The Court of Justice first reflected on the purpose the marketing authorisation in *Clin-Midy v Belgian State* (1984) in order to determine the intent of the provisions harmonised by

27 Up to 1 December 2009 the General Court was named Court of First Instance.

28 Court of Justice of the European Union, *Case-law,* available from www.curia.europa.eu.

29 The systematic collection of case-law was finished on 31 July 2015. Thereafter case-law of the Court of Justice of the EU has been monitored for relevant cases. One such case has been identified which is still pending: Case C-276/15 lodged on 9 June 2015, *Hecht-Pharma GmbH v Hohenzollern Apotheke, owned by Winfried Ertelt.*

30 Preamble to Directive 65/65/EEC, *supra* note 19.

31 Recital 3, Directive 2001/83/EC, *supra* note 21.

Directive 65/65/EEC. In this regard, the court referred to the aforementioned preambles to Directive 65/65/EEC.[32] According to the court Directive 65/65/EEC *"must be interpreted as concerning solely national provisions which are intended to protect public health."* [33] In addition, the court stated, *"it should be stressed that the words 'authorisation to market' in the directive relate solely to an authorisation concerned with the protection of public health".*[34]

The Court of Justice confirmed the bipartite aim in several of its judgments and related the aim to the marketing authorisation requirement. In *Commission v Poland,* the Court of Justice explained that the requirement for a marketing authorisation:

> *"is intended to fulfil the objectives which Directive 2001/83 seeks to attain, namely, first, the elimination of hindrances to trade in medicinal products between the Member States and, second, the protection of public health. As the Advocate General stated in (…) his Opinion, the harmonised marketing authorisation procedure enables costefficient and non-discriminatory market access, while ensuring that the requirements of safeguarding public health are achieved."* [35,36]

Furthermore, Directive 65/65/EEC, and consequently the marketing authorisation requirement, aimed to protect consumers from both unsafe and ineffective medicines. The legislation, therefore, applied to medicinal products "*which are not sufficiently effective or which do not have the effect which consumers would be entitled to expect in view of their presentation"* [37] as the Court of Justice explained in the case *Van Bennekom*. By including extending to ineffective medicinal products Directive 65/65/EEC "*seeks to preserve consumers not only from harmful or toxic medicinal products as such but also from a variety of products used instead of the proper remedies."* [38] The court has confirmed this reasoning in several other judgements.[39]

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32 Case C-301/82, 26 January 1984, ECLI:EU:C:1984:30, *Clin-Midy v Belgian State*, para 5.

33 *Ibid*., para 7. The Advocate General in a subsequent case referred to these considerations and argued that the essential aim of had not changed by then (Case C-440/93, 5 October 1995, ECLI:EU:C:1995:307 *The Queen v Licensing Authority of the Department of Health and Norgine, ex parte Scotia Pharmaceuticals*, Advocate General para 9).

34 C-301/82 *Clin-Midy v Belgian State, supra* note 32, para 9.

35 Case C-185/10, 29 March 2012, ECLI:EU:C:2012:181, *Commission v Poland*, para 27.

36 See also Case C-84/06, 20 September 2007, ECLI:EU:C:2007:535, *Antroposana and Others*, para 36: *"Moreover, that interpretation of the provision in question is, as the Advocate General pointed out in points 56 to 60 of his Opinion, in accordance with the objectives which Directive 2001/83 seeks to attain, namely, the elimination of hindrances to trade in medicinal products between the Member States and the protection of public health."*

37 Case C-227/82, 30 November 1983, ECLI:EU:C:1983:354, *Van Bennekom*, para 17.

38 *Ibid*.

39 Case C-112/89, 16 April 1991, ECLI:EU:C:1991:147, *Upjohn*, para 13; Case C-319/05, 15 November 2007, *Commission v Germany*, para 43.

3. SCOPE FOR THE EU LEGISLATION ON MEDICINAL PRODUCTS

The marketing authorisation requirement may only apply to the products that are in principle regulated by Directive 2001/83/EC. It should be noted that, whereas the scope of the directive has been amended multiple times since the institution of Directive 65/65/EEC, the prohibition to market medicinal products without a marketing authorisation is almost identical to the prohibition established in 1965.

> Article 3 Directive 65/65/EEC: *No proprietary medicinal product may be placed on the market in a Member State unless an authorisation has been issued by the competent authority of that Member State.*
>
> Article 6 (1) Directive 2001/83/EC: *No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 (…) and Regulation (EC) No 1394/2007.*

In 1965, Directive 65/65/EEC only applied to proprietary medicinal products as determined by article 2 of Directive 65/65/EEC.[40] Proprietary medicinal products were *"any ready-prepared medicinal product placed on the market under a special name and in a special pack".*[41][42] Consequently, article 3 of Directive 65/65/EEC only prohibited proprietary medicinal products to be placed on the market without a marketing authorisation. The directive did not regulate, for example, unbranded medicinal products currently known as generic medicinal products.[43]

In 1975, the EU legislator considered that the provisions of the directive were inadequate to regulate several categories of medicinal products.[44] Vaccines, toxins or serums, medicinal products based on human blood or blood constituents, radioactive isotopes and homeopathic proprietary medicinal products were excluded from the scope of Directive 65/65/EEC.[45] These exemptions were undone in 1989 after the conditions for

40 Art. 2 Directive 65/65/EEC: *"The provisions of Chapters II to V shall apply only to proprietary medicinal products for human use intended to be placed on the market in Member States."*
41 *Ibid.,* art. 1 (1).
42 *Ibid.,* art. 2.
43 Lisman and Lekkerkerker (2005), s*upra* note 24.
44 Recital 8 of preamble to Second Council Directive 75/319/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, OJ 1975 L147/13.
45 *Ibid.,* art. 34.

a marketing authorisation were amended except for homeopathic medicinal products. In 1992, it also became prohibited to place homeopathic medicinal products on the market without a marketing authorisation.[46]

Another significant amendment in 1989 was the extension of the scope of Directive 65/65/EEC to industrially produced medicinal products besides proprietary medicinal products.[47] A marketing authorisation became also required for products that did not comply with the definition of proprietary medicinal product. At the same time, the EU legislator explicitly excluded four categories of medicinal products from the scope of Directive 65/65/EEC: medicinal products prepared on the basis of a magistral or officinal formula, medicinal products intended for research and development trials, and intermediate products intended for further processing by an authorised manufacturer.[48] Magistral formula was defined as "*Any medicinal product prepared in a pharmacy in accordance with a prescription for an individual patient."* [49] Officinal formula was defined as *"Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question."* [50] The other two categories were not defined in more detail. In fact, these four categories of medicinal products were also outside the scope of Directive 65/65/EEC prior to the amendment in 1989; since they did not satisfy the definition of proprietary medicinal product.

The distinction between 'proprietary medicinal products' and 'medicinal products' was completely abandoned in 2001 with the enactment of Directive 2001/83/EC which included all industrially produced medicinal products. Since 2004 Directive 2001/83/EC covers all medicinal products that are *"either prepared industrially or that are manufactured by a method involving an industrial process."* [51]

Consequentially, article 2 (1) of Directive 2001/83/EC currently restricts the scope of the directive to medicinal products for human use 'intended to be placed on the market in Member States' which are either 'prepared industrially' or 'manufactured by a method involving an industrial process'.[52] Directive 2001/83/EC does not define those concepts.[53]

46 Art. 6 Council Directive 92/73/EEC widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to medicinal products and laying down additional provisions on homeopathic medicinal products, OJ 1992 L297/8.
47 Art. 2 (2) Directive 65/65/EEC as amended by Directive 89/341/EEC, *supra* note 23.
48 *Ibid.,* art. 2 (3).
49 *Ibid.,* art. 1 (4).
50 *Ibid.,* art. 1 (5).
51 *Ibid.,* art. 2 (1).
52 Joint cases C-544/13 and C-545/13, 16 July 2015, ECLI:EU:C:2015:481, *Abcur v Apoteket*, para 41.
53 *Ibid.,* para 44.

The Court of Justice, however, recently reasoned in *Abcur v Apoteket* that the terms 'prepared industrially' and 'manufactured by a method involving an industrial process' cannot be interpreted narrowly considering that the objective of the EU rules on medicinal products is to protect public health.[54]

Directive 2001/83/EC applies, as the court considered, if the manufacturing process includes a succession of operations, which may, in particular, be mechanical or chemical, in order to obtain a significant quantity of a standardised product.[55] These conditions would typically be fulfilled in case of a standardised production of significant quantities of a medicinal product that are subsequently stocked and sold wholesale, as well as in case of large-scale or serial production of magistral formulae in batches, as the court argued.[56]

Next, other amendments to Directive 2001/83/EC also indicate a wide scope of Directive 2001/83/EC. In 2004, a simplified licensing procedure for traditional herbal medicinal products was established in order to stimulate the licensing of traditional herbal medicines[57] and Regulation (EC) No 1394/2007 issued rules on advanced therapy medicinal products (i.e. gene therapy, somatic cell therapy and tissue engineering).[58] Advanced therapies were basically already within the scope of Directive 2001/83/EC, but a *lex specialis* was deemed necessary, because of the novelty, complexity and technical specificity of advanced therapy medicinal products.[59] The establishment of specific requirements for herbal medicinal products and advanced therapy medicinal products amplifies the idea of a broadening scope of the marketing authorisation requirement. Such products either obtain market approval or are prohibited to be placed on the market.

Currently, Directive 2001/83/EC excludes seven product categories from the scope of the directive similar to Directive 65/65/EEC. Article 3 of Directive 2001/83/EC states that the directive shall not apply to:

54 *Ibid.,* para 47 to 50.

55 *Ibid.,* para 50.

56 *Ibid.,* para 51; See also the pending Case C-276/15 lodged on 9 June 2015, *Hecht-Pharma GmbH v Hohenzollern Apotheke, owned by Winfried Ertelt.* which concerns i.a. the interpretation of the articles 2 and 3 of Directive 2001/83/EC. The case is pending.

57 Directive 2004/24/EC of the European Parliament and of the Council amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ 2004 L136/85.

58 Recital 1 of preambles to Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ 2007 L324/121.

59 *Ibid.,* recital 5 and 6.

1. *Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).*
2. *Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).*
3. *Medicinal products intended for research and development trials (…).*
4. *Intermediate products intended for further processing by an authorized manufacturer.*
5. *Any radionuclides in the form of sealed sources.*
6. *Whole blood, plasma or blood cells of human origin, except for plasma which is prepared by a method involving an industrial process.*
7. *Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.*

Categories one to four are virtually identical to the categories excluded from Directive 65/65/EEC. The fifth category (radiopharmaceuticals) and sixth category (human blood) were already exempted since 1989 through means of other directives.[60] The seventh category (advanced therapy medicinal products) was included after the enactment of Regulation (EC) No 1394/2007 and established a specific so-called hospital exemption.

The relationship between articles 2 (1) and 3 of Directive 2001/83/EC has been interpreted by the Court of Justice in the judgment *Abcur v Apotheket.*[61] Based on the text of the provisions the court concluded that articles 2 and 3 contain consecutive requirements. In order to fall within the scope of Directive 2001/83/EC, a product, "*firstly, must satisfy the conditions laid down in article 2 (1) of that directive and, secondly, must not fall within one of the exceptions expressly provided for in article 3 of that directive."*[62]

Interestingly, in *Abcur v Apotheket* Advocate General Szpunar had contended a different relationship between article 2 (1) and 3 of Directive 2001/83/EC. He considered that

60 Art. 1 Council Directive 89/343/EEC extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals, OJ 1989 L142/16; and art. 1 (1) Council Directive 89/381/EEC extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma, OJ 1989 L181/44.

61 C-544/13 and C-545/13 *Abcur v Apoteket, supra* note 52, para 38 and 39.

62 *Ibid*., The Court of Justice also referred to C-512/12 *Octapharma France* in which the Court of Justice also reasoned that Directive 2001/83/EC applied to medicinal products which are prepared industrially and are intended to be placed on the market in Member States (Case C-512/12, 13 March 2014, ECLI:EU:C:2014:149, *Octapharma France*, para 29 and 38).

in principle any medicinal product would be within the scope of Directive 2001/83/EC except for the products listed in article 3. In a previous case, *Novartis v Apozyt*, Advocate General Sharpston had proposed a similar relation between article 2 (1) and article 3 of Directive 2001/83/EC.[63] From the judgment in *Abcur v Apoteket*, it is now apparent that the Court of Justice does not concur with the line of reasoning of the both Advocate General Szpunar and Sharpston.

In summary, the requirement of a marketing authorisation only applies to medicinal products that fall within the scope of Directive 2001/83/EC. The scope of Directive 65/65/EEC and subsequently Directive 2001/83/EC has been widened to include medicinal products for human use intended to be placed on the market in Member States and that are either prepared industrially or manufactured by a method involving an industrial process (art. 2 (1) Directive 2001/83/EC). The Court of Justice has provided a wide interpretation to the meaning of 'prepared industrially' and 'manufactured by a method involving an industrial process'. Seven product categories have been excluded from the scope of Directive 2001/83/EC by means of article 3. In order to fall within the scope of Directive 2001/83/EC, a product must first satisfy the conditions in article 2(1) of Directive 2001/83/EC and subsequently should not fulfil the conditions in article 3 of the directive. This underscores the importance of the definition of the exemptions. The next section provides a detailed explanation of the exemption for pharmacy preparations, since those products are most relevant in relation to the patient needs outlined in the introduction. The other product categories in article 3 of Directive 2001/83/EC are left aside. Subsequently, sections 5 and 6 focus on two other exemptions, namely for named patient supply and compassionate use, respectively.

4. EXEMPTION FOR PHARMACY PREPARATIONS

Pharmacy preparations, i.e. magistral formula and officinal formula, have been exempted from the scope of Directive 2001/83/EC. In the case *Abcur v Apoteket* the Court of Justice has clarified both categories. The court, however, first recalled that "*generally, provisions which are in the nature of exceptions to a principle must (…) be interpreted strictly."* [64] Accordingly, the court provided restrictive interpretations for 'magistral formula' and 'officinal formula'.

63 Case C-535/11, 11 April 2013, ECLI:EU:C:2013:226, *Novartis v Apozyt*, Advocate General para 68.
64 C-544/13 and C-545/13 *Abcur v Apoteket, supra* note 52, para 54.

Article 3 point 1 of Directive 2001/83/EC contains three cumulative conditions for the exemption for 'magistral formula'.[65] Firstly, the medicinal product must be prepared 'in a pharmacy'. Secondly, the preparation should be in accordance with a medical prescription. More specifically, the medicinal product *"must of necessity be prepared on the basis of a prior prescription issued by a professional qualified to do so"*.[66] Therefore, the medical prescription needs to be issued before the product is prepared. Thirdly, the medical prescription must be 'for an individual patient'. According to the court, *"it follows therefrom that [the] prescription must be for a particular named patient and (…), that patient must be identified before the medicinal product is produced and it must be produced specifically for that patient."*[67]

The exemption for 'officinal formula' in article 3 point 2 of Directive 2001/83/EC also contains three cumulative conditions.[68] Firstly, the medicinal products must also be prepared 'in a pharmacy'.[69] Secondly, the medicinal product needs to be prepared 'in accordance with the prescriptions of a pharmacopoeia'.[70] Thirdly, the medicinal product must be 'intended to be supplied directly to the patients served by the pharmacy in question'.[71] With regard to the third condition, the court stated that *"in order to benefit from the exception […], that medicinal product must be supplied directly by the pharmacy which prepared it to the patients supplied by that same pharmacy."*[72] The latter means that, under article 3 point 2, pharmacies cannot supply pharmacy prepared medicinal products to other pharmacies.

In addition, the court established that for the application of the exemption in article 3 points 1 or 2, it is irrelevant whether there are other medicinal products with the same active substance, same dosage and same pharmaceutical form which have been licensed. For the exemption to apply, it only matters whether the conditions of article 3 point 1 or 2 are satisfied.[73]

65 *Ibid.,* para 58 and 59.
66 *Ibid.,* para 60 and 64. A medicinal prescription is defined in article 1 point 19 of Directive 2001/83/EC as being any medicinal prescription issued by a professional person qualified to do so.
67 *Ibid.,* para 61.
68 *Ibid.,* para 66.
69 *Ibid.*
70 *Ibid.*
71 *Ibid.*
72 *Ibid.,* para 67.
73 *Ibid.,* para 55.

5. EXEMPTION FOR NAMED PATIENT SUPPLY

In 1989, the EU legislator established another exemption, which is referred to as named patient supply.[74] Different from the exemptions for pharmacy preparations discussed above it does not exclude product categories from the scope of the directive. It allows member states to institute legislation to exclude medicinal products from the provisions of the directive under specific conditions. Later the preambles to Directive 2001/83/EC may have somewhat elucidated the reasoning for the exemption and stated that "*It must also be possible for a person established in one Member State to receive from another Member State a reasonable quantity of medicinal products intended for his personal use."*[75] Currently, the exemption is laid down in article 5 (1) of Directive 2001/83/EC in virtually identical wording as the provision in 1989 and states:

> *"A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility." (Article 5 (1) Directive 2001/83/EC as amended by Directive 2004/27/EC)*

Article 5 (1) of Directive 2001/83/EC contains four requirements:

1. the exemption from the directive must be in accordance with national legislation in force;
2. the supply of medicinal products must fulfil special needs;
3. the medicinal product must be supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health care professional; and
4. the medicinal product is for use by his individual patients on his direct personal responsibility.

The exemption for named patient supply in article 5 (1) of Directive 2001/83/EC should be interpreted strictly and its application "*must remain exceptional in order to preserve the practical effect of the marketing authorisation procedure",*[76] *as the* Court of Justice argued in the case *Commission v Poland.* It should only be used "*if that is necessary, taking*

74 Art. 3 (4) Directive 65/65/EEC as amended by Directive 89/341/EEC, *supra* note 23.

75 Recital 30 Preambles Directive 2001/83/EC, *supra* note 21.

76 C-185/10 *Commission v Poland, supra* note 35, para 32; see also para 48; and Case C-143/06, 8 November 2007, ECLI:EU:C:2007:656, *Ludwigs-Apotheke*, para 33 and 35.

account of the specific needs of patients." [77] Therefore, the court provided a restrictive interpretation of article 5 (1) of Directive 2001/83/EC.

Firstly, the concept of 'special needs' in the second requirement of the provision *"applies only to individual situations justified by medical considerations and presupposes that the medicinal product is necessary to meet the needs of the patient."*[78] Secondly, in the context of article 5 (1) 'bona fide unsolicited order' means that *"the medicinal product must have been prescribed by the doctor as a result of an actual examination of his patients and on the basis of purely therapeutic considerations."*[79] Finally, article 5 (1) *"can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market."*[80] This means that no special need exists if there are already authorised medicinal products available on the national market with the same active substances, the same dosage and the same form.[81] In any case, financial considerations do not constitute a special need.[82]

More recently the General Court ruled in *Laboratoires CTRS v Commission* that article 5 (1) allows for the exemption of categories of medicinal products from provisions of Directive 2001/83/EC through their national laws, as long as the strict conditions established in *Commission v Poland* are fulfilled. Member States do not need to exempt medicinal products on a case-by-case basis.

> *"Contrary to the arguments put forward by the Commission at the hearing, that provision [article 5 (1) Directive 2001/83/EC] does not state that a Member State may exclude medicinal products from the provisions of Directive 2001/83 only on a case-by-case basis, rather than on the basis of categories of medicinal products, such as hospital preparations."* [83]

77 C-185/10 *Commission v Poland, supra* note 35, para 33; See also C-143/06 *Ludwigs-Apotheke*, *Ibid*., para 22, in which the Court of Justice first provided particular guidance on the interpretation of article 5 (1) Directive 2001/83/EC and stated that it regards to, firstly, a limited quantity, secondly, in the context of an individual order and, thirdly, which is justified by special needs.

78 C-185/10 *Commission v Poland, supra* note 35, para 34.

79 *Ibid*., para 35; The Court of Justice confirmed its reasoning in Case C-535/11, 11 April 2013, ECLI:EU:C:2013:226, *Novartis v Apozyt*. para 46.

80 C-185/10 *Commission v Poland, supra* note 35, para 36; The Court of Justice confirmed its reasoning in *Novartis v Apozyt, Ibid*., para 46; see also C-544/13 and C-545/13 *Abcur v Apoteket*, s*upra* note 52, para 56.

81 C-185/10 *Commission v Poland, supra* note 35, para 37.

82 *Ibid*., para 38. Cf. Case C-459/00 P(R), 11 April 2001, ECLI:EU:C:2001:217, *Commission v Trenker*, para 109 regarding the precedence of protection of public health over economic considerations.

83 Case T-301/12, 4 July 2013, ECLI:EU:T:2013:346, *Laboratoires CTRS v Commission*, para 50.

The hospital preparations involved in *Laboratoires CTRS v Commission* were defined as *"medicinal products prepared in accordance with the prescriptions of a pharmacopoeia and in compliance with the rules of good practice laid down in French legislation where there is no appropriate medicinal product prepared by a hospital's in-house pharmacy or by that hospital's authorised pharmaceutical establishment […]".*[84] These hospital preparations seem similar to the products prepared by compounding centres referred to in the introduction.

6. EXEMPTION FOR COMPASSIONATE USE

The third exemption from the requirement of a marketing authorisation that will be discussed is the compassionate use program established in article 83 (1) of Regulation (EC) No 726/2004.[85] The compassionate use program differs in nature from the exemptions for pharmacy preparations and named patient supply. The 'compassionate use programme' allows Member States to exempt medicinal products specifically from the prohibition in article 6 (1) of Directive 2001/83/EC.[86] Article 83 (1) of the Regulation states:

"By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3 (1) and (2) of this Regulation available for compassionate use."

Five requirements apply for a compassionate use programme. Firstly, the medicinal product should be eligible to the centralised procedure to obtain a community marketing authorisation.[87] Secondly, the program should focus on the treatment of a group of patients rather than an individual patient as in the named patient supply exemption.

84 *Ibid.*, para 41.

85 Regulation (EC) No 726/2004 mainly contains provisions regarding the centralised procedure to obtain a community marketing authorisation as well as provisions regarding the functioning of the European Medicines Agency. To a large extent Regulation (EC) No 726/2004 may considered to be complementary to Directive 2001/83/EC. (Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ 2004 L136/1)

86 Recital 33 Preamble to Regulation (EC) No 726/2004 (*Ibid.*) clarifies article 83. If possible a common approach regarding criteria and conditions for medicinal products under compassionate should be followed.

87 Art. 3 (1) Regulation (EC) No 726/2004 (*Ibid.)* states which products are eligible to the centralised procedure, i.e. biotechnology medicinal products, medicinal products for the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes, autoimmune diseases and other immune dysfunctions and viral diseases, as well as medicinal products with a new active substance, medicinal product that constitute a significant therapeutic, scientific or technical innovation and in case a community marketing authorisation is in the patient interest.

Next, the medicinal product should be developed for the treatment of a chronically or seriously debilitating disease or a disease that is considered to be life threatening. Fourthly, satisfactory treatment of the patient should not be possible by an authorised medicinal product. Finally, the medicinal product concerned either must be the subject of an application for a marketing authorisation or must be undergoing clinical trials.[88] Due to the latter requirement the exemption of compassionate use is only an exemption to a limited extent. The products under a compassionate use program are expected to acquire a marketing authorisation within a foreseeable future.

7. THE MARKETING AUTHORISATION AS GENERAL RULE

From the previous sections it has become clear that the EU legislator and the Court of Justice envisage a broad scope of Directive 2001/83/EC, while only a limited number of product categories are exempted from the scope under strict conditions. This section stresses that the court has interpreted the requirement of a marketing authorisation as a general rule of the EU legislation on medicinal products.

In *Ortscheit v Eurim-Pharm* (1994) the Court of Justice had to rule on the justification of a provision in German law that prohibited advertisement for unapproved medicinal products. According to the court, the purpose of the contested German prohibition was actually to maintain the marketing authorisation requirement as a general rule and exemptions should remain an exception:

> *"[The contested provision] has the purpose to ensure that the individual importation of medicinal products which have not been authorised remains an exception, to prevent the general requirement of national authorisation under German law from being systematically circumvented."* [89]

This statement was re-established by the Court of Justice in the *Ludwigs-Apotheke* in 2007, when it again had to rule about the German prohibition on advertisement for unapproved medicinal products.[90] The court stated *"Directive 2001/83 is based on the premiss that the marketing of a product which is classified as a medicinal product is conditional on the grant of a marketing authorisation (…)."* [91] In addition, the Court of Justice considered that the prohibition on advertisement for imported non-approved medicinal products, as

88 *Ibid.*, art. 83 (2).
89 C-320/93 *Ortscheit v Eurim-Pharm* [1994] ECR I-05243, para 19.
90 C-143/06 *Ludwigs-Apotheke, supra* note 76, para 31.
91 *Ibid.,* para 33.

the court considered, *"consists in strengthening the exceptional nature of a derogating authorisation to market medicinal products which are not approved and not registered, (…) thereby preserving the practical effect of the marketing authorisation procedure."* [92] The Court of Justice also confirmed the marketing authorisation as a general rule in the cases *Antroposana*[93] and *HLH Warenvertriebs and Orthica*.[94] Moreover, the procedures leading to a marketing authorisation need to be in accordance with the requirements of Directive 2001/83/EC or Regulation (EC) No 726/2004. This was the outcome of the *Antroposana* case, in which the Court of Justice determined that the procedures and requirements to obtain market approval have been completely harmonised by EU law.[95]

It is noteworthy that a specific limitation to the marketing authorisation as a general rule was established by the Court of Justice in the case *Novartis v Apozyt*.[96] Apozyt prepared, using the content of the licensed medicinal products Lucentis (Novartis) and Avastin (Roche), pre-filled ready to use syringes with the exact amount of the active substance as prescribed by the treating physician. Apozyt's method allowed the vials of Lucentis and Avastin to be used for the preparation of multiple injections and, therefore, at a considerably lower price than Lucentis and Avastin.[97]

Advocate General Sharpston in *Novartis v Apozyt* contended that a marketing authorisation would be required for the products of Apozyt. She considered that, based on article 6 (1) of Directive 2001/83/EC, medicinal products require a marketing authorisation to be placed on the market, as well as do any modifications to the product.[98] This obligation, according to the Advocate General, does not end once the product is placed on the market for the first time.[99] The Advocate General refers to the preamble of Directive 2001/83/EC which states that, *"it is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Community through to supply to the public"*. To satisfy this requirement, the Advocate General considers, *"an authorisation must be in place on every occasion on which the product concerned is made available on the market until the point at which that product has, in fact, been*

92 *Ibid.,* para 35.

93 *"it is absolutely clear from the terms of [article 6 (1) of Directive 2001/83/EC] that (…) if medicinal products are to be marketed in the Community, authorisation must first have been obtained, in accordance with the procedures laid down in the directive, for their placing on the market".* (C-84/06 Antroposana [2007] ECR I-07609, para 35.

94 Joined Cases C-211/03, C-299/03 and C-316/03 to C-318/03 *HLH Warenvertriebs and Orthica,* 9 June 2005, ECLI:EU:C:2005:370, para 57. See also C-185/10 *Commission v Poland, supra* note 35, para 26.

95 C-84/06 *Antroposana* [2007] ECR I-07609, para 37 and 41.

96 Case C-535/11, 11 April 2013, ECLI:EU:C:2013:226, *Novartis v Apozyt*.

97 *Ibid.,* para 23.

98 Case C-535/11, 11 April 2013, ECLI:EU:C:2013:226, *Novartis v Apozyt*, Advocate General para 51 and 52.

99 *Ibid.,* 54, 55 and 61.

disposed of by being supplied to the public".[100] Any other interpretation *"would also fail to reflect the general scheme of the legislation"*,[101] which obliges marketing authorisation holders to apply for approval of any variations to the medicinal product.[102]

Nonetheless, the Court of Justice concluded that, the activity performed by Apozyt could not *"be equated with a new placing on the market of a medicinal product"* [103] if the processes *"do not result in any modification of the medicinal product"* [104] and *"that they are carried out solely on the basis of individual prescriptions making provision for them."*[105] Under those circumstances Apozyt is *"not subject to the obligation to hold a marketing authorisation".*[106] Consequently, the court in fact has limited the effect of the marketing authorisation requirement. Medicinal products may to some extent be processed, despite the fact that similar changes to the product by the marketing authorisation holder would require prior approval from the competent authorities.

8. OFF-LABEL USE

In the introduction is has been pointed out that in clinical practice licensed medicinal products may be used off-label. From the analysis of the EU law, we can conclude that off-label use of medicinal products is not specifically regulated by EU law. This has been argued in case-law of the General Court and by Advocate General Sharpston. In *Novartis v Apozyt*, Sharpston asserted that a medical practitioner is free to prescribe an authorised medicinal product off-label:

> *"the fact that the authorisation has been granted in respect of a particular form of treatment will have no impact on the relationship between the medical practitioner and his client. The practitioner will thus be free, with his patient's consent as appropriate, to prescribe for him a product notwithstanding that the product has been authorised for an ailment other than that from which the patient is suffering."*[107]

100 *Ibid.,* para 58.
101 *Ibid.,* para 59.
102 *Ibid.,* para 60.
103 C-535/11 *Novartis v Apozyt,* supra note 96, para 42.
104 *Ibid.*
105 *Ibid.*
106 *Ibid.*
107 C-535/11, *Novartis v Apozyt*, Advocate General, s*upra* note 98, para 79.

Later, in *Laboratoires CTRS v Commission* (2015), the General Court concluded that off-label prescribing[108] is not regulated by EU law:[109]

> *"off-label prescribing is not prohibited, or even regulated, by EU law. There is no provision which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted."*[110]

According to the General Court, "*off-label prescribing is the sole responsibility of the prescribing physician."*[111]

Advertising for off-label uses, however, is prohibited according to EU law since 1992.[112] Directive 2001/83/EC determines that all advertising for medicinal products and advertising must be concordant with the Summary of Products Characteristics and, consequently, the promotion of off-label therapeutic indications is prohibited.[113]

9. IMPLICATIONS AND CHALLENGES

The present study provides a comprehensive overview on EU law and case-law concerning the marketing authorisation requirement for medicinal products in order to illuminate how the marketing authorisation requirement aligns with patient needs. Despite the massive expansion of EU legislation on medicinal products, the prohibition to market unlicensed medicinal products remained in essence unchanged. The primary purpose of the legislation has always been to safeguard public health – both from dangerous and ineffective medicines – while at the same time the legislation should not hinder the development of the pharmaceutical industry or the trade in medicinal products within the EU. On the contrary, the scope of products regulated by Directive 65/65/EEC and subsequently Directive 2001/83/EC has been broadened over time, while the limited number of exemptions is subject to several conditions. In view of the purpose to safeguard public health the Court of Justice has provided a non-restrictive interpretation of the scope of the directive, while it established a restrictive interpretation of the exemptions. The court has consistently considered the marketing authorisation requirement to be the general rule of the EU legislation on medicinal products. All in all, room to manoeuvre for

108 i.e. Off-label use.
109 Case T-452/14, 11 June 2015, ECLI:EU:T:2015:373, *Laboratoires CTRS v Commission*.
110 *Ibid.,* para 79.
111 *Ibid.,* para 82.
112 Art. 2 (1) and (2) Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use, OJ 1992 L113/13.
113 Supra note 21, art. 87 (2) Directive 2001/83/EC.

the use of medicinal products without a marketing authorisation is therefore limited. What do these results mean for the possibilities to serve patient needs in (a changing) clinical practice?

9.1 Pharmacy preparations

In various Member States the preparation of medicinal products by pharmacies has been centralised in so-called compounding centres, i.e. specialised pharmacies that prepare medicinal products on a larger scale and supply the medicinal products to other (local) pharmacies that dispense them to the patient.[114] For example, the Dutch Health Care Inspectorate established a policy on the supply of medicinal product by compounding centres to local pharmacies.[115] The policy allows the supply of pharmacy compounded medicinal products if no licensed therapeutic equivalent medicinal products is available, product specifications support the pharmacotherapeutic rationale and the products is compounded conform Good Manufacturing Practice standards. The recent *Abcur v Apotheket* case illustrated the friction between the supply by compounding centres and the limited legal space provided by Directive 2001/83/EC. That case showed that the exemption from a marketing authorisation for officinal formulae (art. 3 point 2 Directive 2001/83/EC) does not apply to medicinal products prepared on stock by compounding centres and supplied to local pharmacies. The exemption for officinal formulae only applies if the medicinal product is supplied directly to the patient. Compounding centres may still supply medicinal products to other (local) pharmacies under the exemption for magistral formulae in article 3 point 1 of Directive 2001/83/EC. That provision does not require that the medicinal product should be supplied directly to the patient by the pharmacy that prepared the medicine. The *Abcur v Apotheket* case did not change this aspect. Yet, the exemption for magistral formulae requires that the preparation of the product only starts after the receipt of a prescription. It may not be possible to comply with that condition on occasions that demand immediate administration of the medicine, such as on the emergency department of a hospital. If compounding centres are not allowed, or unable, to supply medicinal products under the exemption for officinal or magistral formulae some patients may not have access to medicinal products they need.

Given the *Abcur v Apotheket* case a legal reform may be needed in to facilitate the practice in which medicinal products are prepared by compounding centres and dispensed by other pharmacies. One option may be to amend Directive 2001/83/EC and

114 Scheepers (2010), *supra* note 9.

115 Dutch health care inspectorate, Circulaire 'Handhavend optreden bij collegiaal doorleveren van eigen bereidingen door apothekers', 22 August 2016 *(2016-01-IGZ)* Availible from: http://www.igz.nl/Images/Circulaire%20Handhavend%20optreden%20bij%20collegiaal%20doorleveren%20van%20eigen%20bereidingen%20door%20apothekers%20-%202016-01-IGZ_tcm294-377635.pdf (Last accessed 25 September 2016).

to allow pharmacies to supply pharmacy prepared medicinal products to other (local) pharmacies under strict condition so the marketing authorisation as a general rule would not be circumvented. This would require a lengthy procedure, let alone that the Members States need to agree on the specifics of the amendment.

Another option might be to exempt the preparations of compounding centres through the exemption for named patient supply (art. 5 (1) Directive 2001/83/EC). According to the text of the provision it exempts medicinal products formulated in accordance with the specifications of an authorised health-care professional. Also, it allows for an exemption of categories of products as was established in *Laboratoires v Commission*.[116] In the United Kingdom the law allows the supply of such unlicensed medicinal products (also known as 'specials') on the basis of article 5 (1) Directive 2001/83/EC, under a so-called 'specials license'.[117] The UK law sets out several conditions including the requirements established in *Commission v Poland*.[118] This includes the requirement for a *'manufacturer's specials licence'* to prepare the medicinal products. Additionally, specials may only be prepared if no licensed medicinal product (on-label or off-label) is available in the United Kingdom. This allows patients in the United Kingdom access to unlicensed medicinal products but only under strict conditions.

The application of article 5 (1) Directive 2001/83/EC to exempt unlicensed medical products prepared by compounding centres from the marketing authorisation requirement may seem a rather extensive application of that provision, even though such an application seems not to be precluded by its text. A too extensive application of the exemption could affect the status of, or result in circumvention of, the marketing authorisation as a general rule. Therefore, strict conditions should apply that clearly state to whom and under which circumstances the exemption would apply. For instance, such an exemption should only be allowed in the absence of a licensed equivalent or adequate alternative medicinal product: a medicinal product that is identical or that could equally well serve the patient's needs. The marketing authorisation need to remain the general rule.

9.2 Off-label use

Off-label use of medicinal products is not prohibited, or even regulated, by EU law. However, systematic off-label use as the standard treatment for a disease seems to be at odds with the intent of the marketing authorisation requirement to safeguard public

116 T-301/12 *Laboratoires CTRS v Commission*, *supra* note 83, para 41.

117 MHRA 'The supply of unlicensed medicinal products ("specials") 2014: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf (Last accessed 12 January 2016).

118 C-185/10 *Commission v Poland, supra* note 35.

health through the assessment of the efficacy and safety of medicinal products in regard to well-defined therapeutic indications. From such a perspective, it would be sensible if the competent authorities were provided with an opportunity to assess the benefit-risk balance and potentially extend the label with the "off-label" indication. Examples of related initiatives can be found in both France and the United Kingdom.

France enacted legislation that allows for a renewable temporary license for off-label uses, called 'Temporary Recommendations for Use' (TRU). A TRU may apply in case no equivalent authorised medicinal product (i.e. same active substance, dosage and form) for the therapeutic indication is available.[119,120] In short, a TRU can be granted after a governmental organisation or patient advocacy group has singled an off-label use in an unmet therapeutic need and subsequently the French competent authority has determined a positive benefit-risk assessment based on data provided by the concerned pharmaceutical company or companies. Then a patient monitoring system is established and the French competent authority communicates the TRU (including the indication, posology, adverse effects, etc.) to the French health care professionals. During a TRU the medicinal product may be reimbursed while the pharmaceutical company has to collect data to support the efficacy and safety and apply for an extension of indication through the regular procedures. However, the French experienced difficulties with this legislation. The TRU initially had to provide access to medicines for unmet medical need. Yet, a few years after the introduction the law was amended to accommodate the use of cheaper alternatives despite the availability of an authorised alternative, such as in the case of Avastin versus Lucentis.[121] The French also encountered that the pharmaceutical companies cannot be forced to apply for an extension of indication for a previously off-label indication.[122] In the United Kingdom, an 'Off-patent drugs bill' is had been proposed by a member of parliament, but was blocked by the Minister of Health.[123] The bill should initiate an obligation for the Secretary of State to apply for a license for off-label uses of off-patent medicinal products. Policies and regulations similar to the initiatives in France and the United Kingdom may stimulate that common off-label uses become on-label. Consequently, off-label use may preserve an exceptional nature.

119 ANSM 'Temporary Recommendation for Use (RTUs). Principles and information on the methods used by the ANSM for esthablishment and implementation, 2012. Available from http://ansm.sante.fr/content/download/45542/590551/version/1/file/RTU-english.pdf (Last accessed 12 January 2016).

120 A. Degrassat-Théas, F. Bocquet, M. Sinègre, J. Peigné and P. Paubel, P., 'The 'Temporary Recommendations for Use': A dual-purpose regulatory framework for off-label drug use in France', *Health policy* 119(11) (2015) 1399–1405.

121 *Ibid*.

122 *Ibid*.

123 *Off-patent drugs bill - UK*, 2015. Available from http://services.parliament.uk/bills/2015-16/offpatentdrugs.html (Last accessed 26 September 2016).

9.3 EU guidance

EU Member States have adopted a variety of national rules and policies on pharmacy preparations and off-label use. This raises the question whether there is a need for EU harmonisation of legislation and/or policy to cope with the friction between patient needs in (a changed) clinical practice and the marketing authorisation requirement.[124] The EU may take into account the experiences and the best practices of the Member States such as those of the UK with the specials license. For off-label use the EU may consider the experience of France with the TRU, while it addresses the encountered difficulties. Even though harmonisation of legislation may not be required, or not even be within the EU's competences, the EU may outline the legal context to the Member States and disseminate knowledge on best practice policies. This may reduce Member States' uncertainty on the interpretation of the EU legislation with regard to pharmacy preparations and off-label use. The European Commission has initiated such a study in regard to off-label use, but the outcomes are to be awaited.[125]

10. CONCLUSION

The EU legislator and the Court of Justice have established a strict marketing authorisation requirement with the purpose to safeguard public health that, nevertheless, allows access to unlicensed medicinal products and off-label use of authorised medicinal products in order to satisfy patient needs. Recent case-law of the Court of Justice limited the legal space for the supply of medicinal products prepared by compounding centres acting as pharmacies, which subsequently may hamper patient needs. To ensure patients' access to such medicines would require either an amendment of the exemption for pharmacy prepared medicinal products in the Directive, or to allow the supply of medicinal products prepared by compounding centres under the exemption for named patient supply (art. 5 (1) Directive 2001/83/EC). Off-label use as standard treatment seems to be at odds with the purpose of the intent of the marketing authorisation system, and licensing of off-label therapeutic indications may be a suitable way forward. The EU may provide guidance on how to position off-label use as well as the recent changes in regard the practice of compounding centres in relation to the EU legal framework. Such guidance could enhance a right balance between a strict marketing authorisation requirement and patient needs for unlicensed medicinal products and off-label use in clinical practice in all EU Member States.

124 The extent to which the EU holds legislative powers to regulate off-label use should be further evaluated.
125 Weda (2016), *supra* note 11.

Chapter 4.2

Drug repositioning and repurposing: terminology and definitions in literature

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ABSTRACT

Drug repositioning and similar terms have been a trending topic in literature and represent novel drug development strategies. We analysed in a quantitative and qualitative manner how these terms were used and defined in the literature. In total, 217 articles referred to ‘drug repositioning’, ‘drug repurposing’, ‘drug reprofiling’, ‘drug redirecting’ and/or ‘drug rediscovery’. Only 67 included a definition ranging from brief and general to extensive and specific. No common definition was identified. Nevertheless, four common features were found: concept, action, use and product. The different wording used for these features often leads to essential differences in meaning between definitions. In case a clear definition is needed, for example from a legal or regulatory perspective, the features can provide further guidance.

INTRODUCTION

In 2004, Ashburn and Thor wrote their landmark article 'Drug repositioning: identifying and developing new uses for existing drugs', in which they outlined the opportunities for drug repositioning.[1] They stated that: 'the process of finding new uses outside the scope of the original medical indication for existing drugs is also known as redirecting, repurposing, repositioning and reprofiling'. Drug repositioning is believed to offer great benefits over de novo drug discovery, the traditional way of drug discovery by searching for a new active substance. Ashburn and Thor explained that the development risks would be reduced, because drug repositioning candidates could be developed quicker owing to the use of existing knowledge about the drug.[1] Since the well-known article by Ashburn and Thor, other authors have written about drug repositioning and similar terms.[2] Although Ashburn and Thor defined drug repositioning and suggested that the different terms they mentioned are interchangeable, the different scopes for which these terms are sometimes used by others suggest that they can have different meanings. For instance, Oprea and Mestres[3] related 'drug repurposing' to innovation with already approved drugs, whereas Allarakhia[4] included 'potential drug candidates' as starting material for drug repositioning. Moreover, the definitions used are often vague and unclear and seem to contain different elementsTerminology matters because it prevents misinterpretation and confusion. Weise et al. addressed the proper use of the term 'biosimilar', because they were concerned about the implications of misinterpretation and inconsistent use of this term, which could cause negative perception and impaired acceptance of biosimilars among prescribers and patients.[5] Neubert et al. searched for common definitions of 'off-label' and 'unlicensed use of medicines' for children,[6] because a shared definition among European Union (EU) member states was missing, which made comparison of use of medicinal products in children problematic.

Several governments worldwide are investing in drug repositioning and related activities. For example, the National Centre for Advancing Translational Sciences (NCATS) in the USA has launched the Discovering New Therapeutic Uses for Existing Molecules Programme. The aim of the programme is 'to improve the complex and time-consuming process of developing new treatments and cures for disease by finding new uses for agents that already have cleared several key steps along the development path'.[7] In the UK, researchers can apply for funding for repurposing clinical studies under the Developmental Pathway Funding Scheme of the Medical Research Council (MRC).[8] The Netherlands Organisation for Health Research and Development (ZonMw) funded a project about 'stimulation of drug rediscovery' which relates to drug repositioning.[9] However, these governmental organisations use a different definition than Ashburn and Thor.

In the future, drug-repositioning-related activities could be further stimulated to increase the number of new therapeutic uses that actually reach clinical practice. In the past, regulatory schemes have been established to provide incentives for specific drug development such as for orphan medicinal products and paediatric medicinal products. In the USA and the EU the number of orphan drugs increased substantially as a result of incentives such as specific market exclusivity and fee reductions.[10,11] Similarly, the development of paediatric medicinal products increased in the USA and the EU after the introduction of specific market exclusivity with regard to paediatric indications.[12–14] Under those regulations the definitions that establish what orphan medicinal products and paediatric medicinal products are, determine the applicability of the regulation to a specific product and subsequently whether it benefits from the incentives and has to comply with additional requirements.

Currently, there is no overview of the different terms used for the concept of drug repositioning and of definitions for those terms. In anticipation of the introduction of future incentives to enhance the concept of drug repositioning, we analysed the use of the term drug repositioning and similar terms in academic literature. Our aim was to analyse in a quantitative and qualitative manner how drug repositioning and similar terms were used and defined in academic literature, including an assessment of the nature and frequency of used definitions and differences and commonalities in their features.

APPROACH

We searched PubMed for all articles published until August 2013 using the keywords ‘drug’ AND (‘repositioning’ or ‘repurposing’ or ‘redirecting’ or ‘reprofiling’ or ‘rediscovery’) in the title or abstract. The search was limited to English language and journal articles, thereby excluding books, letters and assay guides.

Articles addressing the repositioning of drugs were selected regardless of the nature of the article (e.g. original research or commentary). However, articles in which the repositioning did not relate to drugs were excluded from the analysis, for example an article about the physical repositioning of implants. For articles with an abstract in PubMed the selection was based on the title and abstract. If no full-text copy was available in any library in The Netherlands, the authors were sent a request for a copy of that article. For articles without an abstract in PubMed a digital copy was extracted from the Utrecht University library to determine its relevance for further analysis. If no digital copy was available the article was excluded.

Articles were first scored for the use of the following terms: 'drug repositioning', 'drug repurposing', 'drug reprofiling', 'drug redirecting' or 'drug rediscovery'. Combinations such as 'drug repositioning or repurposing' were scored twice as 'drug repositioning' and 'drug repurposing'. In addition, other terms that were obviously related to drug repositioning but were not included in the PubMed search, were also noted.

Subsequently, the articles were searched for definitions of any of the abovementioned terms. If an article used several definitions for the same term (e.g. in the abstract and in the main text), the most detailed definition was selected for analysis. Any phrase that included an explanation of the meaning of drug repositioning, for example 'Drug repositioning, or drug repurposing, is …'[15] or 'A more efficient strategy for drug development is to …, so-called drug 'repurposing' or 'repositioning',[16] was considered as a definition. The definitions were analysed for features: particular commonalities or differences between definitions. Definitions that contained multiple references to the same feature were scored multiple times.

The articles were analysed in a quantitative manner for the use of the terms: 'drug repositioning', 'drug repurposing', 'drug reprofiling', 'drug redirecting' or 'drug rediscovery', as well as for definitions of those terms. The number of articles was assessed by year. The features were analysed in a qualitative manner by categorising the wording used for each feature. A chisquare test was performed to compare frequency of specific wording used in the definitions for drug repositioning and drug repurposing.

MAIN FINDINGS

In total, 511 articles were found based on the predefined search in PubMed. One or more of the terms drug repositioning, drug repurposing, drug reprofiling, drug redirecting or drug rediscovery were used in 217 of those articles (Figure 1). Before 2004 no articles about drug repositioning were found and the number of articles started to increase after 2010 in particular (Figure 2). The majority of the articles were published in 2012 and 2013, the year 2013 only included articles published until August 2013. Drug repositioning and drug repurposing were most often used in the selected articles. Of the 217 articles, 138 (64%) referred to drug repositioning and 126 (58%) to drug repurposing. Only five (2%) articles referred to drug reprofiling, five (2%) to drug rediscovery and three (1%) to drug redirecting. In total, 52 articles (24%) used drug repositioning and drug repurposing interchangeably.

A total of 67 (31%) of the 217 articles contained a definition for the used terminology (see Supplementary Material online for a full reference list). Ten examples of definitions as used in these articles are listed in Table 1. These definitions represent the range of definitions from nonspecific to specific as observed in those 67 articles. For instance Cheng et al. referred just to 'new usages'[17] whereas Sistigu et al. specifically stated: 'novel indication underscoring a new mode of action that predicts innovative therapeutic options'.[18]

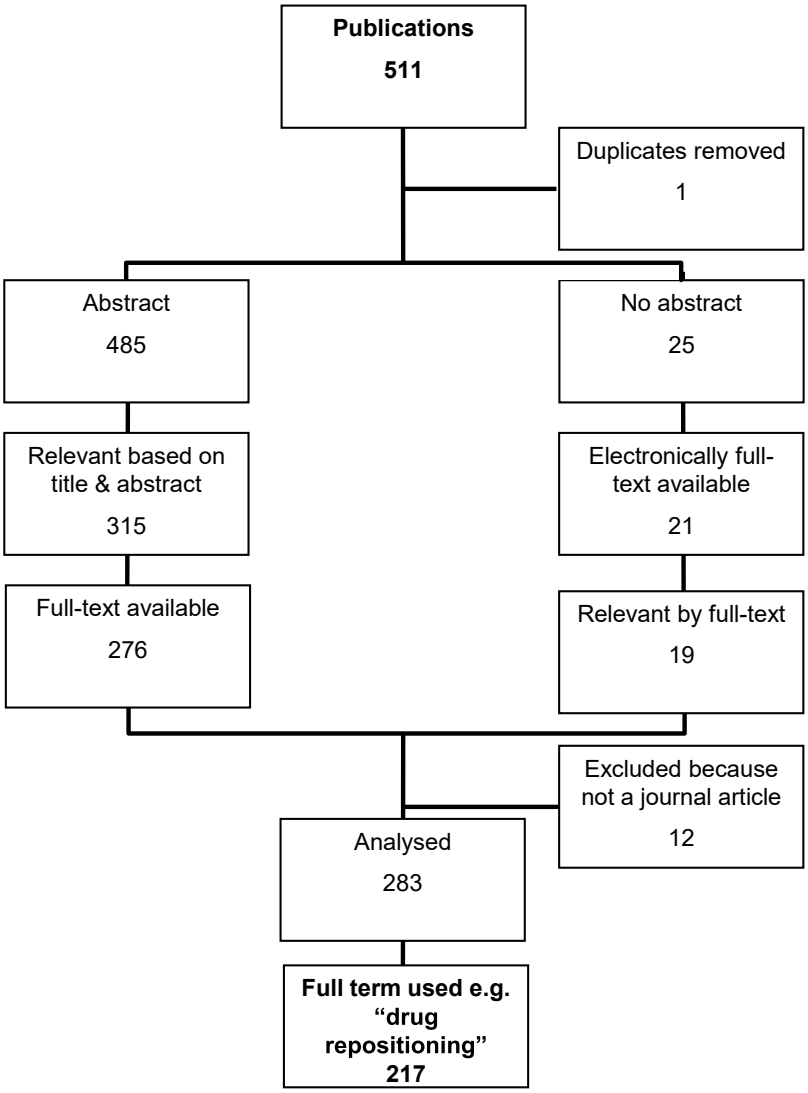

Figure 1: Overview of the results of the PubMed search and the articles eligible for analysis.

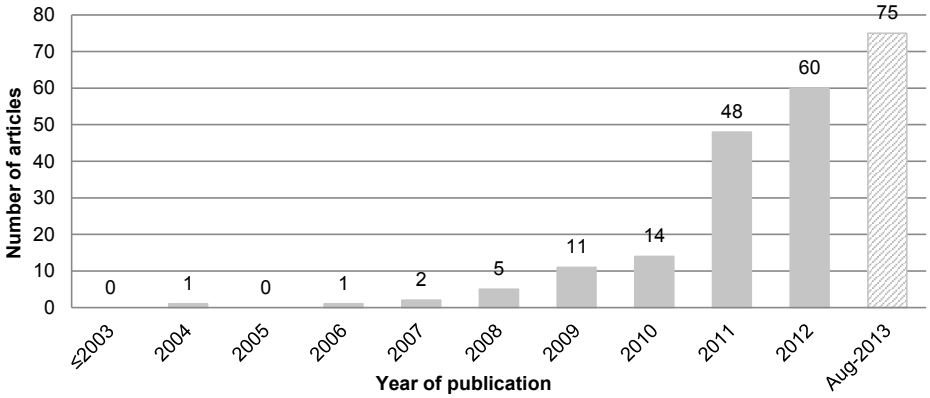

Figure 2: The number of articles using the terms drug repositioning, drug repurposing, drug redirecting, drug reprofiling or drug rediscovery per year.

Table 1: Examples of definitions of drug repositioning and drug repurposing used in the articles analysed.

Definition*	Refs
Drug repositioning is giving new usages for old drugs.	17
Drug repositioning is a concept to reuse existing drugs for new targets.	38
Drug repositioning and drug repurposing is finding a new use for an existing drug.	39
Drug repositioning and drug repurposing refers to the use of an old drug for a new indication.	40
Drug repositioning, drug repurposing, drug redirecting and drug reprofiling is the process of finding new uses outside the scope of the original medical indication for existing drugs.	1
Drug repositioning and drug repurposing is taking an approved drug that has already been optimized for safety and efficacy in a particular indication and obtain regulatory approval for novel therapeutic applications.	3
Drug repositioning refers to the utilisation of a known compound in a novel indication underscoring a new mode of action that predicts innovative therapeutic options.	18
Drug repositioning is a strategy for pharmaceutical R&D in which an established active pharmaceutical ingredient is applied in a new way — for example, for a new indication, and often combined with an alternative method of presentation, such as a novel delivery route.	23
Drug repositioning and drug repurposing is a strategy to find new uses for previously approved drugs and 'parked' or 'off the shelf' molecules that reached the clinic without any safety concerns but did not show sufficient efficacy against their intended primary disease target.	41
Drug repositioning involves finding new indications for existing drugs or potential drug candidates, including those in clinical development whose mechanism of action is relevant to multiple diseases; drugs that have failed to demonstrate efficacy for a particular indication during phase II or III trials but have no major safety concerns; drugs that have been discontinued for commercial reasons; marketed drugs for which patents are close to expiry; and drug candidates from academic institutions and public sector laboratories not yet fully pursued.	4

** The definitions were extracted from the context of the articles and sentences were re-phrased if necessary for grammatical reasons.*

In the definitions four features were identified based on the categorisation of wording used in the retrieved definitions: concept, action, use and product (Table 2). Concept relates to whether drug repositioning is a concept of drug development. It was included in 31 (46%) of the 67 definitions and was referred to as a strategy (n = 10), a process (six articles), an approach (n = 5) and other concept-related wordings (n = 10). The other three features were included in all definitions. Action relates to the main aim of drug repositioning. The action was referred to as: to identify (n = 31), to apply (n = 15), to develop (n = 6) and other action related wordings (n = 4). The feature product describes which type of product is involved in the action. It was referred to by a wide variety of terms including: drugs (n = 4), existing drugs (n = 33), approved drugs (n = 14), old drugs (n = 8), existing compounds (n = 7), abandoned drugs (n = 6), biologicals (n = 2) and other (n = 7). Use relates to what would be the new use, such as a medical application or therapeutic indication. It was referred to as use, usages, application, indication, disease, among others. Within this element three main categories were identified: definitions that refer to terms as use (n = 31), indication (n = 28) and other use-related wordings (n = 14). In all instances it was referred to as being new, novel, alternative, secondary, outside the scope of the original or similar terms indicating that for the purpose of drug repositioning the medicine was or will be used outside the original indication. As can be observed in Table 2, there was a great variety of wording used for the common features for each of the studied terms, often leading to essential differences in meaning between definitions used per term. Between drug repositioning and drug repurposing no disproportionality was observed in the use of specific wording for the common features mentioned in Table 2.

In addition to the five terms searched for in PubMed, six other terms were identified that were used as synonyms of drug repositioning namely: ‘drug re-tasking’,[19,20] ‘indication switching’,[21] ‘indication switch’,[22] ‘therapeutic switching’,[19,23] ‘indication expansion’,[20] ‘candidate or compound repurposing’.[24] The terms ‘in silico drug repositioning’,[15,25,26] ‘on-target repositioning’ and ‘off-target repositioning’[27] were used as a further specification of drug repositioning. In silico drug repositioning refers to drug repositioning by computational screening. On-target repositioning applies a drug’s known pharmacological mechanisms to different therapeutic indications and off-target repositioning attempts to elucidate still unclear pharmacological mechanisms for known molecules.[27] ‘Drug rescue’ was another term sporadically used in the context of drug repositioning, but seemed to have a different scope by specifically focusing on products that failed in the development for their primary intended purpose.[28,29]

Table 2: Number of articles referring to a specific category for each term.

	Drug repositioning	Drug repurposing	Drug redirecting	Drug reprofiling	Drug rediscovery	Total[b]
Total[a]	53	37	2	6	2	67
Use						
Use(s), usages, clinical use, application(s), therapeutic applications, therapeutic uses, modality of use	23	16		1	1	31
Indications, medical indications, therapeutic indications, disease indications, therapies	21	15	1	4		28
Other[c]	12	7	1	1	1	14
Product						
Existing drug(s)/medication(s), known drugs, existing pharmacotherapies	24	19	2	6	3	33
Existing approved drug, (FDA-)approved drugs/medicines, drug approved to treat one condition, previously registered drugs, approved pharmaceutical compounds, marketed drug	10	8			1	14
Old drug(s), established drugs, well-known drugs	8	3				8
Existing compounds, established drug compounds, established active pharmaceutical ingredient, known compound, existing pharmacopeia including failed candidate compounds	5	3			1	7
Abandoned drugs/pharmacotherapies, drug candidate, developmental drugs, developmental drug that failed for its primary intended purpose	3	4			1	6
Drug(s); not otherwise specified	4	1				4
Biological(s); not otherwise specified	1	1		2	1	2
Other[d]	6	6		1	1	7
Action						
Identification/identified/identifying/to identify, discovery/discovers, finding/to find, to seek, screening, to suggest	31	24	1	4	2	39
Applying/to apply/application, using/used/the use/ to reuse, the utilization, making alternative uses,	15	6			1	18
Developing/development, giving	6	4	1	3	1	7
Other[e]	4	5				6

Table 2: Number of articles referring to a specific category for each term. (continued)

Concept	Drug repositioning	Drug repurposing	Drug redirecting	Drug reprofiling	Drug rediscovery	Total[b]
Strategy	8	7				10
Process	6	4	1	3	1	6
Approach	4	3				5
Other[f]	8	8	1	2	1	10

Definitions that referred to multiple terms were scored for each term. Moreover, definitions that included multiple wordings to a feature were scored accordingly. For example, a definition that referred to 'drugs' and 'biological' was scored twice.

[a] *Number of definitions for this term.*

[b] *Total number of definitions for the five terms and the wording used in the definition per feature.*

[c] *For example effect(s), novel indication underscoring a new mode of action that predicts innovative therapeutic options and previously unrecognized, therapeutic activities.*

[d] *For example drugs that have failed to demonstrate efficacy for a particular indication during Phase II or III trials but have no major safety concerns; drugs that have been discontinued for commercial reasons; and marketed drugs for which patents are close to expiry and drug candidates from academic institutions and public sector laboratories not yet fully pursued.*

[e] *For example to obtain regulatory approval for novel therapeutic applications, to promote and to speed up the drug discovery process by identifying.*

[f] *For example action, concept and alternative to de novo drug development.*

DISCUSSION

This study showed that in literature a variety of terms and definitions were used for drug repositioning with drug repurposing as the most common and interchangeable alternative. The definitions identified in this study range from brief and general to extensive and specific. Although no notable differences were identified in the variety of definitions among the five terms mentioned, four features were identified in the definitions: concept, action, use, and product. All definitions contained the latter three features and about half of the definitions contained the feature of concept. However, authors used different wording per feature, often leading to essential differences between definitions, as outlined below.

Use

The identified definitions referred to new uses, usages, clinical use, therapeutics applications, indications, therapeutic indications, therapies and more. Despite the variety of terms, in essence all authors meant the treatment of a disease. The development of a drug for the treatment of new diseases might involve new patient populations, dosage forms or routes of administration. However, wording like a new 'application' does not necessarily mean the treatment of a new disease. It can also relate to the development of a drug for new patient populations, new dosage forms, routes of administration or line of treatment. For example, fentanyl was approved in the 1980s as solution for infusion and nowadays is authorised as nasal spray, transdermal patch, buccal tablet and lozenge for oromucosal use. Those new dosage forms and routes of administration would fall within the scope of drug repositioning as well, which is not necessarily the intention of a person who used 'new application' in a definition of drug repositioning. Less ambiguous wording could better indicate the intended scope of drug repositioning-related activities.

Furthermore, it should be considered what 'new' means. Most definitions refer to new as new, novel, secondary, alternative or outside the scope of the original medical indication. This raises questions regarding from which perspective the use should be new. For instance, would a use be new if previously mentioned in literature but not used in clinical practice? Or is a use considered new as long as it is not included in a marketing authorisation? From his point of view, off-label use, ranging from experimental, for example pregabalin for treatment-resistant insomnia,[30] to common practice, for example nifedipine as a tocolytic, could be a source for drug repositioning because it still might be considered as new.

Product

Authors used a wide variety of terms to indicate the product. Some referred to the product as a 'drug' leaving it open as to whether they meant an active pharmaceutical ingredient

or medicinal product complete with a dosage form and ready to be used. Furthermore, in the identified definitions the product often related to stages of the drug life cycle such as 'drug candidates', 'abandoned drugs', 'approved drugs' and 'old drugs'. However, from the definitions itself it is unclear what is meant by drug candidates, old drugs and abandoned drugs. Drug candidate could indicate that the active pharmaceutical ingredient is still under development for its first intended medical use, when it is discovered to be effective for the treatment of another condition, for example sildenafil for erectile dysfunction and duloxetine for stress urinary incontinence.[1,17] Old drugs could imply that the medicinal products are already on the market and intellectual property protection on the active pharmaceutical ingredient might have expired. An illustration is ibuprofen (Pedea®) which was authorised in Europe in 2004 for the treatment of patent ductus arteriosus, a heart problem in new borns. Abandoned drugs are drugs that failed for their primary intended purpose.

The wording used to describe the product affects the scope of drug repositioning. For instance, definitions that refer to 'new uses for old drugs' exclude new uses for drug candidates, abandoned drugs and recently approved drugs. Furthermore, references to terms such as 'existing drugs' are unclear as well, because they could include drug candidates and/or approved drugs.

The use of the more specific term drug rescue can be considered to indicate the development of new uses for failed or abandoned drugs.[28,29] Interestingly, 'withdrawn' medicinal products were not mentioned as candidates for drug repositioning, despite the fact that thalidomide is one of the most cited and famous examples of drug repositioning.[1,31,32]

Action

The main purpose of drug repositioning results from the wording used to describe the action feature. The action could be: (i) identification of new applications (i.e. screening of active pharmaceutical ingredients to discover or to suggest new uses); (ii) using drugs for new applications (i.e. off-label use in the treatment of actual patient); or (iii) the development of new applications (i.e. development towards a marketing authorisation).

Implications of the findings

Drug repositioning constitutes an emerging and dynamic field of drug development, which includes different and related activities, as is also implied by the wide variety of wording used for the identified common features. The increase in drug-repositioning-related activities, as indicated by the considerable increase in number of publications on this topic, shows that the observed inconsistent use of terminology and ambiguous

definitions might not be problematic from a practical point of view but could merely reflect the different origins and approaches taken by those involved in this dynamic and emerging field. However, currently, drug repositioning might not yet reach its full potential in terms of authorised new treatment options for patients. Many potential new uses are suggested in the literature, which have not yet found their way to clinical practice for example through the inclusion in a marketing authorisation.[21,33–35] As aforementioned, in the past, specific regulatory schemes have been established in similar situations where full benefits lagged behind the potential, such as for orphan medicinal products and paediatric medicinal products. To enhance drug repositioning further, similar incentives might be needed to stimulate this emerging field. From such a perspective a clear definition of drug repositioning and similar terms would be needed, because there would be consequences in terms of benefits and requirements attached to complying with the definition. Legal or regulatory reforms could also take into account how differences in regulatory frameworks (e.g. between the USA and the EU) affect drug development by the concept of drug repositioning, which could be examined in future studies.

The present analysis identified four common features in the definitions currently used in academic literature that could be helpful in constructing definitions in future legal and regulatory reforms to stimulate drug repositioning. In addition, based on our findings, academia, regulators and industry could become aware of the diversity in the current use of terminology and the potential ambiguousness of definitions. In this respect we encourage them to use the term they choose consistently in their own writings and to define it thoroughly by making well-considered choices on the intended scope of the chosen term. The scheme in Figure 3 displays the choices to consider.

Moreover, it might be useful to allocate different terms to different activities when defining terms for the concept of drug repositioning in future legal or regulatory reforms. This might require the use of terms not included in our analysis to clarify the distinction between activities. In this respect it should be noted that we studied terminology as used in academic literature. Outside academic literature terminology and definitions can be used that have not been reflected in academic literature, although a quick scan did not reveal a consistent use of well-defined terminology in other sources.[7,36,37]

A limitation of this study is that not all articles were full-text available (n = 43). This includes 39 of the 315 articles that were considered relevant based on title or abstract and four

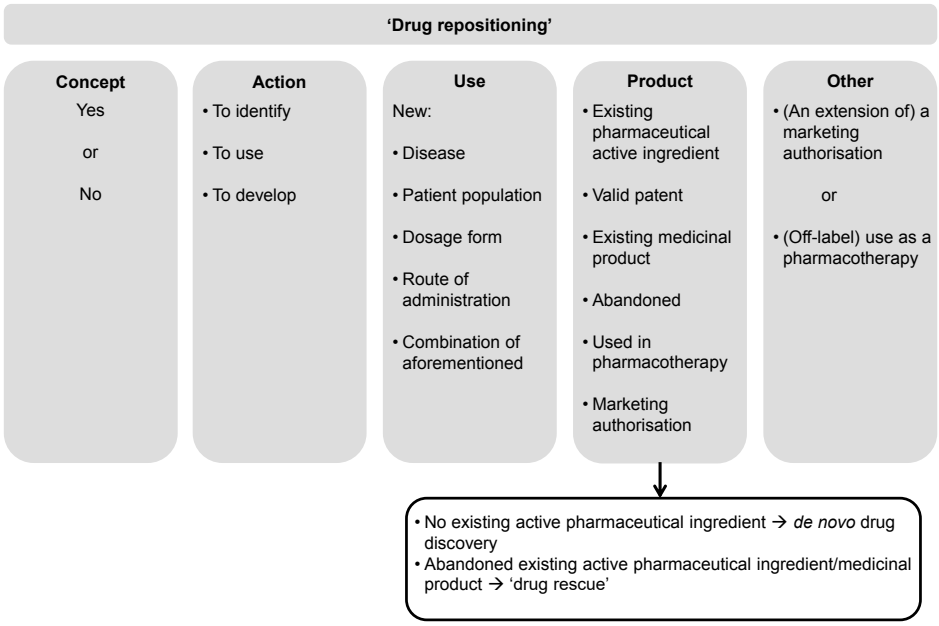

Figure 3: Choices regarding what to include and exclude in a definition of drug repositioning or a similar term.

of the 25 articles that had no abstract in PubMed. This limitation does not affect the meaning of our results, because the articles and definitions included in the study would outnumber the articles and definitions not included. Moreover, we performed an extensive PubMed search with few exclusion criteria. Besides, we checked Embase with the same search strategy, which resulted in a similar list of articles. Therefore, it was decided not to include other databases in this study. However, during the study other terms were identified that were obviously related to the terms that were used for the search. The PubMed search was not extended to those terms. Finally, although this study includes only articles up to August 2013, we have continuously monitored subsequently published literature regarding drug repositioning. We have not noticed any development that would change our conclusions. Therefore, we have no reason to assume that the inclusion of more-recent articles would yield different findings with regard to the consistent use of terminology and definitions.

CONCLUDING REMARKS

The term drug repositioning is frequently used in the literature and has several synonyms such as drug repurposing, which have been used interchangeably. No common definition

of drug repositioning or indeed for other similar terms has been found in the literature. Moreover, the definitions differed significantly in their wording used for the features, often leading to essential differences in their meaning. In the future, incentives might be established to stimulate drug repositioning and related activities that – from a legal or regulatory perspective – require clear terminology and a consistent definition. The four identified common features could provide further guidance in this respect.

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Chapter 5

General discussion

INTRODUCTION

Over the years the decline and the lack of efficiency in the pharmaceutical innovation has been (heavily) debated.[1–3] Various authors have highlighted that pharmaceutical industry delivers fewer new drugs to the market while costs involved have increased at the same time.[4,5] Drug innovation, however, is not limited to the development of new drugs. Innovation continues throughout the drug life cycle and includes both major discoveries (e.g. new therapeutic indications) and incremental improvements (e.g. improved dose regimes). Such innovation has been referred to as post-innovation innovation and is in principle subject to the complex drug regulatory system.[6,7]

In accordance with the drug regulatory system a marketing authorisation is required to place a medicinal product on the market.[8] In the marketing authorisation application, the pharmaceutical company submits data to the competent authority in order to demonstrate the quality, efficacy and safety of its medicinal product in the treatment of a specific disease (i.e. the therapeutic indication). The marketing authorisation application allows the competent authority to thoroughly assess the benefit-risk balance of the medicinal product. If a marketing authorisation is granted it includes official product information that summarizes the characteristics of the medicinal products, including the therapeutic indication and posology.

In the European Union (EU) a marketing authorisation can be obtained through four procedures.[8] The 'centralised procedure' allows a pharmaceutical company to apply for a union marketing authorisation, which is valid in all EU Member States. A union marketing authorisation is processed through the European Medicines Agency (EMA) and subsequently granted by the European Commission. In contrast, the 'national procedure' allows for a marketing authorisation application in a single member state and is processed and granted by a national competent authority. Via the 'decentralised procedure' (DCP) a pharmaceutical company can file for national marketing authorisations in multiple, but not necessarily all, member states through a single procedure. Once a national marketing authorisation has been granted in one or more member states, a pharmaceutical company can request other member states to recognise that marketing authorisation by issuing an identical marketing authorisation through the 'mutual recognition procedure' (MRP).

The marketing authorisation application for a medicinal product with a new active substance includes results from the pharmaceutical company's non-clinical and clinical studies.[8] In the EU such applications are referred to as 'full dossier' applications. For marketing authorisation applications for medicinal products with a known active substance the applicant may also make use of existing knowledge. For example, a pharmaceutical

company may substantiate the efficacy and safety of the medicinal product with a known active substance on data obtained from literature, which is known as a 'well-established use' application. For generic medicinal products the demonstration of efficacy and safety is based on the non-clinical and clinical data submitted for the innovator product, i.e. the original drug, supplemented with a demonstration of bioequivalence with the innovator product. Generic medicinal products therefore tend to be much cheaper than the innovator product. Once a marketing authorisation has been granted (regardless of the aforementioned types of application), the marketing authorisation holder may apply for an extension of the therapeutic indication or additional dosage forms.

To increase the probability to make a sufficient return on investment pharmaceutical companies tend to use a combination of patents and regulatory protection to create a period of exclusivity during which the company is essentially the sole manufacturer of a medicinal product.[9–12] Patents provide the exclusive right to commercialize an invention for a period of twenty years starting upon the patent application and may regard, for instance, the active substance or the use of a drug in a therapeutic indication.[9,10,13] The basic patent may be prolonged once with a maximum of five years through a Supplementary Protection Certificate as compensation for the time between the filing of the patent and the initial marketing authorisation.[14] Regulatory protection includes data exclusivity, market protection and market exclusivity. During the 8 years of data exclusivity upon approval of the innovator product, no generic product version can be licensed.[9,15] That period is complemented by 2 years of market protection during which licensed generic medicinal products cannot be placed on the market.[15,16] Finally, market exclusivity is specific for orphan medicinal products (i.e. medicinal products for rare diseases) and prevents approval of other medicinal products for the same therapeutic orphan indication.[17] Furthermore, the drug regulatory system encompasses regulations on pricing, reimbursement, prescribing and dispensing of medicines, which are covered by EU member states' national legislation.

Drug licensing has moved in the direction of continuous regulatory management throughout the life cycle, for example in form of pharmacovigilance activities.[18,19] Whereas the performance of the drug regulatory system in the early phase of the drug life cycle has been topic of extensive research, its performance in relation to post-innovation innovation has received much less attention.[18,20–26] This is especially true for the post-generic phase of the drug life cycle. In the post-generic phase of the drug life cycle new therapeutic uses can be discovered and ultimately become licensed. This thesis aimed to provide insight in the performance of the drug regulatory system for medicines in the post-innovation phase, including the post-generic phase, of their life cycle.

In this chapter we reflect on the knowledge gained from each study and put this in a broader (societal) perspective. Firstly, we focus on licensing failure in the EU's Decentralised Procedure (DCP) and the Mutual Recognition Procedure (MRP) and assess to what extent obtaining market approval constitutes an insurmountable obstacle for medicinal products with a known active substance. Secondly, we assess to what extent the EU drug regulatory system has proven to be able to license innovation in terms of new therapeutic indications and other uses in the post-innovation phase of the drug life cycle. Thirdly, we reflect on the legal context of post-innovation innovation within the drug regulatory system. We also discuss a number of challenges to be faced within the drug regulatory system to facilitate post-innovation innovation and provide suggestions for regulatory reform in order to enhance post-innovation innovation, especially in the post generic phase of the drug life cycle.

THE MARKETING AUTHORISATION PROCEDURE: AN INSURMOUNTABLE OBSTACLE?

Post-innovation innovation (e.g. new therapeutic indications for a known active substance) may become subject to the drug regulatory system through one of the licensing procedures. This can be as an extension of an existing marketing authorisation or as a new marketing authorisation. In the post-innovation phase of the drug life cycle a shift occurs in the preferred licensing procedures. Whereas new active substances are mostly licensed through the centralised procedure, medicinal products with known active substances are frequently licensed through the European DCP and the MRP.[27–30] Extensive research has been carried out on the performance of the centralised procedure, yet little is known about the performance of the other licensing procedures in terms of licensing failure: the refusal of a marketing authorisation by the regulatory authorities or the withdrawal of the application by the pharmaceutical company.[20–23,31,32] Knowledge about the reasons for licensing failure could boost the performance of these licensing procedures.

In chapter 2.1 we determined the frequency of and determinants for licensing failure of marketing authorisation applications submitted through the DCP. In chapter 2.2 we assessed the outcomes of licensing applications via the DCP and MRP and assessed determinants of licensing failure during CMDh-referral (Co-ordination group for Mutual recognition and Decentralised procedures – human). We defined licensing failure as a case where a company has applied for a license and the regulatory authorities have refused the application or the company has withdrawn the application.

In these chapters we found a similar licensing failure rate of 9.8% in the DCP and 7.9% in the MRP/DCP, respectively. Although the current studies on licensing failure use slightly different methods to estimate such rates, both our studies indicate a low licensing failure rate compared to applications via the EU centralised procedure (overall 27.1%[22] to 29%[23] and 34%[20] to 40%[21] specifically for new active substances) and approval procedures for new molecular entities in the United States (26.5%).[24]

The differences in failure rate are best explained by the large proportion – approximately 9 out of 10 - of marketing authorisation applications for known active substances (i.e. generic and hybrid applications) in the DCP and MRP. In such applications the efficacy and safety of the active substance are already known and the applicant refers to the efficacy and safety data of an already licensed medicinal product. Also, in the MRP the exact same medicinal product has already been licensed by at least one Member State while the applicant requests a marketing authorisation in one or more other Member States. Moreover, the low failure rate may be the result of efficient interaction between European regulators and the pharmaceutical companies to resolve deficiencies in the marketing authorisation application. At predefined moments in the assessment procedure regulators present their major objections and the applicant may submit additional data or clarifications.

Chapters 2.1 and 2.2 also provided insight in the reasons for licensing failure. Both studies observed a wide variety of deficiencies that may cause licensing failure. To that extent our results are comparable to previous studies on licensing failure.[23,24] However, we showed in chapter 2.1 that licensing failure was related to both clinical and quality deficiencies. For licensing procedures for new active substances quality deficiencies were infrequent.[23,24] Pignatti et al. argued that quality deficiencies may be resolved relatively easily throughout a licensing procedure.[23] Pharmaceutical companies may be especially inclined to do so for new active substances, given the considerable financial interests in the development of new medicines.

Given the wide variety of deficiencies in marketing authorisation applications that resulted in licensing failure, there seems to be no ‘magic bullet’ to target licensing failure. Licensing applications suffer from various (combinations of) deficiencies. Deficiencies in the licensing application may be best prevented by interaction between the regulators and the pharmaceutical company in an early stage for example through scientific advice. Compliance with scientific advice has been associated with marketing approval in the European centralised procedure.[22,33] Moreover, the reasons to withdraw a marketing authorisation application may be beyond the raised objections, such as a company’s business strategy and the focus of their product portfolio.

Overall, chapters 2.1 and 2.2 have shown that once a medicinal product has entered the regulatory assessment procedure in the DCP or MRP it is most likely to obtain market approval. It is fair to assume that these marketing authorisation procedures as such do not constitute an insurmountable obstacle. This is similarly true for marketing authorisation applications through the centralised procedure as was shown in literature.[20–23] This conclusion may be encouraging for pharmaceutical companies who intend to engage in post-innovation innovation. However, a limitation to this conclusion is the fact that no data are available on the number of medicinal products for which a licensing application was never submitted.

In future research, other regulatory procedures may be studied. For post-innovation innovation it would be particularly interesting to assess reasons for licensing failure in procedures to obtain approval for an extension of indication of an already licenced medicinal products.

LICENSING POST-INNOVATION INNOVATION: OPPORTUNITIES AND SUCCESSES?

Chapters 3.1 and 3.3 focused on licensing of post-innovation innovation on a European level. From a public health perspective, it is preferable that new indications are developed and the results are included in a marketing authorisation and product information. The application for authorisation allows for an in-depth benefit-risk assessment by the competent authorities and close monitoring of safety issues.[34] Moreover, after approval the new indications will be included in the official product information, e.g. the package leaflet. This provides physicians and patients with reliable information about the use of the product, including posology and potential side effects.

In chapter 3.1 we assessed the quantity and nature of extensions of indication of small molecule medicinal products authorised through the EU centralised marketing authorisation procedure with special attention for the impact of the introduction of a first generic product version. For 26 active substances included in our study we identified 53 extension of indication, which all applied to innovator products. Their occurrence is no surprise. It is common for pharmaceutical companies to increase the usage potential of their medicinal products by extending the therapeutic indications.[7,35] However, previous research did not relate the prevalence of extension of indication to the licensing of a generic competitor.[35,36] We have shown that 92.5% of the extensions of indication were approved prior to the approval of the first generic product version. Only four extensions of the therapeutic indication were approved thereafter.

Chapter 3.3 showed the occurrence of post-innovation innovation with well-known active substances in the EU. Of all medicinal products approved through the centralised marketing authorisation procedure in 2014 and 2015 we identified sixteen medicinal products with an active substance used before 2000 that were licensed for a new therapeutic indication (n=11) or other new innovation (n=5). Besides, two of the four extensions in the post-generic period as identified in chapter 3.1 were licensed as new medicinal products. The results from these two chapters indicate that in the post-generic phase of the drug life cycle post-innovation innovation is primarily licensed as a new marketing authorisation instead of an extension of an existing marketing authorisation. An important issue for further studies is the extent to which post-innovation innovation is licensed through the European DCP or the national licensing procedure in an individual EU member state.

An increase in post-innovation innovation is to be expected in the future based on four observations. Firstly, in chapter 4.2 we showed the increased attention for the development of new uses for known active substances. The number of publications in scientific literature related to that topic has soared between 2004 and 2013. Secondly, a number of governmental organisations have established specific drug development programs.[37] The NIH National Centre for Advanced Translational Sciences has launched a program to facilitate the collaboration between pharmaceutical industry and academia to develop new uses for existing drugs.[38] The UK's 'Developmental Pathway Funding Scheme' may fund the pre-clinical development and early clinical testing of "repurposing" of existing therapies.[39] Also non-profit organisations seek to develop known drugs for new uses such as the international collaboration project Repurposing Drugs in Oncology (ReDO) initiated in Belgium.[40] Thirdly, new innovative uses may be discovered and used in clinical practice without being assessed through an official licencing procedures (i.e. off-label use).[41] The high prevalence of off-label use in clinical practice suggests many more opportunities for innovative use in the post-innovation phase of the drug life cycles.[42–44] Finally, chapter 3.2 demonstrated that clinical research continues even after the introduction of a first generic product version. Within four years before and four years after generic approval almost 2700 and 2100 clinical trials, respectively, were identified for the 24 drugs in our cohort. For most drugs the number of clinical trials tended to halve post-generic, although the number of clinical trials as well as the ratio post:pre-generic varied substantially among drugs. Further research may assess the extent to which the identified clinical trials focus on new therapeutic purposes. Nevertheless, the substantial amount of clinical research conducted in the post-innovation phase of the drug life cycle is likely to yield some further innovation.

LEGAL CONTEXT OF POST-INNOVATION INNOVATION: CONSTRAINT OR GUIDING PRINCIPLE?

Medicinal products are heavily regulated from drug development to drug use. In chapter 4.1 we had a closer look at the European legal context related to post-innovation innovation. We specifically assessed the purpose and scope of the marketing authorisation requirement from a legal perspective. That analysis provided insight into the extent to which the marketing authorisation is considered a general rule as well as into to what extent the legal space for exemptions such as for pharmacy prepared medicinal products and (to a certain extent) off-label use applies. Based on an analysis of EU legislation and case-law we concluded that the EU legislator has established a strict marketing authorisation requirement with the purpose to safeguard public health, which has been confirmed and even underlined by the Court of Justice of the EU through a strict interpretation of the exemptions. The requirement of a marketing authorisation thus constitutes a general rule in the EU legislation on medicinal products.

Exemptions to the marketing authorisation requirement as a general rule are to be interpreted strictly. EU Directive 2001/83/EC allows pharmacies to compound medicinal products for which no marketing authorisation has been granted. That exemption, however, is of a limited nature as we discussed in chapter 4.1. Moreover, the marketing authorisation aims to safeguard public health through the assessment of the efficacy and safety of medicinal products for well-defined therapeutic indications. During the marketing authorisation procedure therapeutic indications are also frequently restricted by the regulatory authorities.[34] From these perspectives off-label use can be considered as an exemption to the regular practice in which medicinal products are used in accordance with their marketing authorisation. To accept pharmacy compounded medicinal products and off-label use of licensed medicinal products as standard therapy seems at odds with the intent of the drug regulatory system. Previous authors already emphasised that off-label prescriptions must remain an exception to the rule of the marketing authorisation.[45] *"In an ideal drug regulation framework, important applications in medical practice should not fall into the area of off-label use"* as was stated by Lenk and Duttge.[46] Accordingly, large scale pharmacy compounded medicinal products (or similar unlicensed medicinal products) and off-label use of licensed medicines may not be considered to be an adequate primary vehicle to provide patients access to post-innovation innovation. Consequently, for post-innovation innovation drug development programs it is more appropriate to aim for (an extension of) a marketing authorisation.

From a legal perspective terminology is particularly relevant. In chapter 4.2 we assessed definitions of drug repositioning, drug repurposing, drug reprofiling, drug redirecting and

drug rediscovery as used in literature. The definitions ranged from brief and general to extensive and specific. The definitions covered a wide variety of different and related activities. The terms may represent various drug development strategies based on an existing active substances as starting point and the aim to develop the drug for a new use, such as a therapeutic indication. Murteira et al. found a similar tangle of definitions for 'drug repositioning', 'drug repurposing' and 'drug reformulation'.[47] As long as the aforementioned terms are only used to indicate a phenomenon, their relative undefinedness and interchangeability may not matter. For any more formal (regulatory) use, however, it is important to provide a sound definition to prevent misinterpretation and confusion, for example if incentives or regulatory requirements would be established. Any such definition may also take into account the notion that post-innovation innovation should in principle become subject to the drug regulatory system through a marketing authorisation.

THE DRUG REGULATORY SYSTEM: UNDER PRESSURE?

On a European level the drug regulatory system originates from the 1960's. Initially the EU legislation only covered proprietary medicinal products, currently known as innovator medicinal products, developed through *de novo* drug discovery: a pharmaceutical company develops and licenses a medicinal product with a new active substance, for which it aims to obtain a sufficient return on investment during an exclusivity period where after generic product versions enter the market. The drug framework has performed reasonably well for decades for this drug development model.[48] However, a number of observations indicate that the drug regulatory system diverges from the needs in clinical practice and society's expectations of the regulation of medicinal products, which subsequently may affect the opportunities for post-innovation innovation.

Needs in clinical practice: pharmacy preparations, off-label use and potential new uses

More and more medicinal products are prepared by compounding centres, i.e. specialised pharmacies that prepare medicinal products on a larger scale and supply the medicinal products to other (local) pharmacies that dispense them to the patient, in order to satisfy patients' needs as licensed medicinal products are unavailable.[49,50] The needed medicine may have never been licenced or the manufacturer may have withdrawn its marketing authorisation for financial reasons. The increasing occurrence of drug shortages adds to the need for pharmacy compounded medicinal products.[51] Also local pharmacies tend to cease their compounding activities.[52] The Council of Europe has acknowledged the importance of (large scale) pharmacy compounded medicinal products for accommodating

the special needs of individual patients in two consecutive resolutions.[53,54] In contrast, the Court of Justice EU has determined that the EU legislation does not allow pharmacy compounding on stock that is not intended for delivery directly to patients supplied by the preparing pharmacy as was shown in chapter 4.1. Such medicinal products would require a marketing authorisation to be placed on the market.[55]

Next, a considerable amount of studies have been published that show the frequent occurrence of off-label use: to treat a therapeutic indication or population for which the medicinal product has not been approved.[42–44,56,57] For example, Radley et al. found that 21% of the overall medication use is off-label, while 73% of those uses were supported by little or no scientific evidence.[57] The prevalence of off-label use varies extensively among drug classes. In analgesics 6% and in medications to lower lipid levels 7% of the prescriptions have been reported as off-label, while among cardiac medications 46%, anticonvulsants 46%, and antiasthmatics 42% of the prescriptions were off-label.[57] In many cases, physicians rely on off-label use in the best interest of their patients' medical needs because a satisfactory on-label treatment is not availible.[58] They could even be obliged to consider off-label use instead of an on-label treatment, if the off-label use is in the best interest of the patient.[59] Besides in a recent case the EU General Court concluded that off-label prescribing is not prohibited, or even regulated, by EU law.[60] These states of affairs regarding pharmacy preparations and off-label use indicate tension between the needs in clinical practice and the drug regulatory system.

Moreover, research on existing drugs continues even after generics have entered the market as discussed in chapter 3.2 and many potential new therapeutic indications are suggested in literature that have not yet found their way to clinical practice.[61,62] For instance, Siles identified three potential new antifungal medicines out of 1,200 FDA approved medicinal products.[63] Bertolini, Sukhatme and Bouche listed twelve well-known active substances with potentially effective in cancer treatment based on at least one randomized clinical trial.[64]

Society's struggle with the need to license

Current practice in various EU member states highlights society's struggle with the marketing authorisation as a general rule (chapter 4.1). In specific cases off-label use, pharmacy compounded medicinal products and other unlicensed medicinal products are used for their financial benefits. A prime example is the use of Avastin (bevacizumab) that is licensed for a number of oncology indications, but is used off-label for the treatment of wet macular degeneration, instead of the more expensive on-label use of Lucentis (ranibizumab), in many EU Member States.[65] Some EU Member States, e.g. France and

Italy, have apparently adopted or amended legislation on off-label use with the intent to allow off-label use for financial reasons, such as with Avastin/Lucentis.[66]

In 2011, France introduced the so-called "Temporary Recommendations for Use" (TRU). A TRU can be granted if on the behest of government organisations or patient advocacy groups, the French competent authority establishes a beneficial benefit-risk balance of an off-label treatment based on data provided by the concerned pharmaceutical company or companies.[45,66] The TRU ensures reimbursement of the medical product in the off-label treatment and obliges the marketing authorisation holder(s) to collect data to support the efficacy and safety and apply for an extension of indication through the regular procedures. The TRU legislation was introduced to control off-label use and to satisfy unmet medical needs. Initially, a prerequisite for a TRU was the absence of an appropriate alternative licensed medicine.[67] In 2012, France aimed to change that condition to 'no appropriate alternative medicine with a marketing authorization […] unless a significant impact for the national health insurance may be avoided', but considered the explicit financial consideration to be in violation with drug regulatory system.[66] Nevertheless, in 2014, a TRU became possible in case 'no medicine with the same active ingredient, dosage and pharmaceutical form with a marketing authorisation was available', which allowed the approval of a TRU for the use of Avastin over Lucentis.[66]

A similar process occurred in Italy. In 1996, off-label use had been prohibited and medicines used off-label were not reimbursed by social security schemes unless the off-label use was included in a list of Italy's competent authority.[68] As a prerequisite to be included on the list there should be no valid therapeutic equivalent. The law was amended in 1998 to allow off-label use if according to the physician the patient could not be treated with an on-label alternative. However, in 2014 the law was amended again in order to allow the Italian competent authority to place medicinal products on the approved off-label list even if authorised therapeutic alternatives are available and for reasons of costs and suitability criteria.[59,69]

Society's struggle with the marketing authorisation as a general rule becomes also apparent in the regulatory decision making. The Dutch Health Technology Assessment agency (Zorginstituut Nederland), for example, has advised to reimburse Avastin instead of Lucentis for the treatment of macular degeneration. It deemed both products equally effective and safe while substantial savings may be established by the use of Avastin.[70] Concerns on off-label use practice in EU member states have been addressed in the EU parliament.[71,72] The European Commission has issued a study on off-label practice in individual member states and will determine the need for coordination off-label practice at EU level.[73]

Another example of such societal struggle is the recent debate in the Netherlands on the use of the licensed Amfexa (dexamfetamine) in the treatment of attention deficit hyperactivity disorder (ADHD) instead of pharmacy compounded medicinal products.[74] The more expensive Amfexa was not fully covered by the health insurance scheme, while dexamfetamine pharmacy preparations were. Politicians also frequently refer to Tecfidera (dimethyl fumarate) as an example of undesirable drug development.[75,76] Tecfidera is approved for the treatment of multiples sclerosis, while cheaper pharmacy compounded medicinal products that contain the same active substance are used to treat psoriasis, as outlined in chapter 3.3. With reference to products such as Amfexa and Tecfidera the Dutch Minister of Health noted that licensing is important, but not at all costs. She intends to explore the possibilities to establish additional rules to prevent a substantial price increase once a pharmacy prepared medicinal product becomes licensed.[74,75]

Society's struggle is also displayed in literature. Dooms et al. have proposed a more pragmatic use of pharmacy-compounded products and evidence-based off-label use of already licensed medicinal products in the treatment of an orphan disease.[77] They argue that prior to the licensing various orphan medicinal products were already available as much cheaper pharmacy compounded medicinal products and off-label use of licensed medicinal products. By those means orphan drug development should focus on unmet medicinal needs.

Lack of incentives for a viable business case

Drug development of a medicinal product in general requires substantial investments. For post-innovation innovation the drug development costs may vary depending on the availability of data about the quality, efficacy and safety of a medicinal product. Nevertheless, further investments may be needed to conduct (additional) clinical trials. For example, as outlined in chapter 3.3, additional clinical trials have been conducted in the development of Tecfidera in the treatment of multiple scleroses. The out-of-pocket costs for phase III drug development for a new active substance have been estimated at 200 to 235 million dollar.[2,78] Additional Phase I and II studies may also be required, for example if the drug is administered in substantial higher doses than the licensed medicinal product.[41] Extensions of indication as studied in chapter 3.1 may require similar investments to study the efficacy and safety in a new therapeutic area. This suggests that post-innovation innovation may require a large investment to establish the efficacy and safety of a known active substance for a new therapeutic indication.

Pharmaceutical companies may recoup development costs during a period of exclusivity. However, adequate tools to establish an exclusivity period as incentive to licensing new therapeutic indications for known active substances are lacking.[59,79,80] Therefore, new

therapeutic indications for known active substances, including off-label uses and uses of pharmacy compounded medicinal products, may not be licensed.[58,81] In the introduction, as well as in chapter 3.1, we noted that pharmaceutical companies benefit less from extension of indications once a generic product version enters the market. Their product may be substituted by a generic product version even for new therapeutic indications.[80] This limits the company's opportunities for a sufficient return on investment. Also off-label use may diminish a company's incentive to apply for an extension of its indications since licensing the off-label use may not enlarge the usage potential of their product.[79] Incentives such as those for paediatric and orphan medicinal products only apply in certain cases, and may still suffer from off-label use of equivalent medicinal products. This lack of incentives constitutes a major obstacle to pharmaceutical innovation and has been considered "one of the greatest impediments to medical progress."[82] As noted previously in chapter 3.3, many of the successful drug repositioning cases may therefore be licensed as new medicinal product with full dossiers.

Furthermore, pricing and reimbursement policies, which are a national responsibility of EU member states, have a strong effect on the opportunities to earn a sufficient return on investment in post-innovation innovation. For example, in the Netherlands reimbursement of a medicinal product may be limited to (average) drug prices of all medicinal products within the same therapeutic class. For various therapeutic classes this average price is too low for pharmaceutical companies to recoup their investments, if they would develop and license a medicinal product within that therapeutic class. The reimbursement limit may even be below the current retail price of pharmacy compounded medicinal products.

Besides, the factors that affect the viability of the business case may be different for large and small pharmaceutical companies. Large pharmaceutical companies tend to develop their products on a global level, or with a focus on large markets such as the United States. The intellectual property prospects constitute a key driver for the drug development programs of large pharmaceutical companies.[83] Smaller companies may be more nationally orientated. Their drug development strategy may be more susceptible to national pricing and reimbursement policies.

Consequences for post-innovation innovation

The combination of the need for pharmacy preparations, off-label use and potential new uses, society's struggle with the need to license new uses of existing drugs and the lack of adequate incentives to do so, suggests that the drug regulatory system is under pressure. Apparently there are needs that cannot be fulfilled with the products within the drug regulatory system. On the one hand the development of new uses for known active substances is believed to offer great benefits over *de novo* drug discovery since it would

be quicker and cheaper than *de novo* drug discovery.[84] On the other hand, in the current drug regulatory system post-innovation innovation may not be a panacea for access to new and licensed treatment options at similar costs of generic and pharmacy prepared medicinal products.

REGULATORY REFORM TO ENHANCE CONTINUOUS INNOVATION

Every new drug is a potential old drug, and ideally regulators, pharmaceutical industry and others aim to use every drug to its full potential. The observed pressure on the drug regulatory system indicates that the current system does not facilitate that potential, at least not in the later phase of the drug life cycle. Regulatory reform may be needed to facilitate post-innovation innovation. In the past the drug regulatory system already has proven not to be static. It has been amended several times to adapt to society's needs. For instance, in 1993 the possibility to license medicinal products under exceptional circumstances was established, followed by the opportunity for a conditional marketing authorization in 2000.[85] Furthermore, in the EU the paediatric regulation entered into force in 2007 with the purpose to stimulate the development of medicines for children.[86] Amendments to the drug regulatory system continue. The EMA has recently finished a pilot on the concept of adaptive pathways, which it will continue to explore in the future.[87] Adaptive pathways form a progressive approach based on existing regulatory tools, e.g. conditional marketing authorisation, to license a medicinal product first in a small patient population with an unmet medical need and to collect additional data over time to extend or restrict its authorised indication. For the major challenge to post-innovation innovation identified in this thesis, i.e. using old medicines to their full potential through further development and obtaining an official market approval for a new use, three options for regulatory reform mentioned in literature may provide solutions: establishment of reasonable intellectual property prospects, the introduction of a stakeholder driven system, and to radically change to the regulatory benefit-risk assessment.

Reasonable intellectual property prospects

As aforementioned the current intellectual property and regulatory protection may regularly not provide adequate exclusivity to earn a sufficient return on investment to license an existing drug for a new use. The provision of adequate exclusivity through the existing intellectual property and regulatory protection or the establishment of new protection mechanisms could boost post-innovation innovation.

A pharmaceutical company can obtain a new use patent and/or additional data exclusivity for a new therapeutic indication of a licensed medicinal product. The problem with such

rights is, as Roin stated, that they are useless to a pharmaceutical company if it cannot enforce those rights.[82] Pharmaceutical companies cannot detect when patients use a generic medicinal product for the protected indication. They lack the infrastructure to enforce their rights, i.e. they do not have access to information relating to the therapeutic indication for which a patient uses a medicinal product. Also pharmacists are frequently unaware of the therapeutic indication of a prescription.[88] Roin has proposed to use e-prescribing and electronic medical records to provide companies insight in the therapeutic indications of prescription and so to be able to enforce their rights with regard to new uses for known active substances.[82] In the Netherlands prescribers already have to state the indication on the prescription when prescribing one of 23 listed medicines in order to enable pharmacists to ensure safe use of medicines.[89] For the purpose of enforcement of intellectual property rights such an approach may have its downsides. Physicians may misreport indications, or commit fraud, especially if drug reimbursement depends on the therapeutic indication.[82] Moreover, further research is needed to assess the legal implications of Roin's proposal, for example, regarding patient privacy interests as well as possible solutions such as de-identification of the medical records.[82] On the upside if therapeutic indications would be included in the prescriptions is that this could contribute to the establishment of the efficacy and safety of a medicinal product in an off-label use and potentially to the licensing of the off-label use.[88]

Next, society has the perception that pharmaceutical companies misuse intellectual property rights to demand prices for new uses of existing drugs that society considers too high.[48,90] That tendency may result in legal and regulatory reform of intellectual property rights and regulatory protection. The Dutch Minister of Health announced that she would discuss the need for a reform of the intellectual property and regulatory protection among her counterparts during the EU presidency of the Netherlands in 2016.[91] She is especially concerned about the unintended effects of market exclusivity provided to orphan medicinal products that may have resulted in restrictions of the therapeutic indications by pharmaceutical companies and high drug prices. At the same time the European Commission is going to assess the functioning of the Supplementary Protection certificate.[92] In that context, the Dutch minister of Health intends to discuss the functioning and appropriateness of the Supplementary Protection Certificate on a EU level.[93] While assessing opportunities for legal and regulatory reform to prevent the (perceived) misuse of intellectual property rights, policy makers could also take into account the opportunities to ensure adequate exclusivity in order to establish a viable and sustainable business case for post-innovation innovation.

Towards a stakeholder driven system

Since the introduction of the drug regulatory system the primacy to apply for an extension of indication of a licensed medicinal product has been with the marketing authorisation holder (the pharmaceutical company).[94] The competent authorities will not asses the benefit-risk balance in a new therapeutic indication as long as the marketing authorisation holder has not submitted an application. It has been suggested that the drug regulatory system may need to abandon this industry driven nature since pharmaceutical companies may regularly lack an incentive for post-innovation innovation.[64,95] In the United Kingdom, members of parliament have proposed the 'Off-patent drugs bill'.[95,96] This bill should initiate an obligation for the Secretary of State to apply for a license for off-label uses of off-patent medicinal products. The bill was supported by a wide range of patient advocacy groups, charities and research organisations.[97] However, the Minister of State at the Department of Health blocked the bill's proceedings by withholding governmental support.[98] The government is of the opinion that patients already have access to new uses of existing drugs through off-label use and prefers to seek a non-legislative solution to increase access to off-patent drugs.[98,99]

Likewise, other stakeholders, e.g. medical associations, could be allowed to submit an application for an extension of indication of a marketing authorisation, including the required scientific data to perform a benefit-risk assessment. Any such change may face serious challenges both from a practical perspective and a more fundamental perspective as a marketing authorisation holder's right of self-determination could be considered to become limited. However, pharmaceutical company's may already face a compulsory licence based on article 31 of the TRIPS Agreement.[100] A compulsory license granted by the government allows a third party to use a patent or other intellectual property right, provided that attempts have been made to reach an agreement with the right holder on reasonable commercial terms and conditions. Furthermore, for plant protection products – which are also subject to strict licensing requirements – third parties can apply for an extension of the authorisation to a use that is minor in nature provided that the extension is in the public interest (art. 51 Regulation EC No 1107/2009). The third party needs to submit the documentation and information to support the application for the extension of use. In the Netherlands the submission of such applications has been allocated to the Trustee Special Authorisations which was established by the stakeholders (i.e. manufactures, suppliers and users of plant protection products).[101] The user of the product is in principle liable for any damage resulting from the use in the newly approved uses, but the trustee also arranged insurance coverage for damages due to those third party extensions of use.[101] These examples show that third parties may interfere with what could be considered as a company's control over its possession.

The establishment of a stakeholder driven drug regulatory system requires further research to assess obstacles and policy options, for example with regard to liability issues and the right to property. In general, pharmaceutical companies, as manufacturer and marketing authorisation holder of a medicinal product, could be held liable for product defects under the Product Liability Directive (Directive 85/374/EEC). But it may be questioned to what extent marketing authorisation holders should be responsible for extensions of indications applied for by third parties and whether there are alternative models to regulate liability issues. Next, both natural and legal persons are entitled to the peaceful enjoyment of their possessions in accordance with article 1 of Protocol 1 of the European Convention on Human Rights.[102,103] It needs to be assessed to what extent the possibility for third parties to apply for an extension of indication is compatible with the right of possession. Potential obstacles, however, should be no reason to refrain from further research into the possibilities of a stakeholder driven system.

Radical changes to the regulatory benefit-risk assessment

Some researchers have proposed a more radical change of the drug regulatory system. Moors, Cohen and Schellekens have debated the failure of the drug regulatory system including the patent system for the development of new drugs.[48] They proposed a drug regulatory system which concentrates on quality issues, manufacturing and distribution of medicinal products, while intellectual property protection should be restricted to substantive innovations. The efficacy and safety could be assessed by the medical and scientific community based on publicly funded research. Similarly Actal, a Dutch advisory board to the government and parliament that focuses on regulatory burden, has advised the Dutch Minister of Health in Augustus 2015 to explore the opportunities for reforms to the drug regulatory system, especially to license medicinal products based on their mechanism of action rather than for specific therapeutic indications.[104,105] This would diminish the regulatory burden in the development of new drugs and increase patient access to medicinal products upon new evidence.

An approach as proposed by Moors, Cohen and Schellekens or Actal could be beneficial to post-innovation innovation as well. In a recent report on off-label use commissioned by the European Commission treatment guidelines were considered as an important tool to facilitate responsible off-label use by various stakeholders.[88] Physicians and other health care professionals already assess the benefits and risks of such uses and decide on inclusion of off-label uses and pharmacy preparations in treatment guidelines. The assessment of the efficacy and safety in medical practice also aligns with initiatives such as PatientsLikeMe, in which patient increasingly take control over their health and assesses medical treatment themselves through their own platforms.[106,107]

These examples also raise questions about the need for an official benefit-risk assessment for a well-defined therapeutic indication in its present form. If society considers medical guidelines to be adequate tools for assurance of the efficacy and safety of drug uses, this implies that there may be no need for a thorough licensing procedure by a competent authority. Accordingly, the assessment of efficacy and safety in the context of treatment guidelines may be sufficient for the initial therapeutic indication of a new drug. Moreover, clinical trial data may become increasingly transparent and allows for an adequate benefit-risk assessment by health care professionals and academics.[108,109] Consequentially, competent authorities could limit their assessment to the quality and manufacturing issues, and potentially a limited review of the drug's safety. This would save pharmaceutical companies and regulators valuable resources.

An increase in uncertainty about efficacy and safety may pose a concern when the requirement for a formal benefit-risk assessment by a competent authority is abandoned. However, so far a certain level of uncertainty is accepted by society for off-label uses. Besides, some authors have argued that regulators should not excessively focus on risks and uncertainties, since such an approach may withhold patients from therapeutic options.[107] They also argued that when regulators consider the acceptable level of uncertainty, they should take into account the opportunity costs: the resources needed to rule out certain risks which cannot be allocated to other research initiatives with a higher public health gain.[107] Furthermore, new regulatory approaches such as the adaptive pathways initiative point towards the acceptance of a higher uncertainty by regulators and society,[110] although the adaptive pathways initiative has been subject to fierce criticism for lowing the regulatory bar and the exposure of patients to high risks.[111]

Obviously, abandoning a formal benefit-risk assessment by a competent authority requires further studies into legal matters and policy options, as well as into consequences for drug development itself. Various questions arise, such as, how should liability issues be regulated, to what extent is pharmaceutical promotion allowed, what is to be included in the patient information, how are intellectual property rights affected, will patients be willing to participate in placebo controlled trials, how could a transition from the current drug regulatory system be managed? Nevertheless, if society truly wishes to adhere to the need for a benefit-risk assessment as part of the licensing procedure, it may also need to adopt a different mindset regarding post-innovation innovation. Society may need to choose between the principles of the drug regulatory framework it established or the reduced cost and other benefits of circumventing that system.

CONCLUSION

The individual studies in this thesis generated empirical data on post-innovation innovation and the EU licensing procedures. They provide insight in the performance of the drug regulatory system for medicines in the post-innovation phase, including the post-generic phase, of their life cycle.

Post-innovation innovation does take place and licensing procedures themselves seem not to constitute an insurmountable obstacle to post-innovation innovation. Pharmaceutical companies obtain approval for new therapeutic indications of their products, but a very limited number of such extensions of indication were approved after the approval of a first generic product version. There seem to be ample opportunities for post-innovation innovation given the continuation of clinical trials, the initiation of projects to develop new uses of existing drugs, and the high prevalence of off-label use. From a legal perspective the marketing authorisation requirement constitutes a general rule in the current framework. Based on that principle, initiatives to develop new uses for known drugs should aim for (the inclusion in) a marketing authorisation. A major obstacle for post-innovation innovation in the post-generic phase of the drug life cycle relates to the lack of incentives for a viable business case – the opportunity to earn a decent return on investment – due to the absence of adequate tools to establish an exclusivity period in regard to a new use of known active substances. The current drug regulatory system is under pressure and not able to optimally facilitate post-innovation innovation. This thesis aims to contribute to the ongoing debate on society's pursuit of new as well as affordable treatment options. Regulatory reform may be needed to use every drug to its full potential.

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Chapter 6

Summary and samenvatting

Chapter 6.1

English summary

SUMMARY

Drug innovation continues after the initial development of a medicinal product, which is also known as 'post-innovation innovation'. Such innovation includes major discoveries, such as new therapeutic indications for which a medicine can be used, as well as incremental innovations, such as the development of new dosages forms, enlargement of the target population and improvements in drug formulations. The development of new therapeutic indications for existing drugs (i.e. drug repositioning), could allow for a quicker and cheaper drug development by the utilisation of current knowledge of the drug, e.g. pharmacokinetic and safety data, compared to *de novo* drug discovery. **Chapter 1** addresses the introduction of a first generic product version, and with that occasion the start of the post-generic phase of the drug lifecycle, as a specific and important moment in the drug life cycle which has several consequences for public health and further innovation. In the post-generic phase the active substance is available for further innovation at low costs. Literature already contains many references to potential new therapeutic indications for existing drugs as well as methods to identify such uses. However, the introduction of a generic product version may also significantly affect the intellectual property prospects of a drug and may limit the opportunities to make a return on investments in innovation during the post-generic phase of the drug life cycle. Pharmaceutical companies may benefit less from extensions of the indication after the approval of a first generic product version than during the initial period of exclusivity, because their products may be substituted by these generic product versions, even for new therapeutic indications. Besides, new therapeutic uses may become common practice as off-label use or as the use of pharmacy prepared medicinal products. The drug regulatory system itself may consequently play an important role in post-innovation innovation. It regulates, for example, the extent and duration of the exclusivity period for new innovations and determines the criteria for the licensing of generic product versions. From a public health perspective it is important that new therapeutic indications and other innovations are not only developed but also licensed. The licensing procedure allows for an in-depth benefit-risk assessment by the competent authorities and ensures the availability of information about the use of the medicinal product, including posology and potential side effects, in the official product information, e.g. the package leaflet. The aim of this thesis is to provide insight in the performance of the drug regulatory system for medicines in the post-innovation phase, including the post-generic phase, of their life cycle from both a regulatory and a legal perspective.

In **chapter 2** we studied licensing failure in the European Union's (EU)Decentralised Procedure (DCP) and the Mutual Recognition procedure (MRP) as those two procedures are frequently used to obtain approval for generic medicinal products. The results of

these studies may help to indicate to what extent obtaining market approval constitutes an obstacle for medicinal products with a known active substance. In **chapter 2.1**, we determined the frequency of and determinants for licensing failure of marketing authorisation applications submitted via the DCP. We assessed marketing authorisations application procedures that were submitted between 2008 and 2012 with the Netherlands as leading authority and assessed the nature of remaining major objections. In total 492 procedures were completed during the study period, of which 48 (9.8%) failed: 8 were refused, 40 were withdrawn. The procedures were about as often withdrawn or refused after day 70 (n = 12) as after day 120 (n = 7), 180 (n = 12) or 210 (n = 10). For 7 procedures, no day 70 assessment report was available, leaving 41 procedures for analysis of the major objections. A total of 93 major objections were identified in 34 of the procedures. The nature of the major objections varied widely and included both quality (48 major objections) and clinical (45 major objections) issues. The relative low failure rate identified in our study may be related to the regular interaction between competent authorities and applicants during the procedure. Some degree of licensing failure may be inevitable, as failure may also be affected by the financial feasibility or willingness to resolve major objections, as well as other reasons to withdraw an application besides the raised major objections.

Subsequently, in **chapter 2.2** we focused on licensing failure in the DCP and MRP. We provided a comprehensive overview of the outcomes of marketing authorisation applications via those procedures and assessed determinants of licensing failure during CMDh (Co-ordination group for Mutual recognition and Decentralised procedures–human) referral procedures. We analysed all MRP/DCP procedures to the CMDh from January 2006 to December 2013 and scored the reasons for starting a referral procedure. In addition, we conducted a survey under pharmaceutical companies to estimate the frequency of licensing failure prior to CMDh referrals. During the study period, 10392 MRP/DCP procedures were finalised. Three hundred seventy-seven (3.6%) resulted in a referral procedure, of which 70 (18.6%) resulted in licensing failure, defined as refusal or withdrawal of the application. The frequency of CMDh referrals decreased from 14.5% in 2006 to 1.6% in 2013. Of all referrals, 272 (72.1%) were resolved through consensus within the CMDh, the remaining 105 (27.8%) were resolved at the level of the Committee for Medicinal Products for Human Use (CHMP). Most referrals were started because of objections raised about the clinical development program. Study design issues and objections about the demonstration of equivalence were most likely to result in licensing failure. An estimated 11.1% of all MRP/DCP procedures resulted in licensing failure prior to CMDh referral. Whereas the absolute number of MRP/DCP procedures resulting in a referral has reduced substantially over the past years, no specific time trend could be observed regarding the frequency of referrals resulting in licensing failure. This study

suggested that the increased knowledge at the level of companies and regulators has reduced the frequency of late-stage failure of marketing applications via the MRP/DCP.

In **chapter 3**, we studied to what extent the drug regulatory system allowed for innovation in the form of licensing new therapeutic indications and other new uses during the post-innovation phase of the drug life cycle. In **chapter 3.1**, we assessed the quantity and nature of extensions of indication of small molecule medicinal products authorised through the European Medicines Agency (EMA) throughout the drug product lifecycle with special attention for the impact of the introduction of a first generic competitor. We extracted the small molecule medicinal products authorised since the beginning of the EU centralised procedure, including those later withdrawn, up to 31 August 2013 from the EMA-website. We selected the medicinal products with active substances first authorised in the EU through the EMA and grouped the medicinal products by active substance. Active substances were eligible for further analysis, if the first generic product version per active substances had been licensed market for at least one year. Per active substance, the medicinal products' European Public Assessment Reports were screened for references to 'extensions of indication'. Initial new indications of subsequent products (with the same active substance) were also considered as an extension of indication. Extensions of indication were only counted the first time an indication was approved per active substance. We found 26 active substances with one or more generic product versions with a follow-up period of at least one year, leading to a data set which comprised in total 186 products: 65 innovator products and 121 generic products. The median number of innovator and generic products per active substance was 2 [interquartile range (IQR) 2–4] and 4 (IQR 2–6), respectively. The median length of the innovator period was 11.2 years (IQR 11.0–12.3 years), whereas it was 3.6 years (IQR 2.5–4.1 years) for the generic period. We identified 53 extensions of indication, of which two concerned changes to the posology (i.e. paediatric posology). The majority (n = 49, 92.5%) of the extensions of indication was approved during the exclusivity period of the innovator product. Thus, extensions of indication were mainly authorised a few years before approval of the first generic product version and ceased thereafter. Regulatory rethinking might be needed for a sustainable stimulation of extensions of indications in the post-generic period of a drug product lifecycle.

Yet, it was unclear whether the virtual absence of extensions of indication in the post-generic phase of the drug life cycle could be attributed to a reduction in the number of conducted trials after entry of a generic product version or to a general disincentive to apply for an extension of indication even though clinical trials were conducted. Therefore, we examined whether the introduction of a first generic product version was associated with changes in the number of clinical trials and their funding source in **chapter 3.2**.

Clinicaltrials.gov was searched for clinical trials conducted with drugs of the first cohort of small molecule medicinal products authorised through the EMA with a generic product version as identified in chapter 3.1 (excluding the two combination products). Within four years before and four years after generic approval a total of 2689 and 2069 clinical trials were identified for 24 drugs, respectively. The median number of clinical trials per drug was 73 (IQR 30-144) pre-generic and 41 (IQR 21-102) post-generic. After correction for the increase in clinical trial registration over time the median ratio post:pre-generic was 0.6 (IQR 0.4-0.7). The median ratio was similar for industry and non-industry funded clinical trials: 0.5 (IQR 0.4-0.8) and 0.6 (IQR 0.5-0.8), respectively, indicating that the number of clinical trials decreased regardless of the funding source. Even with a decrease in clinical trials a considerable amount of clinical research still remained. The extent to which clinical research was reduced differed extensively between medicines and for individual medicines clinical research even increased. Our findings indicate that multiple factors besides the introduction of a first generic product version in the EU may be of influence which may be specific for individual drugs. To what extent the clinical trials focus on new therapeutic purposes warrants further research.

Current leads for new innovations for well-known drugs may not always result in an authorised drug therapy. In order to exploit such leads, it is important to learn from drugs which made it to an official marketing authorisation. In **chapter 3.3**, we aimed to characterise well-known drugs approved for new innovations: a new therapeutic indications or other innovation. We also aimed to obtain insight in (regulatory) hurdles and opportunities for drug repositioning. From the EMA-website we extracted all drugs approved in 2014 and 2015 and excluded drugs based on a true generic, biosimilar or informed consent application. We identified drugs used in clinical practice before 1 January 2000 and we determined whether those drugs were authorised for a new therapeutic indication or another new innovation. An in-depth analysis was conducted among three of the first drug repositioning cases approved after 1 January 2014: Ketoconazole HRA for the treatment of Cushing's syndrome, Tecfidera (dimethyl fumarate) for the treatment of multiple sclerosis, and Hemangiol (propranolol) for the treatment of proliferating infantile haemangioma. In total, 11 of the 121 drugs approved in the study period were approved for a new therapeutic indication and 5 drugs for another new innovation. Half of the 16 well-known drugs with a new innovation were licensed by small-sized pharmaceutical companies, 7 drugs by a medium-sized company and 1 drug by a large-sized company. Scientific advice was provided to 93 (76.9%) of all drugs in our cohort, but only to 7 (44%) of the well-known drugs approved for a new innovation. Large companies applied for scientific advice for 89% of all their drugs approved in the study period, but small-sized companies did so for 50% of all their drugs and only in 38% for their well-known drugs with a new innovation. The majority of the drugs in our cohort was approved based on a

full-dossier marketing authorisation application: 97 (80.2%) of all approvals and 9 (56%) of the well-known drugs. The analysis of three drug repositioning cases indicated that the viability of the business case for the development of such products may depend on a specific window of opportunity within a therapeutic area and the possibility to establish a relative exclusivity. Based on this study we encourage pharmaceutical companies to carefully consider their opportunities within the current drug regulatory system and to make full use of the opportunities to obtain scientific advice from the regulators. In addition, new strategies and opportunities may be needed to ensure the development and licensing of new innovations for well-known drugs and the optimal use of existing knowledge.

In **chapter 4**, we positioned post-innovation innovation within the legal context of the drug regulatory system. In **chapter 4.1** we had a closer look at the European legal context related to post-innovation innovation. Over the past fifty years EU legislation on medicinal products has expanded massively. It requires that medicinal products obtain a marketing authorisation before being placed on the market. In the best interest of public health, a marketing authorisation is granted after competent authorities have established a positive benfit-risk balance in the treatment of a specific disease. Nevertheless, physicians frequently prescribe medicinal products off-label as well as use unlicensed pharmacy prepared medicinal products in order to satisfy their patients' needs. To provide a better understanding to what extent the need for a marketing authorisation aligns with patient needs chapter 4.1 aimed to examine the purpose and scope of the EU marketing authorisation requirement. We assessed the EU legislation and case-law of the European Court of Justice over the past fifty years. Our analysis showed that despite the massive expansion of EU legislation on medicinal products, the prohibition to market unlicensed medicinal products remained in essence unchanged. The primary purpose of the legislation has always been to safeguard public health – both from dangerous and ineffective medicines – while at the same time the legislation should not hinder the development of the pharmaceutical industry or the trade in medicinal products within the EU. The scope of products regulated by the EU legislation on medicinal products has been broadened over time, while the number of exemptions is still limited and subject to several conditions. In view of the purpose to safeguard public health the European Court of Justice has provided a non-restrictive interpretation of the scope of the legislation, while it established a restrictive interpretation of the exemptions. The court has consistently considered the marketing authorisation requirement to be the general rule of the EU legislation on medicinal products. Recent case-law of the European Court of Justice limits the legal space for the supply of medicinal products prepared by compounding centres acting as pharmacies, which subsequently may hamper patient needs. To ensure patients' access to such medicines would require either an amendment of the exemption

for pharmacy prepared medicinal products, or to allow the supply of medicinal products prepared by compounding centres under the exemption for named patient supply (art. 5 (1) Directive 2001/83/EC). Furthermore, off-label use as standard treatment seems to be at odds with the purpose of the intent of the marketing authorisation system, and licensing of off-label therapeutic indications may be a suitable way forward. The EU may provide guidance on how to position and to allow off-label use as well as the practice of compounding centres in relation to the EU legal framework. Such guidance could enhance a right balance between a strict marketing authorisation requirement and patient needs for unlicensed medicinal products and off-label use in clinical practice in all EU Member States.

From a legal perspective terminology is particularly relevant to prevent misinterpretation and confusion. In **chapter 4.2** we analysed in a quantitative and qualitative manner how drug repositioning and similar terms were used and defined in academic literature, including an assessment of the nature and frequency of used definitions and differences and commonalities in their features. Our PubMed search resulted in 217 articles that referred to ‘drug repositioning’, ‘drug repurposing’, ‘drug reprofiling’, ‘drug redirecting’ and/or ‘drug rediscovery’. In total, 67 articles included a definition ranging from brief and general to extensive and specific. The definitions covered a wide variety of different and related activities. Nevertheless, four common features were found: concept, action, use and product. The different wording used for these features often leads to essential differences in meaning between definitions. In case a clear definition is needed, for example from a legal or regulatory perspective, the features can provide further guidance.

In **chapter 5**, we reflected on the knowledge gained from each study and put this in a broader (societal) perspective. We considered that the drug regulatory system diverges from the needs in clinical practice and society’s expectations of the regulation of medicinal products, which subsequently may affect the opportunities for post-innovation innovation. More and more medicinal products are prepared by compounding centres in order to satisfy patients’ needs in case licensed medicinal products are unavailable. No marketing authorisation has been granted for those medicinal products. At the same time, off-label use is common practice. These states of affairs regarding pharmacy preparations and off-label use indicate tension between the needs in clinical practice and the drug regulatory system to provide licensed treatment options. In addition, a growing body of research indicates many potential new therapeutic indications for known active substances even after generics have entered the market, which have not yet found their way to clinical practice. Moreover, current practice in various EU member states highlights society’s struggle with the marketing authorisation as a general rule considering that off-label use and the use of pharmacy compounded medicinal products are promoted in the political

debate or even through regulatory reform. We argued that even for post-innovation innovation substantial investments may be required. However, adequate tools to establish an exclusivity period as incentive to license new therapeutic indications for known active substances are lacking. In addition, pricing and reimbursement policies seem to limit the opportunities to establish a viable business case. We posed that the need for pharmacy preparations, off-label use and potential new uses in combination with society's struggle with the need to license new uses of existing drugs and the lack of adequate incentives to do so, suggests that the drug regulatory system is under pressure. Regulatory reform may be needed to facilitate post-innovation innovation. We outlined three options for regulatory reform mentioned in literature that may enhance post-innovation innovation: establishment of reasonable intellectual property prospects, the introduction of a stakeholder driven system (instead of a marketing authorisation holder driven system), and/or to radically change the regulatory benefit-risk assessment towards a system in which the benefit-risk assessment is essentially conducted by the medical and scientific community. The studies in this thesis provide some insight in the opportunities and challenges for post-innovation innovation within the drug regulatory system and could be a starting point for further debate about such regulatory reform.

Chapter 6.2

Nederlandse samenvatting

SAMENVATTING

Voordat een nieuw geneesmiddel tot de markt wordt toegelaten en artsen het geneesmiddel kunnen voorschrijven, moet de fabrikant gegevens indienen over de kwaliteit, effectiviteit en veiligheid van het geneesmiddel. De bevoegde autoriteiten zoals het College ter Beoordeling van Geneesmiddelen en de het Europese agentschap voor de geneesmiddelenbeoordeling (EMA) beoordelen de gegevens in het licht van de therapeutische indicatie (de aandoening) waarvoor de fabrikant het geneesmiddel heeft ontwikkeld. Als de beoordelingsautoriteiten de baten-risicobalans positief achten, wordt een handelsvergunning verleend, wat ook wel bekend staat als registratie van het geneesmiddel.

Na de toelating van het geneesmiddel tot de markt gaat de ontwikkeling van dat geneesmiddel echter door. Dit wordt ook wel *post-innovation innovation* genoemd. Dergelijke innovaties kunnen zowel grote ontdekkingen zijn, zoals de ontwikkeling van een nieuwe therapeutische indicatie voor een geneesmiddel, als incrementele innovatie, zoals de ontwikkeling van een nieuwe toedieningsvorm, uitbreiding van de beoogde patiëntenpopulatie of verbeteringen aan de formulering van het geneesmiddel. De ontwikkeling van nieuwe therapeutische indicaties voor bestaande geneesmiddelen (aangeduid met de term *drug repositioning*), biedt in vergelijking met *de novo* geneesmiddelontwikkeling waarbij een geneesmiddel met een nieuwe werkzame stof wordt ontwikkeld, mogelijkheden voor snellere en goedkopere geneesmiddelontwikkeling door gebruik te maken van bestaande kennis, zoals gegevens over de farmacokinetiek en veiligheid van het geneesmiddel.

In **hoofdstuk 1** beschrijven we de introductie van een eerste generieke versie van een geneesmiddel als specifiek en belangrijk moment in de levenscyclus van een geneesmiddel met diverse gevolgen voor de volksgezondheid en voor verdere innovatie met dat geneesmiddel. Kortgezegd is een generiek geneesmiddel een kopie van het originele geneesmiddel. Aanvankelijk is het originele geneesmiddel beschermd tegen concurrentie van een generieke versie, bijvoorbeeld door octrooien, maar na tien tot twintig jaar kunnen de eerste generieke versies van het geneesmiddel worden geregistreerd. Vanaf dat moment begint – wat we noemen – de postgenerieke fase van de levenscyclus van het geneesmiddel. Generieke geneesmiddelen zijn vaak veel goedkoper dan het originele geneesmiddel. In de postgenerieke fase van de levenscyclus van een geneesmiddel is de werkzame stof ook tegen lage kosten beschikbaar voor verdere ontwikkeling. Bovendien bevat de wetenschappelijke literatuur reeds tal van verwijzingen naar potentiële nieuwe therapeutische indicaties voor bestaande geneesmiddelen en naar methoden om zulke nieuwe toepassingen te onderzoeken. De introductie van een eerste generieke versie

van een geneesmiddel kan echter van grote invloed zijn op de mogelijkheden om voor nieuwe innovaties voldoende exclusiviteit te genereren als stimulans om de investeringen in de nieuwe innovatie terug te verdienen. Farmaceutische bedrijven die het originele geneesmiddel op de markt hebben gebracht, profiteren na introductie van de eerste generieke versie mogelijk minder van de uitbereidingen van de therapeutische indicaties dan daarvoor. Vanaf dat moment kunnen hun producten namelijk worden vervangen door de generieke versies, zelfs voor de nieuwe therapeutische indicaties. Ditzelfde geldt voor uitbereidingen van de indicatie voor generieke geneesmiddelen. Overigens kunnen nieuwe therapeutische toepassingen van bestaande geneesmiddelen ook een andere weg naar de klinische praktijk vinden. Nieuwe therapeutische toepassingen kunnen gaan behoren tot de algemene behandelpraktijk op basis van off-label gebruik van geregistreerde geneesmiddelen of als apotheekbereidingen. In die gevallen is de baten-risico balans van het geneesmiddel niet door de autoriteiten beoordeeld. Regulering van geneesmiddelen kan dus grote invloed hebben op *post-innovation innovation*, bijvoorbeeld door het beperken in tijd en omvang van de bescherming van innovatie en het toelaten van generieke geneesmiddelen.

Vanuit het oogpunt van de volksgezondheid is het echter belangrijk dat nieuwe therapeutische indicaties en andere nieuwe innovaties niet alleen worden ontwikkeld, maar ook worden onderworpen aan het officiële beoordelingsproces door de bevoegde autoriteiten. Dat proces biedt aan de bevoegde autoriteiten de mogelijkheid om de effectiviteit en veiligheid van een geneesmiddel bij een bepaalde toepassing af te wegen. Door de officiële toelating beschikken beroepsbeoefenaren en patiënten ook over adequate documentatie, inclusief een bijsluiter, met informatie over het gebruik van het geneesmiddel, zoals over de dosering en mogelijke bijwerkingen. Het doel van dit proefschrift was om vanuit regulatoir en juridisch perspectief inzicht te geven in het functioneren van het systeem van geneesmiddelenregulering in de *post-innovation* fase, inclusief de postgenerieke fase, van de geneesmiddelenlevenscyclus.

Een handelsvergunning kan via vier verschillende procedures worden verkregen, waarbij een handelsvergunning wordt verleend voor de hele Europese Unie, voor één lidstaat, of voor meerdere lidstaten. In **hoofdstuk 2** hebben we onderzoek gedaan naar het falen van aanvragen tot marktoelating in de Europese Decentrale Procedure en de Wederzijdse Erkenningsprocedure. Via deze procedures kan de fabrikant in een keer een handelsvergunning verkrijgen voor meerdere lidstaten. Beide procedures worden vaak toegepast voor de toelating van generieke geneesmiddelen. De resultaten van de onderzoeken in dit hoofdstuk helpen om inzicht te bieden in de mate waarin het verkrijgen van marktoelating een barrière vormt voor geneesmiddelen met een bekende werkzame stof. In **hoofdstuk 2.1** hebben we onderzoek gedaan naar de frequentie

van en determinanten voor het falen van handelsvergunningsaanvragen ingediend via de Decentrale Procedure. Onder falen werd verstaan dat de aanvraag niet leidde tot het verlenen van een handelsvergunning. Dit kan zijn doordat de aanvrager van de handelsvergunning de aanvraag heeft introkken of dat de bevoegde autoriteiten de aanvraag hebben geweigerd. Daartoe analyseerden we de aanvraagprocedures van handelsvergunningen ingediend van 2008 t/m 2012 met Nederland als leidende autoriteit in de beoordelingsprocedure. We beoordeelden de zwaarwegende bedenkingen van de beoordelingsautoriteit bij het door het farmaceutische bedrijf ingediende dossier met gegevens over de kwaliteit, effectiviteit en veiligheid van het geneesmiddel. In totaal vonden we 492 afgeronde beoordelingsprocedures gedurende de studieperiode waarvan er 48 (9.8%) faalden. In 8 procedures werd de aanvraag geweigerd en in 40 procedures werd deze ingetrokken. De procedures faalden ongeveer even vaak na dag 70 (n = 12) van de beoordelingsprocedure, als na dag 120 (n = 7), dag 180 (n = 12) of dag 210 (n = 10). Zeven procedures faalden voor dag 70 waardoor er geen rapport beschikbaar was om de zwaarwegende bedenkingen te analyseren. Bijgevolg konden van 41 procedures de zwaarwegende bedenkingen worden geanalyseerd. Een totaal van 93 zwaarwegende bedenkingen werd gevonden in 34 beoordelingsprocedures. De aard van de zwaarwegende bedenkingen verschilde sterk en wij vonden zowel bedenkingen met betrekking tot de onderbouwing van de kwaliteit van de geneesmiddelen als ten aanzien van de klinische gegevens in het ingediende registratiedossier. Dat een relatief laag percentage van de procedures in onze studie faalde komt mogelijk door de frequente interactie tussen de beoordelingsinstanties en de aanvrager van de handelsvergunning. Dat een bepaald percentage van de aanvragen faalt lijkt niet te voorkomen. Het falen van procedures hangt namelijk ook af van de financiële haalbaarheid en bereidheid van farmaceutische bedrijven om de zwaarwegende bedenkingen op te lossen.

In **hoofdstuk 2.2** richtten we ons op het falen van handelsvergunningsaanvragen in de Europese Decentrale Procedure en de Wederzijdse Erkenningsprocedure. We gaven inzicht in de uitkomsten van handelsvergunningsaanvragen via beide procedures en onderzochten determinanten voor het falen van de aanvragen gedurende de verwijzing naar de zogenaamde *Co-ordination group for Mutual recognition and Decentralised procedures– human* (CMDh). We analyseerden alle verwijzingsprocedures naar de CMDh tussen januari 2006 en december 2013 en beoordeelden van die procedures de reden voor de verwijzing naar de CMDh. Tevens hielden we een enquête onder farmaceutische bedrijven om te bepalen hoe vaak handelsvergunningsaanvragen faalden zonder dat een verwijzingsprocedure naar de CMDh werd gestart. In de studieperiode werden 10392 MRP/DCP toelatingsprocedures afgerond. Daarvan resulteerden er 377 (3,6%) in een verwijzing naar de CMDh. Van die 377 leidden 70 (18,6%) procedures na de verwijzingsprocedure niet tot het verlenen van een handelsvergunning. Die aanvragen

werden geweigerd door de beoordelingsautoriteiten of ingetrokken door de aanvrager. De frequentie van verwijzen naar de CMDh is afgenomen van 14,6% in 2006 naar 1,6% in 2013. Van alle verwijzingen werden er 272 (72,1%) opgelost op basis van consensus in de CMDh. De overgebleven 105 (27,8%) werden opgelost na behandeling in het Committee for Medicinal Products for Human Use (CHMP) van de EMA. De meeste verwijzingen naar de CMDh werden gestart vanwege bezwaren ten aanzien van het klinisch ontwikkelingsprogramma van het geneesmiddel. Kwesties met betrekking tot het studieontwerp en het aantonen van de gelijkwaardigheid van geneesmiddelen, zoals de gelijkwaardigheid van een generiek geneesmiddel met het originele geneesmiddel, leidden het vaakst tot het falen van een handelsvergunningsaanvraag. We schatten het aantal procedures dat faalde zonder verwijzing naar de CMDh op 11,1%. Hoewel het absolute aantal verwijzingen naar CMDh substantieel de afgelopen jaren daalde, werd geen specifieke trend over de tijd in het aantal verwijzingen naar de CMDh waargenomen. Op basis van dit onderzoek werd gesuggereerd dat een toename in kennis bij zowel de farmaceutische bedrijven als de beoordelingsinstanties ertoe heeft geleid dat minder handelsvergunningsaanvragen nog aan het einde van de beoordelingsprocedure faalden.

In **hoofdstuk 3** onderzochten we in welke mate het systeem voor de regulering van geneesmiddelen mogelijkheden bood voor het registreren van nieuwe therapeutische indicaties of andere nieuwe innovaties in de post-innovation fase van de levenscyclus van een geneesmiddel. In **hoofdstuk 3.1** beoordeelden we de kwantiteit en de aard van indicatie-uitbereidingen van chemisch gesynthetiseerde geneesmiddelen (‘kleine moleculen’) die zijn toegelaten via de Europese geneesmiddelbeoordelingsautoriteit EMA met een specifieke focus op de impact van de toelating van een eerste generieke versie. We selecteerden op basis van documenten op de EMA-website alle chemisch gesynthetiseerde geneesmiddelen die via de Europese centrale procedure zijn toegelaten, of toegelaten en later teruggetrokken, sinds het instellen van die procedure t/m 31 augustus 2013. In de volgende stap selecteerden we alle geneesmiddelen met een werkzame stof die voor het eerst is toegelaten als geneesmiddel in de EU via de EMA. Vervolgens werden de geneesmiddelen gegroepeerd per werkzame stof. De werkzame stoffen kwamen in aanmerking voor nadere analyse indien een eerste generieke versie per werkzame stof tenminste een jaar geleden was geregistreerd. Per werkzame stof werden de Europese publieke beoordelingsrapporten van de betrokken geneesmiddelen gescreend op indicatie-uitbereidingen. Nieuwe indicaties voor latere geneesmiddelen met dezelfde werkzame stof werden eveneens gescoord als indicatie-uitbreiding. Bovendien werden indicatie-uitbreidingen alleen de eerste keer gescoord dat de werkzame tof werd goedgekeurd voor die toepassing. We vonden 26 werkzame stoffen waarvoor één of meer generieke versies waren geregistreerd met een follow-up periode van ten minste één jaar. Dit betrof in totaal 186 producten: 65 innovatorproducten (de originele

geneesmiddelen) en 121 generieke producten. De mediaan van het aantal producten per werkzame stof was 2 [interkwartielafstand (IQR) 2–4] voor de innovatorproducten en 4 (IQR 2–6) voor de generieke producten. De mediane lengte van de innovatorperiode was 11,2 jaar (IQR 11,0–12,3 jaar), terwijl dit 3,6 jaar (IQR 2,5–4,1 jaar) was voor de generieke periode. We hebben 53 indicatie-uitbreidingen geïdentificeerd. Twee daarvan betroffen wijzigingen in het doseringsregime (dat wil zeggen het toevoegen van een specifieke kinderdosering). Het merendeel (n = 49, 92,5%) van de indicatie-uitbreidingen werd toegelaten gedurende de periode waarin de innovator een zekere mate van exclusiviteit genoot, namelijk een paar jaar voorafgaand aan de toelating van een eerste generieke versie van het geneesmiddel. Hervormingen van regulatoire systemen zullen nodig zijn voor het duurzaam stimuleren van indicatie-uitbreidingen in de postgenerieke fase van de levenscyclus van een geneesmiddel.

Het bleef echter onduidelijk of het nagenoeg ontbreken van indicatie-uitbreidingen in de postgenerieke fase van de geneesmiddelenlevenscyclus moest worden toegeschreven aan een vermindering in het aantal klinische studies of aan het gebrek aan een stimulans voor de aanvraag van een indicatie-uitbreiding. In **hoofdstuk 3.2** werd daarom onderzocht of de introductie van een eerste generieke versie van een geneesmiddel geassocieerd was met veranderingen in het aantal klinische studies en de financiering daarvan. In Clinicaltrials.gov werd gezocht naar alle studies met geneesmiddelen met werkzame stoffen zoals geïdentificeerd in hoofdstuk 3.2 (met uitsluiting van de twee combinatieproducten). In de vier jaar voor en vier jaar na toelating van de eerste generieke versie werden voor de 24 geneesmiddelen respectievelijk 2689 en 2069 klinische studies gevonden. Het mediane aantal klinische studies per geneesmiddel was 73 (IQR 30-144) in de pregenerieke en 41 (IQR 21-102) in de postgenerieke fase. Na correctie voor de toename in registratie van klinische studies door de tijd heen was de mediane ratio post-pre-generiek 0,6 (IQR 0,4-0,7). De mediane ratio was vergelijkbaar voor door de industrie en niet door de industrie gefinancierd onderzoek, respectievelijk 0,5 (IQR 0,4-0,8) en 0,6 (IQR 0,5-0,8). Deze ratio's wijzen erop dat het aantal klinische studies afneemt na toelating van een eerste generieke versie ongeacht de bron van de financiering. Zelfs met een afname in het aantal klinische studies vindt er een aanmerkelijk hoeveelheid klinisch onderzoek plaats in de postgenerieke fase van de geneesmiddelenlevenscyclus. Daarentegen verschilde de mate waarin het klinisch onderzoek afnam substantieel tussen geneesmiddelen en voor sommige geneesmiddelen nam het klinisch onderzoek zelfs toe. Onze bevindingen wijzen erop dat diverse factoren van invloed zijn op de hoeveelheid klinisch onderzoek in de postgenerieke fase en dat de combinatie van factoren uniek kan zijn per geneesmiddel. Of het klinisch onderzoek in de postgenerieke fase gericht is op het ontwikkelen van nieuwe therapeutische toepassingen vereist nader onderzoek.

De verwijzingen in de wetenschappelijke literatuur naar potentiële nieuwe toepassingen van bestaande geneesmiddelen vertalen zich niet altijd in een nieuwe goedgekeurde toepassing voor zulke geneesmiddelen. Om deze aanknopingspunten voor nieuwe toepassingen optimaal te benutten is het belangrijk om te leren van geneesmiddelen die voor een nieuwe toepassing zijn geregistreerd. In **hoofdstuk 3.3** onderzochten we daarom welbekende geneesmiddelen die zijn goedgekeurd voor een innovatie: een nieuwe therapeutische indicatie of een andere innovatie. We beoogden ook om inzicht te krijgen in de regulatoire obstakels en mogelijkheden voor *drug repositioning*. We extraheerden een overzicht van alle geneesmiddelen toegelaten in 2014 en 2015 van de EMA-website en excludeerden de geneesmiddelen die waren toegelaten op basis van een zogenaamde *true generic, biosimilar en informed consent* aanvraag. We identificeerden alle geneesmiddelen die reeds voor 1 januari 2000 in de klinische praktijk werden toepast en beoordeelden of die geneesmiddelen waren goedgekeurd voor een nieuwe therapeutische indicatie of een andere innovatie. Tevens analyseerden we drie *drug repositioning* cases in meer detail: Ketoconazole HRA (ketoconazol) voor de behandeling van het syndroom van Cushing, Tecfidera (dimethylfumaraat) voor de behandeling van multiple sclerosis, en Hemangiol (propranolol) voor de behandeling van prolifererende infantiele hemangiomen. In totaal waren 11 van de 121 geneesmiddelen in het geselecteerde cohort geregistreerd voor een nieuwe therapeutische indicatie en 5 geneesmiddelen waren geregistreerd voor een andere innovatie. De helft van de 16 welbekende geneesmiddelen met een innovatie werd ontwikkeld door klein farmaceutische bedrijven, 7 door bedrijven van gemiddelde grootte en 1 door een groot farmaceutisch bedrijf. Voor 93 (76,9%) van de geneesmiddelen werd wetenschappelijk advies verleend, maar dit was slechts het geval voor 7 (44%) van de welbekende geneesmiddelen met een innovatie. Grote bedrijven vroegen wetenschappelijk advies voor 89% van hun geneesmiddelen die werden toegelaten in de studieperiode, terwijl kleine bedrijven dit deden voor 50% van hun geneesmiddelen en slechts voor 38% van hun welbekende geneesmiddelen met een innovatie. Het merendeel van de geïncludeerde geneesmiddelen werd toegelaten op basis van een handelsvergunningsaanvraag met een volledig dossier: 97 (80,2%) van alle toelatingen en 9 (56%) van de welbekende geneesmiddelen. De analyse van de drie *drug repositioning* cases leerde ons dat de levensvatbaarheid van de *business case* voor het ontwikkelen van dergelijke geneesmiddelen voor nieuwe innovaties afhangt van specifieke kansen binnen een therapeutisch gebied en de mogelijkheid om een zekere mate van exclusiviteit te creëren. Vanuit het oogpunt van stimulering van *post-innovation innovation* is het belangrijk dat bedrijven de mogelijkheden binnen het huidige regulatoire systeem zorgvuldig te overwegen en optimaal gebruik te maken van de mogelijkheden om wetenschappelijk advies te verkrijgen van de beoordelingsautoriteiten. Daarnaast zijn nieuwe strategieën en mogelijkheden nodig om te zorgen dat innovaties voor

welbekende geneesmiddelen worden ontwikkeld en toegelaten, waarbij optimaal gebruik wordt gemaakt van de bestaande kennis over die geneesmiddelen.

In **hoofdstuk 4** bekeken we *post-innovation innovation* vanuit een juridisch perspectief. In **hoofdstuk 4.1** bestudeerden we de Europese juridische context die verband houdt met *post-innovation innovation*. Gedurende de afgelopen 50 jaar is de omvang van de Europese wetgeving ten aanzien van geneesmiddelen enorm toegenomen. Voor een geneesmiddel moet een handelsvergunning worden verleend voordat het geneesmiddel wordt toegelaten tot de markt. Vanuit het oogpunt van de volksgezondheid wordt een handelsvergunning pas verleend nadat de beoordelingsautoriteiten hebben vastgesteld dat de baten-risico balans positief is. Zij beoordelen de baten-risico balans met het oog op de behandeling van een specifieke aandoening. Om te voorzien in de behoefte van hun patiënten passen artsen geneesmiddelen echter vaak ook off-label toe (dat wil zeggen het toepassen van een geregistreerd geneesmiddel voor een andere toepassing dan waarvoor het officieel is goedgekeurd). Om dezelfde reden schrijven artsen ook ongeregistreerde apotheekbereidingen voor. Om inzicht te bieden in de mate waarin het vereiste van een handelsvergunning aansluit bij de behoefte van patiënten bestudeerden we in hoofdstuk 4.1 het doel en de reikwijdte van het vereiste van een handelsvergunning. We analyseerden de Europese wetgeving en de jurisprudentie van het Europees Hof van Justitie van de afgelopen vijftig jaar. Onze analyse liet zien dat ondanks de enorme uitbreiding van de Europese wetgeving ten aanzien van geneesmiddelen, het verbod om geneesmiddelen zonder handelsvergunning op de markt te brengen in essentie niet is veranderd. Het voornaamste doel van de wetgeving is altijd geweest om enerzijds de volksgezondheid te beschermen - zowel tegen onveilige als ineffectieve geneesmiddelen – terwijl anderzijds de ontwikkeling van de farmaceutische industrie en de handel in geneesmiddelen binnen de EU niet wordt afgeremd. Sinds de invoering van Europese geneesmiddelenwetgeving zijn steeds meer categorieën geneesmiddelen onder de reikwijdte van die wetgeving gebracht. Tegelijkertijd is het aantal uitzonderingen op de wetgeving nog steeds zeer beperkt en onderhevig aan strikte voorwaarden. Vanuit het oogpunt van de bescherming van de volksgezondheid heeft het Europees Hof van Justitie een ruime interpretatie gegeven aan de reikwijdte van de wetgeving, terwijl het hof een beperkende interpretatie heeft gegeven aan de uitzonderingen. Het hof heeft consistent overwogen dat het vereiste van een handelsvergunning de hoofdregel vormt van de Europese geneesmiddelenwetgeving. Recente jurisprudentie van het Europees Hof van Justitie beperkt tevens de juridische ruimte voor het leveren van geneesmiddelen bereid door zogenaamde grootbereiders, die geneesmiddelen bereiden onder de vlag van een apotheek. De beperkte uitleg van de uitzondering voor apotheekbereidingen kan leiden tot een beperking in mogelijkheden om patiënten in hun behoeften aan geneesmiddelen te voorzien. Het waarborgen van de toegang van patiënten tot dergelijke geneesmiddelen

vereist een wijziging van de Europese geneesmiddelenwetgeving of het toepassen van een andere uitzonderingsgrond in de Europese wetgeving, zoals de uitzondering voor zogenaamde *named patient supply*. Voorts lijkt off-label gebruik als standaardbehandeling strijdig met het doel van het systeem van handelsvergunningen waarin geneesmiddelen voor een specifieke therapeutische indicatie worden onderzocht en beoordeeld. Het opnemen van zulke off-label toepassingen in een handelsvergunning lijkt daarom de geëigende weg. De EU zou lidstaten een leidraad kunnen bieden voor de wijze waarop en voorwaarden waaronder zij off-label gebruik en het leveren van apotheekbereidingen door grootbereiders binnen de Europese regulering van geneesmiddelen kunnen positioneren en mogelijk maken. Zo'n leidraad kan ertoe bijdragen dat in alle EU-lidstaten een goede balans ontstaat tussen het strikte vereiste van een handelsvergunning en de noodzaak van het gebruik van ongeregistreerde geneesmiddelen en off-label gebruik om te voorzien in de behoeften van patiënten.

Vanuit juridisch perspectief is terminologie relevant om verkeerde interpretatie en verwarring te voorkomen. In **hoofdstuk 4.2** deden we daarom een kwantitatieve en kwalitatieve analyse naar definities van de term 'drug repositioning' en vergelijkbare termen in de academische literatuur. Daarbij keken we naar hoe vaak een definitie voor zo'n term werd gegeven en of in die definities gemeenschappelijke elementen konden worden herkend. De geformuleerde zoekopdracht in PubMed resulteerde in 217 artikelen die de term(en) 'drug repositioning', 'drug repurposing', 'drug reprofiling', 'drug redirecting' en/of 'drug rediscovery' hanteerden. Van die artikelen bevatten er 67 een definitie welke varieerde van kort en algemeen tot uitgebreid en gedetailleerd. Deze definities dekten een grote variëteit aan verschillende en gerelateerde activiteiten. Desondanks hebben we in de definities vier gemeenschappelijke elementen gevonden: concept, actie, toepassing en product. De bewoording die werd gebruikt voor elk van deze elementen leidde meermaals tot essentiële verschillen in de betekenis tussen definities. Indien een heldere definitie nodig is, bijvoorbeeld vanuit een juridisch of regulatoir perspectief, dan kunnen de geïdentificeerde elementen worden gebruikt bij het opstellen van een definitie.

Hoofdstuk 5 bevat een algemene discussie en plaatst de uitkomsten van de individuele hoofdstukken in een breder maatschappelijk perspectief. We overwogen dat het systeem van geneesmiddelenregulering begint af te wijken van de behoefte in de klinische praktijk en de maatschappelijke verwachtingen. Dit kan van invloed zijn op de mogelijkheden voor *post-innovation innovation*. Steeds meer geneesmiddelen worden bereid door grootbereiders om te voorzien in de behoefte van patiënten, in het geval er geen geregistreerd adequaat alternatief beschikbaar is. Deze geneesmiddelen hebben geen handelsvergunning. Tegelijkertijd is off-label gebruik onderdeel van de gangbare medische praktijk. Dit gebruik is geen onderdeel van de handelsvergunning. Deze gang

van zaken met betrekking tot off-label gebruik en apotheekbereidingen duidt op frictie tussen enerzijds de behoefte in de klinische praktijk en anderzijds het uitgangspunt van het systeem van geneesmiddelenregulering om te voorzien in *geregistreerde* behandelopties. Tegelijkertijd is er steeds meer onderzoek beschikbaar dat wijst op potentiële nieuwe therapeutische indicaties voor bekende werkzame stoffen zelfs nadat een eerste generieke versie van het geneesmiddel is geregistreerd. Bovendien wijzen actuele praktijken in EU-lidstaten op een maatschappelijke worsteling met het vereiste van een handelsvergunning als hoofdregel. Dit blijkt bijvoorbeeld uit het feit dat off-label gebruik en het gebruik van apotheekbereidingen wordt gestimuleerd in het politieke debat of zelfs middels wijzigingen van de nationale wet- en regelgeving.

Tevens stelden we dat ook voor *post-innovation innovation* substantiële investeringen nodig kunnen zijn. Het ontbreekt echter aan adequate mogelijkheden om een zekere mate van exclusiviteit te creëren als stimulans voor het registreren van een nieuwe therapeutische indicatie voor een bekende werkzame stof. Daarbij komt dat het beleid ten aanzien van de prijs en de vergoeding van geneesmiddelen een beperkend effect kan hebben op de mogelijkheden voor *post-innovation innovation* in de postgenerieke fase van de geneesmiddelenlevenscyclus. In hoofdstuk 5 stellen we dat de behoefte aan apotheekbereidingen, off-label gebruik en potentiële nieuwe toepassingen van bestaande geneesmiddelen in combinatie met de maatschappelijke worsteling met het vereiste om nieuwe toepassingen officieel te registreren en het gebrek aan stimulansen om dat te doen, suggereert dat het huidige systeem van geneesmiddelenregulering kraakt. Hervorming van wet- en regelgeving met betrekking tot geneesmiddelen lijkt noodzakelijk om *post-innovation innovation* adequaat te faciliteren. Daartoe hebben we op basis van literatuur drie oplossingsrichtingen beschreven die mogelijk ook *post-innovation innovation* kunnen stimuleren: het creëren van adequate mogelijkheden om het intellectueel eigendom van de innovatie te beschermen, de introductie van een door belanghebbenden in plaats van handelsvergunninghouders gedreven systeem, en/of een radicale wijziging van de baten-risico beoordeling richting een beoordeling die in essentie wordt uitgevoerd door de medische en academische gemeenschap. De studies in dit proefschrift bieden enig inzicht in de kansen en uitdagingen voor *post-innovation innovation* in het systeem van geneesmiddelregulering en kunnen daarmee bijdragen aan het publieke debat over mogelijke hervormingen van dit systeem.

Chapter 7

Addendum

Chapter 7.1

Dankwoord

DANKWOORD

Dit proefschrift zou er niet zijn geweest zonder inzet van velen. Op deze plaats bedank ik graag iedereen die aan het proefschrift heeft bijgedragen. Een aantal personen wil ik in het bijzonder bedanken.

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Chapter 7.2

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Chapter 7.3

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Chapter 7.4

About the author

Joris Langedijk was born in Utrecht on November 25, 1984. He graduated at the College Blaucapel in Utrecht in 2003 and obtained a Bachelor's degree in Pharmacy at Utrecht University in 2007 and a Pharmacist degree (MSc, PharmD) in 2010. In 2011 Joris obtained a Bachelor's degree in Dutch law (cum laude) and a Master's degree in Dutch law in 2015. After graduating as a pharmacist Joris worked almost a year as a pharmacist in the hospital pharmacy of the Zuwe Hofpoort hospital in Woerden. From april 2011 he worked on the studies presented in this thesis as a PhD student at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences, Faculty of Science of Utrecht University under the supervision of Prof. Dr. H.G.M. Leufkens, Dr. M.D.B. Schutjens, Dr. A.K. Mantel-Teeuwisse and Dr. D.S. Slijkerman. He combined this research with a position at the legal and public affairs department of the Dutch Medicines Evaluation Board (MEB), as well as for a shorter period as regulatory project leader at one of the pharmacotherapeutic groups of the MEB. In March 2016 Joris started working as corporate counsel at Brabers Corporate Counsel in The Hague.