Evidence generation on benefits and risks of medicines and its impact on regulatory and downstream decision-making

Lourens T. Bloem

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The studies presented in this thesis have been conducted under the umbrella of the Regulatory Science collaboration between the Dutch Medicines Evaluation Board (CBG-MEB) and the Utrecht Institute for Pharmaceutical Sciences (UIPS). The CBG-MEB is dedicated to ensuring that licensed medicinal products during their whole lifecycle have a positive benefit-risk. This role requires intensive collaboration with academic and clinical partners in order to develop new assessment and decision-making methods, to engage with the clinic and to strengthen regulatory science. This PhD thesis aims to go beyond its scientific merits as such by delivering science, learning and insight to promote public health.

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The waves of *The Herd* are a metaphor for the dynamic process of evidence generation. Their evolution and convergence reflect the ever-evolving nature of evidence and knowledge. On a personal note, they reflect my passion for nature and sports. *The Herd* was shot at Bondi Beach (Sydney), Australia. In Sydney, I discovered my passion for science during my master's research project at the University of Technology Sydney and the University of New South Wales.

Evidence generation on benefits and risks of medicines and its impact on regulatory and downstream decision-making

Genereren van bewijs over baten en risico's van geneesmiddelen en de impact ervan op regulering en verdere besluitvorming

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– Stucwerk Dichtkunst

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Chapter 1

General introduction

Welke therapie heeft kuren?
Hoe lang kan een leven duren?
Wie heeft geen lucht voor lange adem
En wat voor waarde heeft je pijn
Kan de vraag niet louter medisch zijn-
want die pil slikken we samen

– Stucwerk Dichtkunst

Chapter 1.1

Introduction: towards evidence generation throughout the medicine lifecycle

Regulation of medicines: striking a balance

The contemporary European medicines regulatory system is complex with various national and supranational actors that interact within an extensive legislative framework. It aims to protect and promote public health, first and foremost by requiring a marketing authorisation (MA) before a medicine is marketed. This requires evidence of three core aspects: quality of the medicine and its individual components, efficacy within a specified population ('indication'), and safety when used by that population.[1] Provided that there is evidence of sufficient quality of a medicine, evidence on efficacy and safety are balanced against each other as part of a benefit-risk assessment.[2] The weights of benefits and risks may differ depending on the intended indication and/or availability of other relevant medicines.[3] Finally, when the benefit-risk balance is considered positive, an MA will be granted.

However, like any type of decision-making, regulatory decision-making on medicines is dependent on the availability of evidence and always subject to some extent of uncertainty. These uncertainties can be addressed by regulatory requirements for further evidence generation, through for example monitoring of safety concerns or post-authorisation studies. In addition, new contexts of use, such as use by a broader patient population or in another indication, may also facilitate newly available evidence. At the same time, new evidence may also highlight new uncertainties. Therefore, regulators continuously stimulate evidence generation and perform benefit-risk assessments throughout the medicine lifecycle.[4] Dependent on the outcome, regulatory actions may be considered that range from labelling of for example adverse drug reactions (ADR) in the Summary of Product Characteristics (SmPC) to revocation of the MA.

Importantly, the current thinking on this lifecycle approach to evidence generation and assessment considers not only that it should continue after the initial MA, but also that evidence generation should be thoroughly planned already as early as before initial MA. Moreover, since other decision-makers in the medicine lifecycle are informed by and/or (partly) dependent on evidence generation for regulatory decision-making, the need to carefully consider their preferences and where possible involve them in the planning of evidence generation is acknowledged.[4]

Consequently, the current lifecycle approach to evidence generation and assessment ensures the continued development of the benefit-risk profile and the use of medicines. However, it slowly evolved that way, largely in response to continuing pharmaceutical innovation and crises of medicines' safety, and will likely continue to evolve. Below, we discuss how this evolution took place, along four major historical developments.

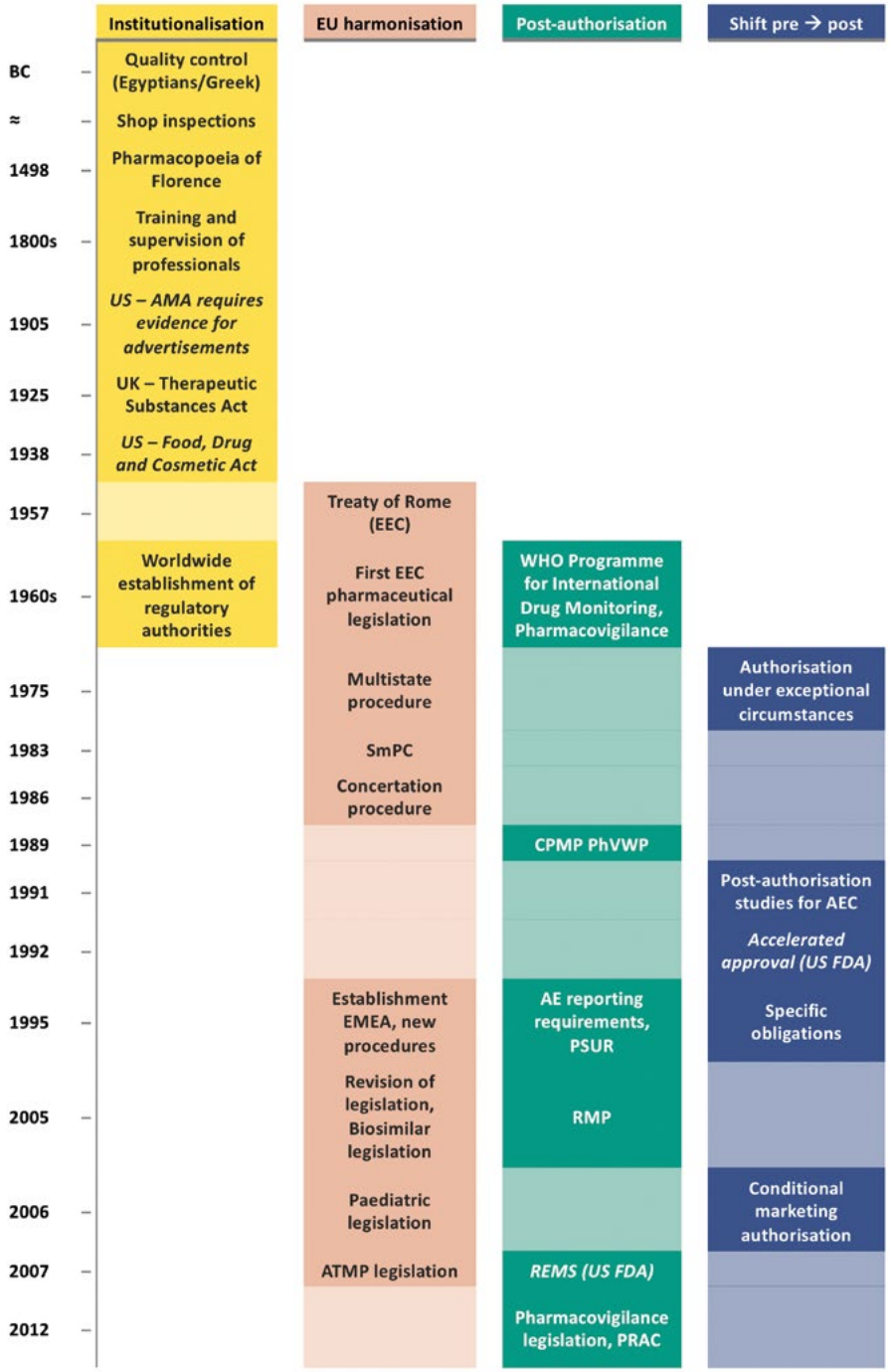
Insight into this process helps to understand the current regulatory lifecycle approach and the importance of studying it.

Evolution of the European regulatory system

Four major developments in the evolution of the European regulatory system and the resulting lifecycle approach to evidence generation can be discerned: i) the institutionalisation of regulation, first by healthcare professionals and later by governments, ii) the European harmonisation of regulation, iii) the use of post-authorisation regulatory evidence requirements to complement pre-authorisation evidence, and iv) the shift from pre-authorisation regulatory evidence requirements to the post-authorisation phase of the medicine lifecycle. Note that a summary of these four developments and the main events that contributed to them is discussed below and visualised in Figure 1. A more extensive, chronological overview of the historical background of the regulatory system, and all sources and references (including the reference list) are provided in Chapter 1.2.

First, the *institutionalisation of regulation* seems first observable among the ancient Egyptians and Greek. At the time, 'regulation' mainly concerned control of quality aspects of medicines to address adulteration, without systematic requirements to generate evidence. Up to and including the Middle Ages, regulatory measures aimed to reduce contamination and adulteration and comprised the setting of pharmacopoeial standards for and inspections of compounding activities. While quality control was initially enforced by local authorities, professional organisations such as those in the United Kingdom (UK) started contributing to it in the 1800s through, for example, training and supervision.

The regulatory role of the professional organisations grew in response to the 'pharmaceutical revolution' of the late 19th and early 20th century. Many of the medicines produced at that time underwent mass advertising to healthcare professionals and the public but lacked efficacy or were merely toxic. To protect patients, in 1905, the American Medical Association started to require evidence of quality, safety and basic efficacy before publishing advertisements of new medicines in their journal. Only thereafter, in response to safety concerns about biological medicines in the UK in the 1920s and a safety crisis in the United States (US) in the 1930s, did these governments start to require pre-marketing evidence of quality and safety. However, it required the thalidomide tragedy in the late 1950s and early 1960s for governments worldwide to also demand evidence of efficacy. Thalidomide, also known under brand names such as Contergan, Softenon, and Distaval, had


Institutionalisation
EU harmonisation
Post-authorisation
Shift pre → post
BC
Quality control (Egyptians/Greek)
≈
Shop inspections
1498
Pharmacopoeia of Florence
1800s
Training and supervision of professionals
1905
US – AMA requires evidence for advertisements
1925
UK – Therapeutic Substances Act
1938
US – Food, Drug and Cosmetic Act
1957
Treaty of Rome (EEC)
1960s
Worldwide establishment of regulatory authorities
First EEC pharmaceutical legislation
WHO Programme for International Drug Monitoring, Pharmacovigilance
1975
Multistate procedure
Authorisation under exceptional circumstances
1983
SmPC
1986
Concertation procedure
1989
CPMP PhVWP
1991
Post-authorisation studies for AEC
1992
Accelerated approval (US FDA)
1995
Establishment EMEA, new procedures
AE reporting requirements, PSUR
Specific obligations
2005
Revision of legislation, Biosimilar legislation
RMP
2006
Paediatric legislation
Conditional marketing authorisation
2007
ATMP legislation
REMS (US FDA)
2012
Pharmacovigilance legislation, PRAC

caused significant malformations to infants whose mother had used it during pregnancy, often as hypnotic or antiemetic. In response, national regulatory agencies were established that required evidence of quality, safety *and* efficacy in order to obtain an MA.

Second, the *European harmonisation of regulation* comprises progressive efforts to harmonise European regulation of medicines as of the 1960s, in order to protect public health while facilitating the establishment of a common European market and the free movement of medicines. This set European-wide evidentiary requirements and allowed optimal use of expertise to ensure capacity to assess the generated evidence. In 1957, the European Economic Community (EEC) was created by the Treaty of Rome. In 1965, the first European pharmaceutical legislation was passed, which was followed by multiple Directives and Regulations. Importantly, these introduced the legal concept that benefits ('therapeutic advantages') must outweigh risks and included legislation for several European regulatory pathways. Initially, the inception of the multistate procedure in 1975 aimed at so-called 'mutual recognition' of MAs, i.e. the granting of an MA for a medicine with an existing MA in another Member State. In addition, the inception of the 'concertation procedure' followed in 1986. This procedure facilitated the harmonisation of MA decisions for medicines developed by biotechnological processes – for which it was mandatory – and for other 'high-technological' medicines – for which it was optional. In both procedures, the EEC Committee for Proprietary Medicinal Products (CPMP) played an important role. It functioned as an arbitrator if Member States could not agree on the outcome of the multistate procedure, and as assessor of the dossiers submitted for the concertation procedure. However, its opinion was not binding and could thus be ignored by Member States, which happened often.

Figure 1 (left) Visualisation of four major developments in the evolution of the European regulatory system and the lifecycle approach to evidence generation

Italic text indicates events outside Europe. AE, adverse event; AEC, authorisation under exceptional circumstances; AMA, American Medical Association; ATMP, advanced therapy medicinal product; BC, before Christ; CPMP, Committee for Proprietary Medicinal Products; EEC, European Economic Community; EMEA, European Agency for the Evaluation of Medicinal Products; EU, European Union; FDA, Food and Drug Administration; PhVWP, pharmacovigilance working party; PRAC, Pharmacovigilance Risk Assessment Committee; PSUR, periodic safety update report; REMS, risk evaluation and mitigation strategy; RMP, risk management plan; SmPC, Summary of Product Characteristics; UK, United Kingdom; US, United States; WHO, World Health Organization

To facilitate the exchange of information about authorised medicines between Member States, the SmPC was devised. This document should be kept up to date with any decisions made by the responsible regulatory authority. Relevantly, it soon also functioned as an important means to communicate information about the safe and effective use of medicines to healthcare professionals.

The role of the CPMP changed when the European Single Market and European Union (EU) were established in 1993. In the same year, a new pharmaceutical Directive and Regulation were passed that came into force as of 1 January 1995. These established the European Agency for the Evaluation of Medicinal Products (EMEA), which now housed and supported the CPMP, and replaced the multistate and concertation procedures with the mutual-recognition and centralised procedures, for which the CPMP (arbitration) opinions were now binding. The centralised procedure ensured that increasingly complex medicines were assessed using the available scientific expertise, resulting in uniform decisions throughout the EU. Between 1995 and 2020, the mandatory scope of the centralised procedure has been progressively widened, most significantly in 2005. That year marked several important changes to the regulatory system, including a complete revision of the legislation that supported the centralised procedure. Moreover, the names EMEA and CPMP were changed into European Medicines Agency (EMA) and Committee for Medicinal Products for Human Use (CHMP), respectively. Subsequently, these revisions were followed by specific legislation concerning for example biosimilars, paediatric medicines and advanced therapy medicinal products (ATMP).

Third, the use of *post-authorisation regulatory evidence requirements* to complement pre-authorisation regulation started following the thalidomide tragedy, when the importance of pharmacovigilance was recognised. Nowadays, pharmacovigilance is defined as "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem*",[5] but it has slowly evolved that way. In the 1960s, several governments developed (spontaneous) reporting systems for adverse events, which was supported and further facilitated by the World Health Organisation (WHO) International Drug Monitoring programme. In the EEC, the CPMP considered post-authorisation safety issues from its beginning, initially by itself and from 1989 by its pharmacovigilance working party. These activities comprised for example the establishment of a safety communication system, the organisation of pharmacovigilance hearings and the incorporation of safety information in the SmPC.

When the EMEA was established in 1995, pharmacovigilance was more comprehensively covered in European legislation and the EMEA became responsible for coordinating pharmacovigilance activities in the EU. Important activities comprised obligations for companies to immediately report serious adverse events and periodically report all other adverse events, including a scientific assessment of their causal relationship to the respective medicine, so-called periodic safety update reports (PSUR). This same legislation set out detailed procedures for so-called 'variations' of an existing MA to address any new learnings about the medicine, including their incorporation in the SmPC. Around this time, the 'benefit/risk' assessment and profile and the need to monitor this profile post-authorisation were explicitly addressed in legislation, but a more proactive approach that allowed planning of evidence generation and benefit-risk assessment during the lifecycle was only launched ten years later, in 2005. An important new tool that facilitated this was the Risk Management Plan (RMP), which includes an overview of safety concerns, pharmacovigilance activities and risk minimisation measures. Relevantly, the RMP allowed regulators to require pharmacovigilance activities such as post-authorisation safety studies (PASS). Around the same time, the Institute of Medicine in the US advised that the Food and Drug Administration (FDA) should also employ a lifecycle approach to benefit-risk assessment. This resulted in a risk planning tool similar to the RMP and an increased mandate to require PASSs. While the RMP was initially required for some medicines, in 2012 it became obligatory for all medicines. This year also saw the inception of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), the possibility to require PASSs and post-authorisation efficacy studies (PAES) as a condition of the MA, and various other pharmacovigilance-related measures.

Fourth, the *shift from pre- to post-authorisation regulatory evidence requirements* strengthened the lifecycle approach by allowing a less strict boundary between the pre- and post-authorisation phase through spreading of the initial evidence requirements. The European precursor to this regulatory concept may be considered the 'authorisation under exceptional circumstances' (AEC), which has been possible as of 1975. This regulatory pathway allowed a company that was unable to provide 'comprehensive evidence' in case of rare diseases, insufficient scientific knowledge, or medical ethical reasons, to obtain an MA. While the AEC was conditional on supply restrictions and provision of information to healthcare professionals concerning evidence gaps, there were no requirements for further evidence generation. Such requirements followed in 1991, when a third condition was added to perform post-authorisation studies to allow a reassessment of the benefit-risk profile. In 1993, the term 'specific obligations' was introduced to describe these post-authorisation studies, among others. Also, for AEC granted through the centralised procedure,

specific obligations had to be reviewed annually by the EMA. However, it seems that being unable to provide comprehensive evidence was not always strictly interpreted since medicines were often granted a 'full' or standard MA (SMA) after provision of additional evidence post-authorisation.

Around the same time, an important regulatory development was ongoing in the US, initiated by the AIDS epidemic. In response to fierce activism for increased availability of and access to medicines to treat AIDS, new regulatory pathways were introduced in the US in the early 1990s. Among others, these enabled the FDA to require pre-authorisation evidence from fewer trials or based on surrogate rather than clinical endpoints, supplemented with evidence from post-authorisation studies to confirm earlier findings.

In Europe, a similar pathway was introduced in 2006: the conditional marketing authorisation (CMA). One year earlier the additional evidence requirements for AEC became *"in particular concerning (...) safety"*, and the AEC became truly 'exceptional'.[6] The resulting gap between the SMA and AEC was filled by the CMA. For medicines that addressed an unmet medical need, it allowed the provision of less comprehensive evidence pre-authorisation, while requiring submission of further evidence post-authorisation through the imposition of specific obligations. This shift of evidence requirements clearly led to uncertainties regarding efficacy and safety pre-authorisation, due for example limited patient enrolment in pivotal trials, a short duration of follow-up, the lack of a control arm or the use of surrogate endpoints. Although the uncertainties should be outweighed by the benefits to patients of immediate availability of the new medicine, it is important to recognise that uncertainties also impact other decision-makers in the lifecycle that may perhaps weigh them differently. To follow-up on the uncertainties, the progress on these specific obligations is reviewed annually and the validity of the CMA limited to one-year intervals and coupled to this review. Ultimately, if the specific obligations are fulfilled, comprehensive evidence is provided and the benefit-risk balance remains positive, the CMA will be converted into an SMA that is no longer subject to specific obligations. The CHMP clarified that AEC should not be granted if CMA was more appropriate, with an aim to limit AEC to those situations where the evidence remained non-comprehensive throughout the medicine lifecycle.

Altogether, the contemporary perspective on medicine regulation considers that development of medicines, and thus the need for further evidence generation, is never finished. There will always be remaining uncertainties that may need to be addressed. Therefore, regulators stimulate evidence generation and assessment throughout the

medicine lifecycle through, e.g., requests for post-authorisation studies, monitoring of specific adverse events and PSURs. When the resulting evidence impacts the benefit-risk balance of a medicine, either positively or negatively, regulatory actions such as the broadening or restriction of an indication or the addition of a new warning or ADR to the SmPC can specify the benefit-risk balance and optimise the use of a medicine. Of course, it may also trigger requirements for further studies or monitoring. The European centralised procedure has evolved into the main pathway to exert these responsibilities for new innovative medicines, of which the number continues to increase (Figure 2).

Need for regulatory science to evaluate the regulatory system

The above illustrates that regulation of medicines has been ever-evolving, but that the last 60 years since the thalidomide tragedy have seen the steepest increase in regulatory activity in human history. In response to persistent safety issues, societal demands for safe medicines stimulated the existence of regulation in the first place and later the continued development of pharmacovigilance. Moreover, societal demands have also driven innovation in regulatory decision-making to provide development incentives for orphan and paediatric medicines. The current state of science is another driver, of innovative medicines that need to be regulated but also of innovative regulatory decision-making itself. Innovative medicines that have driven innovation in regulatory decision-making were for example biological medicines and ATMPs. In addition, use of broader types of scientific evidence – such as real-world evidence – and new methods to assess them enabled regulators to better characterise the benefit-risk balance and decide on appropriate regulatory actions. It is thus most likely that the regulatory system will continue to evolve, in response to further scientific and technological advance, as well as to societal discussion and demands – though hopefully no longer because of safety crises.

However, the regulatory system and the changes made to it are continuously subject to debate; whether it indeed protects and promotes public health or predominantly hampers innovation, by delaying or even preventing medicines to become available to patients, and where the balance between the two should ideally be struck,[7, 8] the 'evidence versus access trade-off'.[9] Drug regulatory science is a scientific field that can inform this debate through evaluations of the regulatory system; of how evidence affects decision-making by regulators and other decision-makers during the medicine lifecycle. Such evaluations can provide learnings for how to deal with the evidence versus access trade-off.[10] Notably, in addition to evaluating the regulatory system, drug regulatory science also comprises the development and validation of

new standards and tools for regulatory decision-making, and the investment of regulators to understand and apply state of the art science for their assessments.[11]

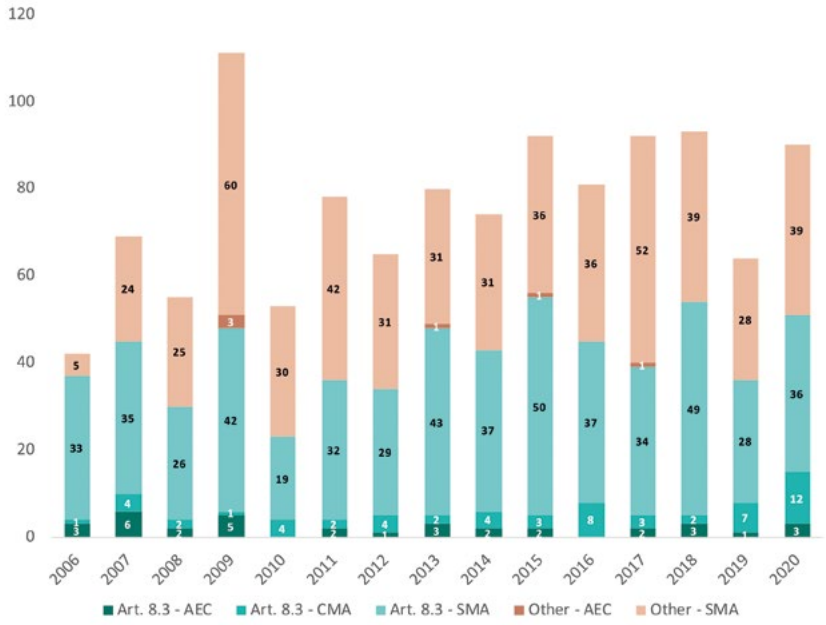


Figure 2 Number of medicines authorised yearly by the European Medicines Agency in 2006-2020
AEC, authorisation under exceptional circumstances; Article 8.3, authorisations based on full dossiers; CMA, conditional marketing authorisation; Other, authorisations not based on full dossiers, for example generics, biosimilars, fixed dose combinations; SMA, standard marketing authorisation

Studies that evaluate whether the regulatory system protects and promotes public health and whether it enables innovation can investigate the processes of evidence generation, regulatory assessment and regulatory decision-making. In addition, they can investigate factors that influence decision-making outcomes such as regulatory actions and factors that are associated with impact of regulatory decision-making outcomes on other decision-makers. These studies may employ a wide range of research methods. For this thesis, we identified three important bodies of drug regulatory science literature that evaluate aspects of evidence generation for regulatory decision-making during the medicines lifecycle, to which we aimed to contribute throughout the thesis.

First, evaluations of early access pathways such as the CMA are often performed because of the timing of evidence generation. As discussed above, a shift from pre- to post-authorisation evidence in theory enables timely access to medicines, while ensuring that important uncertainties about the benefit-risk balance are addressed. Indeed, previous research has shown that the evidence that supported CMAs was less comprehensive than the evidence that supported SMAs, predominantly concerning benefits, including fewer randomised controlled trials (RCT), fewer patients and fewer clinical endpoints.[12-14] However, drug regulatory science studies have questioned whether post-authorisation studies that aim to supplement this evidence and confirm the benefit-risk balance are indeed conducted – within the agreed timeframe or even at all – and whether uncertainties are indeed resolved.[15-17] Consequently, some have called for stricter regulatory action to protect patients, such as limited use of CMA, higher pre-authorisation evidence standards and better incentives to ensure the timely conduct of post-authorisation studies.[16, 17]

Second, evaluations of the occurrence of post-authorisation regulatory actions enable insights in the role of post-authorisation evidence generation for the characterisation of the benefit-risk balance, and potential factors associated with this characterisation process. Often, drug regulatory science studies focus on the evaluation of post-authorisation safety-related regulatory actions (SRRA). These SRRAs respond to new evidence concerning safety such as ADRs, and involve SmPC updates, Direct Healthcare Professional Communications (DHPC), withdrawals, or a combination thereof.[18-24] A relevant additional focus of such studies is the identification of factors associated with SRRAs. Factors that have been explored in such studies are mostly medicinal, clinical development or regulatory characteristics, including type and pharmacotherapeutic class of medicine, therapeutic area, orphan designation, trial design, patient exposure, review time and regulatory pathway. Such factors may inform and improve future regulatory decision-making about, for example, enhanced monitoring for ADRs. Moreover, closely related studies performed evaluations of the functioning of the RMP, as a tool to facilitate the process of learning about and prevention of ADRs.[25, 26] However, less often, studies assessed efficacy-related regulatory actions, such as amended indications.[20, 23, 27]

Third, evaluations of evidence generation for regulatory decision-making also necessitate evaluating its consequences outside the regulatory domain. During the medicine lifecycle, decision-makers other than regulators play an important role in facilitating patient access to new medicines. Such decision-makers often exert their responsibilities after regulatory decision-making on MA has taken place – hence the term ‘downstream decision-maker’ – and may (partly) rely on the evidence that

supported the MA. Therefore, it is imperative to evaluate how such 'regulatory evidence' affected their decision-making.

In the EU, an important group of downstream decision-makers are the national health technology assessment (HTA) agencies. These may decide or advise whether a medicine will be reimbursed by national governments.[28, 29] Since these decisions may facilitate or hamper patient access, HTA agencies are often called the fourth hurdle to patient access.[30] Commonly, they evaluate the value of medicines relative to jurisdiction-specific comparators.[31] These evaluations comprise at least relative effectiveness assessments (REA), but may also include cost-effectiveness assessments, budget impact analysis, and other considerations.[32] While in general the clinical evidence for regulatory decision-making may also be acceptable for HTA decision-making on REAs, given the shared focus on the evaluation of efficacy and to a lesser degree safety,[33] uncertainties in this evidence may be weighed differently.[34-36] Therefore, regulatory and HTA agencies strive to optimally align their processes and assessments.[37] However, given the differences in responsibilities and place in the (inter)national healthcare space, complete alignment is not feasible or even desirable. Therefore, drug regulatory science studies provide an important means to identify aspects that represent uncertainty in evidence generated for regulatory decision-making and their impact on HTA decision-making outcomes. Such aspects are for example whether medicines are indicated for orphan diseases,[38, 39] uncontrolled clinical trials[36, 40] and use of early access pathways.[41, 42]

Another important group of downstream decision-makers in the medicine lifecycle are healthcare professionals, who, often together with patients, decide on whether to prescribe certain medicines. To aid in this decision, they may be informed through guidelines or other assessments of the clinical benefit of medicines that at least partly rely on evidence that was initially generated for regulatory decision-making.[43] Drug regulatory science studies play an important role in evaluating whether and how evidence generated for regulatory decision-making affects the perceived clinical benefit and may impact use in clinical practice. This is especially important in therapeutic areas where it is common for medicines to be authorised based on limited evidence concerning clinical endpoints, such as cancer[14, 44] or orphan diseases.[45] There, healthcare professionals may have too high expectations of the clinical benefit.[46]

This thesis acknowledges that evidence regarding efficacy (benefits) and/or safety (risks), the type of MA, and the variety of decision-makers, including regulatory agencies, HTA agencies, and healthcare professionals, are important factors in the

lifecycle approach to evidence generation for regulatory decision-making. It evaluates the role of these factors and thereby provides insights into the functioning of the regulatory system. Thereby, this thesis provides an important contribution to the drug regulatory science field.

Thesis objective

The objective of this thesis is to provide insights into evidence generation on benefits and risks throughout the medicine lifecycle, and how it affects decision-making by regulatory and downstream decision-makers in the European Union.

Thesis outline

Table 1 provides an overview of the studies included in this thesis and the elements of evidence generation throughout the medicine lifecycle that these studies will address. To adequately address this lifecycle approach and the fact that the regulatory system is continuously subject to changes and adjustments, we applied a longitudinal approach and long follow-up for many of these studies. This allows a better understanding of not only whether something occurred or not, but also how and why.

First, in **Chapter 1.2**, we provide an extensive, chronological overview of the historical background of the European regulatory system to support the trends identified in this introduction.

In **Chapter 2**, we address evidence generation for European regulatory decision-making. In Chapter 2.1, we study the CMA pathway and specifically the specific obligations that are imposed to address remaining uncertainties. By following these specific obligations during the post-authorisation phase, we characterise changes made to them and determine the timing of data submission. Additionally, we identify drug-, procedure- and obligation-related factors associated with change, to facilitate regulatory learning about how post-authorisation evidence generation to resolving uncertainties may take place. In Chapter 2.2, we signal that, contrary to how regulatory assessments are performed, integrated scientific evaluations of regulatory learning about both the benefits and risks of medicines are rarely performed. Therefore, we perform an in-depth characterisation of medicine lifecycles that includes all relevant post-authorisation regulatory actions during ten years of follow-up, i.e. regulatory actions that reflect new information with either a positive or a negative impact on benefits and risks, and the relations between them. The regulatory actions comprise changes to the MA, DHPCs and all newly available clinical information in the SmPC.

Table 1 Overview of studies in this thesis

		Lifecycle phase		Evidence		Decision-maker			MA type
Chapter	**Short description**	**(Pre-)MA**	**Post-MA**	**Benefits**	**Risks**	**EMA**	**HTAs**	**HCPs**	
2.1	Changes to specific obligations		X	X[a]		X			CMA
2.2	Evaluation of post-approval regulatory actions		X	X	X	X			Any
2.3	Complexity of the assessment process and post-approval regulatory actions		X	X	X	X			Any
3.1	Associations between uncertainties and reimbursement	X	X	X[a]			X		Any
3.2	Role of post-approval studies in HTA		X	X[a]			X		CMA
3.3	Evidence and clinical benefit of cancer drugs	X	X	X	X			X	CMA, SMA

CMA, conditional marketing authorisation; EMA, European Medicines Agency; HTA(s), health technology assessment (agencies); HCPs, healthcare professionals; MA, marketing authorisation; SMA, standard marketing authorisation

[a] In these studies, the focus was *predominantly* on benefits

In Chapter 2.3, we further evaluate these regulatory actions. We study whether a composite measure of pre-authorisation aspects that reflect complexity of EMA's assessment process is associated with these post-authorisation regulatory actions. These aspects include longer assessment procedure, MA decisions not taken by consensus but by majority vote, re-examination procedures after initially negative MA decisions, and concerns about the methodological robustness of clinical trials.

In **Chapter 3**, we address perspectives of downstream decision-makers on regulatory evidence generation, to evaluate how patient access may be affected. In Chapter 3.1 and 3.2 we address the role of HTA agencies. First, Chapter 3.1 concerns the impact of evidence generation for initial regulatory decision-making for a new medicine on initial HTA decision-making. We consider that when studying impact of uncertainty identified during regulatory decision-making on HTA decision-making, it may be important to evaluate a diverse set of regulatory uncertainty aspects rather than to evaluate them separately. Therefore, we focus on uncertainty identified by the EMA regarding the methodology of pivotal clinical trials, uncertainty regarding the clinical outcome demonstrated by these trials and uncertainty regarding the clinical relevance of these outcomes. This study assesses whether a higher level of such uncertainty is associated with negative REAs and negative overall reimbursement recommendations by national HTA agencies. Second, Chapter 3.2 concerns the impact of evidence generation for post-authorisation regulatory decision-making on HTA decision-making. In this chapter, we again focus on the CMA pathway, because of its typical requirements for post-authorisation studies. We investigate whether evidence resulting from these studies is used by HTA organisations within REAs and if so, how these studies affect HTA assessments. Finally, in Chapter 3.3 we switch to the clinical decision-maker perspective. Whereas in the other chapters we do not focus on medicines for a specific disease, in this chapter we focus on medicines to treat cancer. We consider that evidence regarding important clinical endpoints such as overall survival and quality of life is rarely available at the time of their authorisation. Additionally, we observe that many cancer medicines are granted a CMA, inherently supported by limited evidence. Since these evidence limitations may impact the judgments of the clinical benefit of these medicines in clinical practice, we compare the availability of evidence and demonstrated clinical benefit of CMA versus SMA cancer indications, thereby taking into account the contribution of post-authorisation studies for CMA indications. To assess the clinical benefit for this study, we apply the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS).

Finally, in **Chapter 4**, we discuss the results of the preceding chapters in their broader research and policy contexts and provide recommendations for the future.

Chapter 1.2

History of the European regulatory system

Early medicines

Medicines have been around perhaps as long as humans themselves. Archaeologists have discovered that Homo sapiens, Homo neanderthalensis and other human ancestors likely used plants to prevent or treat diseases already as long as 790,000 years ago.[47] Moreover, there is evidence that a female Homo neanderthalensis ate specific plants to treat a dental abscess, using plants that contained the anaesthetic and anti-inflammatory 'salicin' (a prodrug of salicylic acid) and the antibiotic producing fungus species *Penicillium rubens*.[48, 49] It took tens of thousands of years until Johann Buchner discovered salicin in 1828,[50] and another 100 years until Alexander Fleming discovered penicillin in 1928.[51]

From limited regulation of quality...

Despite the long and widespread use of these and other medicines, they have rarely been subject to systematic control of their safety and efficacy – by some form of governmental or professional authority – before modern times. Although there are relevant exceptions among for example the ancient Egyptians and Greek,[52] for long, the control of medicines has mainly concerned their quality, aiming to reduce contamination and adulteration. Among others, this control comprised early non-obligatory pharmacopoeial standards such as Dioscorides' *De Materia Medica*, and inspections of medicine-sellers' shops. During the Middle Ages, several kingdoms and city authorities introduced formal laws to safeguard the quality of medicines. In addition to the pharmacopoeial standards and inspections of shops, these laws comprised separation of the professions of physician and apothecary, examination of apothecaries' skills, introduction of an apothecary oath, and public preparation of apothecary products.[52, 53]

It was not until the Renaissance that the presumably first official and obligatory pharmacopoeia in Europe was issued: the *Nuovo receptario composto dal famossisimo Chollegio degli eximii Doctori della Arte et Medicina della inclita cipta di Firenze*, which was issued by the guild of physicians and pharmacists in 1498 and applicable to all apothecaries in the city of Florence. Thereafter, a multitude of pharmacopoeias for other cities followed. Notably, the *Pharmacopoeia Londinensis* – first published in 1618 – applied throughout England, which was the first time a pharmacopoeia applied to a political unit larger than a city. The following ages, newer versions of pharmacopoeias were issued.[52, 54, 55] Also, professional pharmacists' and chemists' organisations were founded, such as those in the United Kingdom (UK) in the 1800s, which standardised the training of professionals as a means to prevent adulteration, among others.[52, 56]

Until the 19th century, apothecaries were the main discoverers and developers of new medicines. However, when the knowledge of chemistry and pharmacology advanced in the 19th century and the industrial revolution took place, the pharmaceutical industry emerged and gradually replaced apothecaries in this role.[52, 57-59] The oldest pharmaceutical company – Merck – was founded as an apothecary in Darmstadt, Germany, in 1668 and was likely the first company to move towards the industrial production of medicine in the first half of the 19th century.[60, 61] In the second half, Felix Hoffman at Bayer modified the molecular structure of salicylic acid – the active metabolite of salicin – to reduce its adverse effects. This resulted in acetylsalicylic acid, which was marketed as Aspirin in 1899.[62] In 1904, Aspirin became available as tablet rather than loose powder, which allowed exact dosing and prevented adulteration.[62] This illustrates how the pharmaceutical industry could contribute to the quality of medicines. Importantly, Aspirin was the first medicine to undergo mass advertising activities, with information distributed to over 30,000 physicians.[63] Also, it received an enormous uptake in daily life, including recognition in popular literature.[62]

... to regulation of safety, efficacy, and the balance between them...

Increasing proportions of medicines were manufactured by pharmaceutical companies, but proper methods of assessing clinical efficacy still had to be established around the start of the 20th century.[64] While we thank (forefathers of) many of our current medicines, including hypnotics, anaesthetics, antipyretics and analgesics, to those early pharmaceutical companies,[59, 60] many other available medicines lacked effectiveness, and some were mainly toxic. Whether efficacious or not, most medicines were commonly known as 'patent medicines' (also called 'secret' or 'proprietary' medicines) that often had trademarked names – rather than being truly patented – and were heavily advertised in medical journals and public press both in Europe and the United States (US).[57, 65-68]

Then, in 1905, the American Medical Association decided that it's journal, the JAMA, would only publish advertisements of medicines that had been tested and approved by its newly inaugurated Council on Pharmacy and Chemistry.[57, 68] The Council's tests comprised quality, safety and basic efficacy evaluations that were published in the JAMA[68] – perhaps the earliest form of a more comprehensive and proactive review of medicines. However, US laws that were issued around that time did not require any proactive review. First, the Biologics Control Act was issued in 1902, shortly after 22 children had died from two different contaminated vaccines. The Act focused specifically on quality control of viruses, serums, toxins, and anti-toxins *"and analogous products"*, and required among others the licensing of biologics

manufacturers.[69] Thereafter, the Pure Food and Drugs Act of 1906 again required no proactive review, but acted against adulterated and misbranded medicines to prevent that they would cause safety issues. The introduction of a more proactive review took until 1938, after a safety crisis with Elixir Sulfanilamide, which contained the poisonous liquid diethylene glycol.[7, 53, 55, 68, 70, 71] The new Food, Drug, and Cosmetic Act required that for each medicine safety testing *"by all methods reasonably applicable"* should be performed and demonstrated to the US Food and Drug Administration (FDA).[55, 68] Importantly, this Act highlights the shift from regulatory control by healthcare professionals to that by the state.

In the meantime, in most of mainland Europe including the Netherlands, regulation of medicines was still focused on quality control by healthcare professionals – mainly pharmacists.[72] However, in the UK, separate steps towards more stringent governmental regulation were taken. Arsphenamine (Salvarsan) had been discovered as a treatment against syphilis by Paul Ehrlich in Germany in 1907. He had developed a hypothesis about a 'magic bullet' or 'chemotherapy' – a medicine that could be specifically targeted towards a micro-organism and would not harm the human body – which resulted in this discovery.[73] However, during World War I, it became unavailable to many countries including the UK. Patents and trademarks were suspended to allow UK companies to manufacture arsphenamine, but they soon noticed that it was difficult to control impurities, which caused safety and efficacy issues. Considering the biological mechanism of action, chemical tests proved inadequate to facilitate the manufacturing of a safe and efficacious medicine, and clinical data were required. The UK Medical Research Committee (later Council) played an important role in regulating arsphenamine in the UK: it oversaw and stimulated the process of gathering these clinical data, and approved every batch of the product before marketing.[52, 73, 74] In response to these concerns about biological standardisation, the Therapeutic Substances Act of 1925 required a license to manufacture medicines *"of which the purity or potency cannot be adequately tested by chemical means"*.[53, 74, 75] In addition to setting standards for (testing of) quality, purity and potency, the Act also regulated many other aspects that are presently regulated, including training of personnel, manufacturing and testing facilities, labelling, recording of batch numbers and quality assurance of imported substances.[52, 53, 75] Its scope initially included vaccines, toxins, antigens, sera, antitoxins, arsphenamine and its derivatives, insulin, and pituitary extract, but was progressively broadened through the years.[52, 75, 76]

Although clinical trial designs slowly became more rigorous,[64, 68, 74, 77] pre-marketing evidence of efficacy was not required during the larger part of the 20th century in most countries. Notable exceptions comprise the Scandinavian countries, especially

Norway and Sweden that required among others that medicines were 'medically justified' before marketing as early as 1928.[7, 78, 79] However, it would require another major safety crisis before the contours of current regulatory systems were established in other countries. In 1956, thalidomide was first marketed in Federal Republic of Germany and thereafter in many other countries over the world,[52, 55] for a variety of indications and known under various brand names including Contergan, Softenon, Distaval, Talimol, and Kevadon.[55] Because a single injection did not cause acute toxicity, it was claimed to be safe – also during longer term use.[55] However, in 1959, cases of peripheral neuropathy after thalidomide use were reported,[55] followed in 1961 by cases of infants with significant malformations – i.e., phocomelia.[52, 55, 80] These teratogenic effects seemed to have occurred after maternal use of thalidomide during pregnancy, often as hypnotic or antiemetic.[52, 55, 70, 80] Importantly, doctors that disseminated their observations of the events and their suspicion of thalidomide playing a role helped to stop the tragedy.[81, 82] Worldwide withdrawal of thalidomide-containing medicines followed. The US was spared the disaster because the FDA had not yet authorised it due to safety concerns about peripheral neuropathy.[55, 71] In response, in the 1960s and 1970s, countries worldwide founded or changed the mandate of existing regulatory agencies to require evidence of quality, safety *and* efficacy of a medicine before it could be authorised for marketing.[7, 55]

As discussed earlier, in Europe, several Scandinavian countries already had a relatively sophisticated regulatory system in place before the thalidomide tragedy. Similarly, the Dutch government had adopted an Act in 1958 to establish the 'College ter Beoordeling van Verpakte Geneesmiddelen' – later renamed 'College ter Beoordeling van Geneesmiddelen' (Medicines Evaluation Board) – that already required pre-authorisation evidence of quality, safety and efficacy.[78, 83] However, the Act was only carried into effect in 1963 in response to the thalidomide crisis.[78, 84] Notably, the Board was the only European regulatory agency with an executive committee whose opinion was binding. All other agencies advised another licensing authority.[55, 85]

Around the same time, the European Economic Community (EEC) – created by the Treaty of Rome in 1957[86] – issued its first Directive that harmonised national pharmaceutical legislation, with an aim to facilitate the establishment of a common European market and the free movement of medicines. Directive 65/65/EEC set the standard for medicine regulation in its Member States[87]: Belgium, France, Germany, Italy, Luxembourg and the Netherlands, and many others in the following decades.[86] Many pieces of legislation followed to further harmonise medicine regulatory activities. This legislation covered (precursors of) most aspects that currently constitute the European medicine regulatory system, including detailed evidence requirements

and slow but steady progression towards EEC-wide regulatory procedures. The EEC Committee for Proprietary Medicinal Products (CPMP) would guide these procedures, and act as arbitrator when Member States disagreed, or as primary assessor when it concerned innovative medicines. However, since its opinions were not binding, Member States could still take their own decision (Table 1).

While Table 1 lists a multitude of important developments that contributed to the regulatory harmonisation process, one development in particular should be discussed here. In 1983, companies were required to provide a Summary of Product Characteristics (SmPC) together with their MA application, to be assessed and agreed by the regulatory authorities. This should facilitate the exchange of information between Member States.[88] Shortly thereafter, the CPMP published an SmPC guideline that outlined a specific order of information (listing the section on 'Clinical particulars' early in the document) to optimise its relevance as an information source for healthcare professionals.[89, 90] Moreover, legislation about the advertising of medicines to healthcare professionals required that this should be done in line with the SmPC.[91] Thus, the SmPC became an important means to communicate information about the safe and effective use of medicines to healthcare professionals.

Table 1 Important developments in the EEC/EU pharmaceutical legislation for human medicines (1965-1995)*

Legislation	Contents
Council Directive 65/65/EEC[87] 26 January 1965	**Definitions and requirements** *"Safeguard public health … by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community"* • Definition of 'medicinal product' • Requirement for authorisation of medicines before placing on the market • Requirement for submission of quality, pre-clinical and clinical data[a] • Refusal of MA in case of insufficient quality, safety and efficacy • Five-year validity of MA • Options to revoke or suspend existing MA • Labelling requirements, including package leaflet

Table 1 *Continued*

Legislation	Contents
Council Directive 75/318/EEC[95] 20 May 1975	**Standards and protocols** • Specification of quality, pre-clinical and clinical data required by Directive 65/65/EEC • First mention that benefits ('therapeutic advantages') must outweigh risks • First mention of 'comprehensive data' • New pathway: exceptions for data requirements, conditional on supply restrictions and provision of information[b]: ○ Rare diseases ○ Insufficient scientific knowledge ○ Medical ethical reasons • MSs may require package leaflets
Council Directive 75/319/EEC[96] 20 May 1975	**CPMP, CPMP procedure and further requirements**[c] • Inception of the CPMP for arbitration and the CPMP procedure[d]: mutual recognition of an existing MA by at least five other MSs • CPMP opinion not binding • Option to require additional data during the MA procedure • Requirements for manufacturing, including authorisation and a qualified person • Need for inspections of manufacturers and option to withdraw medicines from the market • Need for a review of MAs granted before Directive 65/65/EEC, within 15 years
Council Directive 83/570/EEC[88] 26 October 1983	**SmPC, assessment reports and revised CPMP ('multistate') procedure** • Requirement for an SmPC, to be kept up to date after MA • Requirement for authorities to draw up assessment reports for medicines containing a 'new active substance' • Revised CPMP ('multistate') procedure: at least two other MSs • Option for oral or written explanation in case of a negative MS opinion • First mention of a 'balance' ("*between effectiveness and risk*")
Council Recommendation 83/571/EEC[97] 26 October 1983	**Scientific guidelines** • Publication of so-called 'Notes for guidance' to guide the interpretation of the standards and protocols Directive
Council Directive 87/18/EEC[98] 18 December 1986	**GLP** • Requirement to comply with GLP
Council Directive 87/21/EEC[99] 22 December 1986	**Abridged applications** • Exceptions for submission of quality, pre-clinical and clinical data[e]
Council Directive 87/22/EEC[100] 22 December 1986	**Concertation procedure for high-technology medicines** • Mandatory for medicine developed through biotechnological processes • Optional for other innovative medicines • Required when an MA in more than one country is sought • Assessment by the CPMP, though opinions not binding • First mention of a 'rapporteur'

Table 1 *Continued*

Legislation	Contents
Council Recommendation 87/176/EEC[101] 9 February 1987	**Scientific guidelines** • Publication of so-called 'Notes for guidance' to guide the interpretation of the standards and protocols Directive
Council Directive 88/320/EEC[102] 9 June 1988	**Verification and inspection of GLP**[f]
Council Directive 89/341/EEC[103] 3 May 1989	• **Package leaflet and GMP** • Requirement for a package leaflet • Requirement to comply with GMP • Provision of information for third countries
Commission Directive 91/356/EEC[104] 13 June 1991	**Principles and guidelines of GMP**
Commission Directive 91/507/EEC[105] 19 July 1991	**Update of quality, pre-clinical and clinical data requirements**[g] • Adaptation to state-of-the-art science, including requirement to comply with GCP • First mention of 'benefit/risk' assessment and profile, including to monitor it post-authorisation[h] • Third condition for applications in exceptional circumstances: post-authorisation studies[i]
Council Directive 92/27[106] 31 March 1992	**Consolidation of and further requirements for labels and package leaflets**
Council Directive 93/39/EEC[93] 14 June 1993	**Mutual-recognition, pharmacovigilance and post-authorisation** • Replacement of the multistate procedure with the mutual-recognition procedure, with CPMP opinions now binding • Need for establishing national pharmacovigilance systems • Requirements for pharmacovigilance for national MAs, including a qualified person and (periodic) reporting of adverse reactions • Introduction of the term 'variation' with further specification to be developed • First mention of 'specific obligations', including the option to carry out further studies post-authorisation, for applications in exceptional circumstances • Recognition of potential environmental risks of medicines
Council Regulation (EEC) No 2309/93[92] 22 July 1993	**EMEA and the centralised procedure**[j] • Establishment of the EMEA ○ To house and support the CPMP ○ To coordinate pharmacovigilance ○ To coordinate GLP, GMP and GCP oversight

Table 1 *Continued*

Legislation	Contents
	• Replacement of the concertation procedure with the centralised procedure, including variations, specific obligations, and the possibility to appeal • Annual review of specific obligations • Requirements for pharmacovigilance for MAs through the centralised procedure, including a qualified person and (periodic) reporting of adverse reactions • Need for an environmental risk assessment • CPMP opinions now binding
Commission Regulation (EC) No 540/95[107] 10 March 1995	**Non-serious, unexpected adverse reactions** • Detailed requirements for periodic reporting • Specification of conditions requiring variation of MA
Commission Regulation (EC) No 541/95[108] 10 March 1995	**Specification of variations and rules of procedure I** • For national MAs
Commission Regulation (EC) No 542/95[109] 10 March 1995	**Specification of variations and rules of procedure II** • For centralised MAs

CPMP, Committee for Proprietary Medicinal Products; EEC, European Economic Community; EU, European Union; EMEA, European Agency for the Evaluation of Medicinal Products; GCP, good clinical practice; GLP, good laboratory practice; GMP, good manufacturing practice; MA, marketing authorisation; MS, Member State; SmPC, Summary of Product Characteristics

* Excluding legislation concerning wholesale distribution, classification of supply, advertising, and patentability; as well as further specifications of concepts introduced by earlier EEC legislation

[a] With exceptions for certain medicines or medicines that contain active constituents for which such data is already available in the scientific literature

[b] Later known as 'authorisation under exceptional circumstances'

[c] Not applicable to immunological medicinal products, radiopharmaceuticals, medicinal products derived from human blood or human plasma, and homeopathic medicinal products, for which separate Council Directives were later issued, i.e., 89/342/EEC, 89/343/EEC, 89/381/EEC, and 92/73/EEC, respectively

[d] Initially also called the 'CPMP procedure'

[e] For medicines that are 'essentially similar' to already authorised medicines (later known as 'informed consent' and 'generic' applications) and medicines of which the constituents have a 'well established medicinal use'

[f] Updated with Commission Directive 90/18/EEC of 18 December 1989

[g] Now including immunological medicinal products, radiopharmaceuticals and medicinal products derived from human blood or human plasma

[h] *"... in order to monitor the benefit/risk assessment after marketing authorization has been granted, any change to the data in the dossier, any new information not in the original application and all pharmacovigilance reports, shall be submitted to the competent authorities."*

[i] *"the applicant completed an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile"*

[j] Initially mandatory for certain biological medicines and optional for other innovative medicines

The process of regulatory harmonisation in the EEC culminated in 1995 when, following the establishment of the European Single Market and the European Union (EU) in 1993,[86] the European Agency for the Evaluation of Medicinal Products (EMEA) was established.[92] Along with the EMEA, a centralised procedure for regulation of innovative medicines was established,[92] and a 'mutual recognition' procedure to ensure harmonisation of regulatory decision-making for other medicines.[93] The opinions of the EMEA's main scientific committee, the CPMP, were now binding for all concerned Member States (Table 1).[92, 93]

While an extensive discussion about the worldwide harmonisation of medicine regulation is out of scope here, it is relevant to note that many of the EEC evidence requirements became blueprints for worldwide evidentiary standards through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As of 1990, the ICH formed an international platform for regulatory authorities and the pharmaceutical industry of Europe, Japan and the US to formulate guidelines and technical requirements.[94]

... throughout the medicine lifecycle

The thalidomide tragedy did not only result in the common requirement for pre-authorisation evidence of quality, safety and efficacy, but also prompted regulatory follow-up during the post-authorisation phase, specifically concerning safety. The evolution of study designs to provide robust evidence of efficacy still limited the provision of evidence of safety. While the generally restricted clinical trial patient population allowed identification of adverse drug reactions (ADR) that occurred frequently and early after a new medicine was first used, it limited identification of rare and later occurring ADRs, and generalisability to the often-broader requested indication, let alone other potential indications.[110, 111] As of 1962, the FDA required companies to report adverse events, to establish frequencies of known ADRs and identify new potential ADRs.[112] Also, it had just started its spontaneous reporting system for adverse events.[113] Shortly thereafter, in 1964, the UK started a similar system, the Yellow Card Scheme.[114] It's Committee on Safety of Drugs clearly recognised the need for post-authorisation follow-up:

"No drug which is pharmacologically effective is entirely without hazard. The hazard may be insignificant or may be acceptable in relation to the drug's therapeutic action. Furthermore, not all hazards can be known before a drug is marketed; neither tests in animals nor clinical trials will always reveal all the possible side effects of a drug.

These may only be known when the drug has been administered to large numbers of patients over considerable periods of time."[115]

Similar concerns were raised about evidence of efficacy in the 1980s – among others by Brian Strom and colleagues[116-119] –, but it would take years before these would be addressed by regulatory requirements.

In the late 1960s and early 1970s, the World Health Organisation (WHO) contributed substantially to the formation of and collaboration between national and international systems for the spontaneous reporting of adverse events, through its Programme for International Drug Monitoring.[120] This occurred also in response to the thalidomide tragedy, since the lack of a worldwide system to share adverse event information had prevented the early recognition of thalidomide-induced phocomelia.[121] Since then, the programme has expanded extensively, from ten member countries at its inception to 148 in 2021.[122] Closely to the inception of the programme, the use of the term 'pharmacovigilance' seems to have started,[123] which is currently defined as *"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem"*.[5]

On the European level, the CPMP considered matters of pharmacovigilance since its inception in 1975 and was supported therein by a pharmacovigilance working party from 1989 onwards.[124] Their activities comprised for example the establishment of a safety communication system, the organisation of pharmacovigilance hearings and the incorporation of safety information in the SmPC However, pharmacovigilance was only formally addressed in legislation as of 1991[105] and the pharmacovigilance activities were specified as of 1995, along with the inception of the mutual recognition and centralised procedures.[92, 93, 107] These activities comprised the immediate reporting of serious adverse events by companies to the regulatory authorities, as well as the periodic reporting of all newly available data on adverse events together with a scientific evaluation of any causal relationship (later known as periodic safety update reports [PSUR]). Importantly, at the same time, detailed procedures for 'variation' of an existing MA and the option to require further studies 'in exceptional circumstances' were also introduced (Table 1).[92, 93, 108, 109] Together, these provisions ensured more comprehensive regulatory (safety-related) follow-up of medicines throughout their lifecycle, rather than solely pre-authorisation.

Further regulatory innovation in the 21st century: new types of medicines, early access pathways and proactive pharmacovigilance

Around the turn of the century, important new legislation was passed that provided incentives for the development of medicines for rare diseases, so-called 'orphan medicines',[125] and that required that clinical trials were performed according to good clinical practice.[126] Shortly thereafter, most of the other existing pharmaceutical directives and the regulation concerning the EMEA and the centralised procedure (Table 1) were consolidated and replaced by one Directive[1] and one Regulation, which also changed the names of the EMEA and CPMP to European Medicines Agency (EMA) and Committee for Medicinal Products for Human Use (CHMP).[6] However, in addition to bundling the legislation already in force, it also added important new elements (Table 2) and formed the basis for further legislation, including that concerning biosimilars,[127] (incentives for developing) medicines for paediatric use,[128] and advanced therapy medicinal products (ATMPs).[129] Additionally, for yet unauthorised medicines, the new decentralised procedure allowed Member States to cooperate during the assessment of MA applications in multiple states, while the existing mutual-recognition procedure was restricted to situations where a medicine was already authorised in a Member State. These procedures were overseen by a coordination group (CMDh).[127]

The new legislation also formed the basis for the conditional marketing authorisation (CMA) (Table 2), which came into force as of April 2006.[130] This new pathway mimicked the Accelerated Approval pathway in the US, which had been introduced in the early 1990s in response to fierce activism for increased availability of and access to medicines to treat AIDS. Together with other pathways it enabled the FDA to require pre-authorisation evidence from fewer trials or based on surrogate rather than clinical endpoints. The benefit-risk balance should then be confirmed by additional evidence from post-authorisation studies. These pathways were aimed at medicines for life-threatening diseases, including AIDS, and explicitly considered severity of disease and availability of alternative treatments in the benefit-risk assessments.[131]

Similarly, the CMA is available for medicines that are used to treat, prevent or diagnose seriously debilitating or life-threatening diseases and address an unmet medical need. For these medicines, a CMA can be granted based on less comprehensive clinical evidence than required for an SMA. In addition, the CMA is also available for medicines that address public health emergencies such as a pandemic. For these medicines, less comprehensive evidence can also include pharmaceutical and non-clinical evidence. The granting of a CMA is conditional on requirements that i) the benefit-risk balance is positive; ii) it is likely that comprehensive evidence is generated

through specific obligations for post-authorisation studies and other evidence; iii) an unmet medical need is fulfilled; and iv) the remaining uncertainties are outweighed by the benefit of immediate availability. Moreover, it is valid for one year and can be renewed for one-year intervals based on annual assessments of the specific obligations and the benefit-risk balance. Once these are fulfilled, comprehensive evidence is provided, and the benefit-risk balance remains positive, the CMA can be converted to an SMA that is no longer subject to specific obligations.[130]

Table 2 Important new legislative elements in Regulation (EC) No 726/2004 concerning human medicines

New elements	Explanation
Widened mandatory scope for the centralised procedure	In addition to biological medicines: orphan medicines and medicines that contain a new active substance and are indicated for the treatment of HIV/AIDS, cancer, neurodegenerative disorders, diabetes (immediately); auto-immune diseases, immune dysfunctions and viral diseases (after four years)
Accelerated assessment	Reduction of duration of the assessment procedure from 210 days to 150 days, for medicines of major therapeutic interest
Compassionate use	Use of a medicine before it is authorised, when authorised medicines are insufficient
Conditional MA	Granting of a temporary MA that is subject to specific obligations, to be reviewed and renewed annually. Further specified in Commission Regulation (EC) No 507/2006.
Article 58 opinions	Assessment of medicines for use outside the European Union, in cooperation with the World Health Organisation
Scientific advice	Enhancement of provision of scientific advice, including formal procedures and a scientific advice working party (later SAWP)
Increased transparency	Among others, the publication of European Public Assessment Reports (EPAR)
Incentives for non-big pharma (SMEs)	Increased assistance and fee reduction

CPMP, Committee for Proprietary Medicinal Products; EC, European Commission; EMEA, European Agency for the Evaluation of Medicinal Products; MA, marketing authorisation; SME, small and medium-sized enterprise

The CMA incorporated regulatory aspects that were already used for the AEC regulatory pathway since 1975 and the early 1990s (Table 1). While the AEC was essentially available for medicines for which it was not possible to generate comprehensive evidence,[95] it had also allowed authorisation in a CMA-like manner, i.e., ultimately undergoing conversion to SMA after provision of additional evidence post-authorisation.[132] However, the CHMP clarified that the CMA applies to situations where the generation of comprehensive evidence is ultimately considered feasible,

while the AEC is now restricted to situations where this seems not feasible. Therefore, the AEC should not be granted if CMA is more appropriate.[133] Importantly, the use of the AEC or CMA pathway is inherently associated with acceptance of a higher level of uncertainty. This follows naturally from the less comprehensive evidence that is available at the time of initial MA. However, the source of uncertainty may differ from medicine to medicine, e.g., it may arise from a low number of patients studied in the pivotal trial(s), a short duration of follow-up of these patients, the lack of a control to obtain comparative safety and efficacy estimates, or the use of surrogate rather than clinical endpoints.[133, 134] Interestingly, the concept of medical need had already been used by the Norwegian regulatory agency as of 1938, but, in contrast, it was used to restrict the number of authorised medicines.[79]

Table 3 Selection of medicines withdrawn for safety reasons in Europe[18, 21, 135-140]

Year	Active substance	Type of medicine	Adverse events
2004	Rofecoxib	Analgesic	Cardiovascular
2008	Lumiracoxib	Analgesic	Hepatic
2009	Rimonabant	Anorectic	Psychiatric
2010	Benfluorex	Anorectic	Cardiac
2010	Rosiglitazone	Antidiabetic	Cardiac
2010	Sibutramine	Anorectic	Cardiovascular
2010	Sitaxentan	Antihypertensive	Hepatic
2012	Buflomedil	Vasodilator	Cardiac, neurological
2012	Meprobamate	Sedative	Neurological, psychiatric
2013	Nicotinic acid / laropiprant	Hypolipidemic	Bleeding, myopathy, infections, diabetes
2016	Fusafungine	Antibiotic	Allergic
2017	Gadodiamide, gadopentetic acid, gadoversetamide	Gadolinium contrast agents	Brain deposition
2018	Flupirtine	Analgesic	Hepatic
2018	Daclizumab beta	Immunosuppressant	Immune-related
2019	Cinoxacin, flumequine, nalidixic acid, pipemidic acid	Antibiotics	Tendon-, muscle- and joint-related, neurologic, psychiatric
2020	Ingenol mebutate	Chemotherapeutic (topical)	Skin cancer

Finally, the most recent regulatory development that is relevant to this thesis and for which the Directive and Regulation discussed earlier formed the basis, is the pharmacovigilance legislation. The Directive and Regulation already provided pharmacovigilance measures with respect to centrally and nationally (including mutual-recognised and decentralised) authorised medicines, respectively.[1, 6] However,

despite efforts throughout the more recent history of medicine regulation, safety issues continued to occur (Table 3). Therefore, a more proactive pharmacovigilance strategy was gradually developed.[141] First, the concept of the Risk management Plan (RMP) was devised in 2005.[127] The data required by EMA now included *"A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce."*,[127] which was further specified by a CHMP guideline.[142] The RMP enabled regulators to proactively monitor and address safety issues throughout the medicine lifecycle. This included their early identification and characterisation, but also prevention or minimisation of their occurrence.[142] At the same time, legislation allowed for a lifecycle approach to benefit-risk assessment: *"In order that the risk-benefit balance may be continuously assessed, the competent authority/Agency may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable."*[6, 127] A similar development had been ongoing in the US, where the Institute of Medicine advised that the FDA should also employ a lifecycle approach to benefit-risk assessment to allow early discovery of potential safety issues. This resulted in the Risk Evaluation and Mitigation Strategy (REMS), which is similar to the RMP, and an increased mandate to require post-authorisation studies.[143]

Thereafter, further important upgrades in 2012 included the inception of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) to provide recommendations and advice to the CHMP and CMDh on pharmacovigilance matters; a broader definition of 'adverse reaction' – now also including medication errors and effects as a consequence of off-label use; the requirement for a RMP for every medicine; harmonisation of pharmacovigilance measures for medicines that contain the same active substance(s) or medicines authorised in more than one Member State, including single assessment of PSURs; prioritisation of the Eudravigilance database as the single point for reporting adverse reactions; the possibility to subject medicines to 'additional monitoring' of potential adverse reactions; and the possibility to require PASS and PAES as a condition of the MA.[144-146] This legislation was accompanied with a set of guidelines on Good Pharmacovigilance Practice (GVP).[147] Lastly, in 2014, in addition to existing requirements for post-authorisation studies for specific medicines (such as those granted CMA or AEC), general situations that may require a PAES were specified. These situations included the study of clinical outcomes or disease progression to substantiate evidence on surrogate endpoints, specific combinations with other medicines, specific subpopulations, long-term efficacy, or 'real-world' estimates of effectiveness, or if the benefit-risk balance is questioned.[148] Thirty years after Brian Strom and colleagues highlighted the need for post-authorisation efficacy studies, this was finally addressed.[116-119]

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Chapter 2

Evidence generation for regulatory decision-making

Er is geen tijd meer om te dwalen
Ons in het duister te verliezen
We moeten- om onheil te voorkomen-
soms tussen twee kwaden kiezen
Is voorwaardelijk geen straf
als het uit wijsheid is geboren
We volgen nauwgezet je stappen
op nieuwe wegen zonder sporen

– Stucwerk Dichtkunst

Chapter 2.1

Postauthorization changes to specific obligations of conditionally authorized medicines in the European Union: a retrospective cohort study

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Abstract

When medicines are granted a Conditional Marketing Authorization (CMA) in Europe, specific obligations are requested to obtain comprehensive data on benefits and risks. We performed a retrospective cohort study to characterize obligations, examine changes to their description and due dates after initial authorization, determine timing of data submission relative to due dates, and identify drug-related, procedure-related and obligation-related factors associated with change. We identified 69 obligations for 26 medicines conditionally authorized between 2006 and 2016. We found 39 changes to 27 obligations (39% of obligations), of which four substantially changed the obligation. For 55% of obligations, data submission was delayed. Eleven factors were associated with change, including the use of CMA as a rescue option. The results are potentially indicative of a continuous search by regulators to reduce uncertainties. Submission delays impact public health negatively by prolonging exposure of patients to unknown risks, particularly when the level of uncertainty is high.

Introduction

One of the major challenges for contemporary medicines marketing authorization (MA) is to provide timely access to medicines while ensuring that remaining uncertainties about the benefit-risk profile are adequately addressed. To resolve uncertainties, data need to become available postauthorization, often as part of requests for postmarketing studies by regulators. However, whether these studies are actually conducted, whether this happens in an acceptable and agreed-upon timeframe, and, ultimately, whether uncertainties are indeed resolved is subject to debate in several jurisdictions.[1-13] Recently, we and others found that studies are not completed in time[8, 10-12] and knowledge gaps are not filled,[7, 9-11] whereas the conduct of additional studies is not enforced and regulatory decisions are not revised.[7, 11] These observations led to a call for stricter regulatory action to protect patients.[7-10, 12]

Postauthorization studies are particularly important for authorization pathways that aim to provide timely access to medicines that address an unmet medical need, such as the United States Accelerated Approval program, Canada's Notice of Compliance with Conditions policy, and the European Union (EU) Conditional Marketing Authorization (CMA). In general, for these pathways, less conclusive data on benefits and risks, and, therefore, a higher degree of uncertainty, is accepted as compared to standard authorization pathways. Uncertainties may follow from: a lower number of patients studied prior to authorization; shorter duration of follow-up; the (single-arm) design of pivotal studies; or the use of a surrogate end point rather than a clinical end point. These uncertainties are accepted by regulators, provided that drug developers commit to the provision of additional data postauthorization.

In the case of the EU CMA pathway, imposed mandatory postauthorization studies are called specific obligations. They are imposed in addition to tools used to identify and characterize uncertainties in all EU marketing authorization pathways, such as the Risk Management Plan and Periodic Safety Update Reports. To keep track of the progress and results of obligations, the CMA is subject to an annual renewal process instead of the conventional 5-year renewal. During annual renewal, the benefit-risk balance of the medicine is re-assessed together with an assessment of the progress and results (when available) of ongoing and completed obligations. An in-depth description of this process is provided in Box S1.

Previous research flagged concerns about the progress and results of postauthorization studies in the context of the CMA pathway.[6, 8, 9] These studies

created awareness of possible concerns about compliance, but there are still several unanswered questions about the commitments to conduct specific obligations in the postauthorization phase. First, we know little about the process of annual renewals and the fate of obligations over time. A previous study by the European Medicines Agency (EMA) revealed that changes were made to obligations after initial authorization and concluded that this only concerned few obligations and mainly nonmajor changes.[14] This study did, however, neither follow obligations over time nor examine the type of obligations that were changed or delayed. Second, we lack data on whether there are any factors associated with changes to obligations. Knowledge about such factors can be instrumental for regulators to identify the best way to learn about a medicine's benefit-risk profile and resolve remaining uncertainties within a reasonable timeframe. Therefore, the aim of the present study is to characterize changes made to obligations over time, determine timing of data submission and identify drug-related, procedure-related and obligation-related factors associated with change.

Results

Cohort description

Between March 29, 2006, and December 31, 2016, 35 medicines were granted a CMA. Of these, three vaccines and six medicines with either <1 year of follow-up or lack of a renewal before the end of the study period were excluded. Of the remaining 26 medicines (characteristics provided in Table S1), no CMAs were revoked by the EMA or withdrawn by the company and 50% of the CMAs were converted to a standard MA during the study period. We included all 69 specific obligations for these 26 medicines (median 2 per medicine, interquartile range (IQR) 1–2; Table 1). Of these, two obligations were imposed after a medicine was approved, both for panitumumab. Almost 75% of the obligations (n = 51) had been removed by the end of follow-up. In 22 cases, this coincided with the conversion of the CMA into a standard MA. The vast majority (n = 48) were removed because they were considered fulfilled, except for 3 obligations for darunavir. These were downgraded to postauthorization studies that, although mandatory, were no longer a condition for maintaining the CMA, because the requested data were already available or no longer considered relevant.

Changes to specific obligations

During follow-up (median 2 renewals including conversions, IQR 1–4), we identified 39 changes in 27 obligations (39% of all obligations). Changes involved a change in due date (n = 17; 44%), which were all extended; a change in (text) description (n = 5; 13%, as explained in Box S1); or a change in description and due date (n = 17; 44%), of which all but two were extended. Of 27 changed obligations, 19 were changed once, 5 were changed twice, 2 were changed thrice, and 1 was changed four times. The median time-to-first-change was two renewals (IQR 1–2; actual time 673 days, IQR 385–833). All obligations and the changes made to them are visually depicted in Figure 1, which shows a "heat map" of changed obligations, ranging from most (often) changed to least changed.

Further analysis showed that most description changes had either a negligible (n = 8/22) or minor impact (n = 10/22) on the initially requested activity. The remaining four description changes had a major impact. They affected four different obligations of four different medicines. An overview of the description changes, the assessment of impact, and reasons for change is provided in Table S2. Additionally, the process of identification of the obligations and changes is shown in a flowchart in Figure 2.

Table 1 Characteristics of obligations (n=69) and assessment of associations between drug-related, procedure-related and obligation-related factors and change to specific obligations

Factor	No change n=42 (%)	Change n=27 (%)	RR*	95% CI
Drug-related				
Marketing authorization applicant size				
Big pharma	39 (61)	25 (39)	Ref.	N/A
Small and medium-sized enterprises	3 (60)	2 (40)	1.0	0.33-3.1
Drug type				
Small molecule	30 (67)	15 (33)	Ref.	N/A
Biological/ATMP	12 (50)	12 (50)	**1.5**	**0.84-2.7**
Indication				
Infectious disease	15 (68)	7 (32)	Ref.	N/A
Oncology	24 (57)	18 (43)	1.3	0.67-2.7
Other	3 (60)	2 (40)	1.3	0.37-4.3
FDA approval				
Regular approval	8 (53)	7 (47)	Ref.	N/A
Accelerated approval	29 (62)	18 (38)	0.82	0.43-1.6
No approval	5 (71)	2 (29)	**0.61**	**0.17-2.2**

Table 1 *Continued*

Factor	No change n=42 (%)	Change n=27 (%)	RR*	95% CI
Size of studies delivering main/pivotal evidence at MAA				
0-500 patients	25 (57)	19 (43)	Ref.	N/A
>500 patients	17 (68)	8 (32)	0.74	0.38-1.4
Procedure-related				
Prospective use of CMA pathway				
No	23 (53)	20 (47)	Ref.	N/A
Yes	19 (73)	7 (27)	**0.58**	**0.28-1.2**
CHMP experience with CMA pathway				
Imposed in 2006-2008	21 (68)	10 (32)	Ref.	N/A
Imposed in 2009-2016	21 (55)	17 (45)	1.4	0.75-2.6
Accelerated assessment during MA procedure				
No	39 (60)	26 (40)	Ref.	N/A
Yes	3 (75)	1 (25)	**0.63**	**0.11-3.5**
Re-examination during MA procedure				
No	27 (61)	17 (39)	Ref.	N/A
Yes	15 (60)	10 (40)	1.0	0.56-1.9
Scientific advice or protocol assistance (SA/PA) received before authorization				
No	17 (61)	11 (39)	Ref.	N/A
Yes	25 (61)	16 (39)	0.99	0.55-1.8
Adherence to SA/PA				
No	13 (68)	6 (32)	Ref.	N/A
Yes	10 (53)	9 (47)	**1.5**	**0.66-3.4**
No advice provided	19 (61)	12 (39)	1.2	0.55-2.7
Scope of Commission Regulation (EC) No 507/2006 – Orphan designation				
No	27 (60)	18 (40)	Ref.	N/A
Yes	15 (63)	9 (38)	0.94	0.50-1.8
Scope of Commission Regulation (EC) No 507/2006 – Treatment for seriously debilitating or life-threatening disease				
No	6 (67)	3 (33)	Ref.	N/A
Yes	36 (60)	24 (40)	1.2	0.45-3.2
Argumentation for unmet medical need				
No satisfactory method of diagnosis, prevention or treatment authorised	10 (63)	6 (38)	Ref.	N/A
Other	32 (60)	21 (40)	1.1	0.52-2.2
CHMP agreement on MA				
Consensus	25 (68)	12 (32)	Ref.	N/A
Majority	17 (53)	15 (47)	1.4	0.80-2.6

Table 1 *Continued*

Factor	No change n=42 (%)	Change n=27 (%)	RR*	95% CI
MA procedure active time				
≤200 days	5 (56)	4 (44)	Ref.	N/A
201-210 days	21 (64)	12 (36)	0.82	0.35-1.9
>210 days	16 (59)	11 (41)	0.92	0.39-2.2
MA procedure clock-stop time				
≤160 days	22 (69)	10 (31)	Ref.	N/A
>160 days	20 (54)	17 (46)	**1.5**	**0.79-2.7**
MA procedure calendar time				
≤1 year	19 (73)	7 (27)	Ref.	N/A
>1 year	23 (53)	20 (47)	**1.7**	**0.85-3.5**
Obligation-related				
Addressed uncertainty				
Clinical effect	34 (58)	25 (42)	Ref.	N/A
Other	8 (80)	2 (20)	**0.47**	**0.13-1.7**
Study status				
Ongoing study	29 (71)	12 (29)	Ref.	N/A
New study	7 (39)	11 (61)	**2.1**	**1.1-3.8**
Other obligation (no study)	6 (60)	4 (40)	1.4	0.56-3.3
Study design				
Interventional	35 (63)	21 (38)	Ref.	N/A
Observational	1 (33)	2 (67)	**1.8**	**0.75-4.2**
Other obligation (no study)	6 (60)	4 (40)	1.1	0.46-2.4
Development phase addressed by obligation				
Late clinical (phase 3)	18 (51)	17 (49)	Ref.	N/A
Early clinical	13 (87)	2 (13)	**0.27**	**0.072-1.0**
Post-clinical	11 (58)	8 (42)	0.87	0.46-1.6

ATMP, advanced therapeutic medicinal product; CHMP, Committee for Medicinal Products for Human Use; CMA, conditional marketing authorization; FDA, Food and Drug Administration (United States); MA, marketing authorization; MAA, marketing authorization application; N/A, not applicable

* associations based on disproportionality in bold

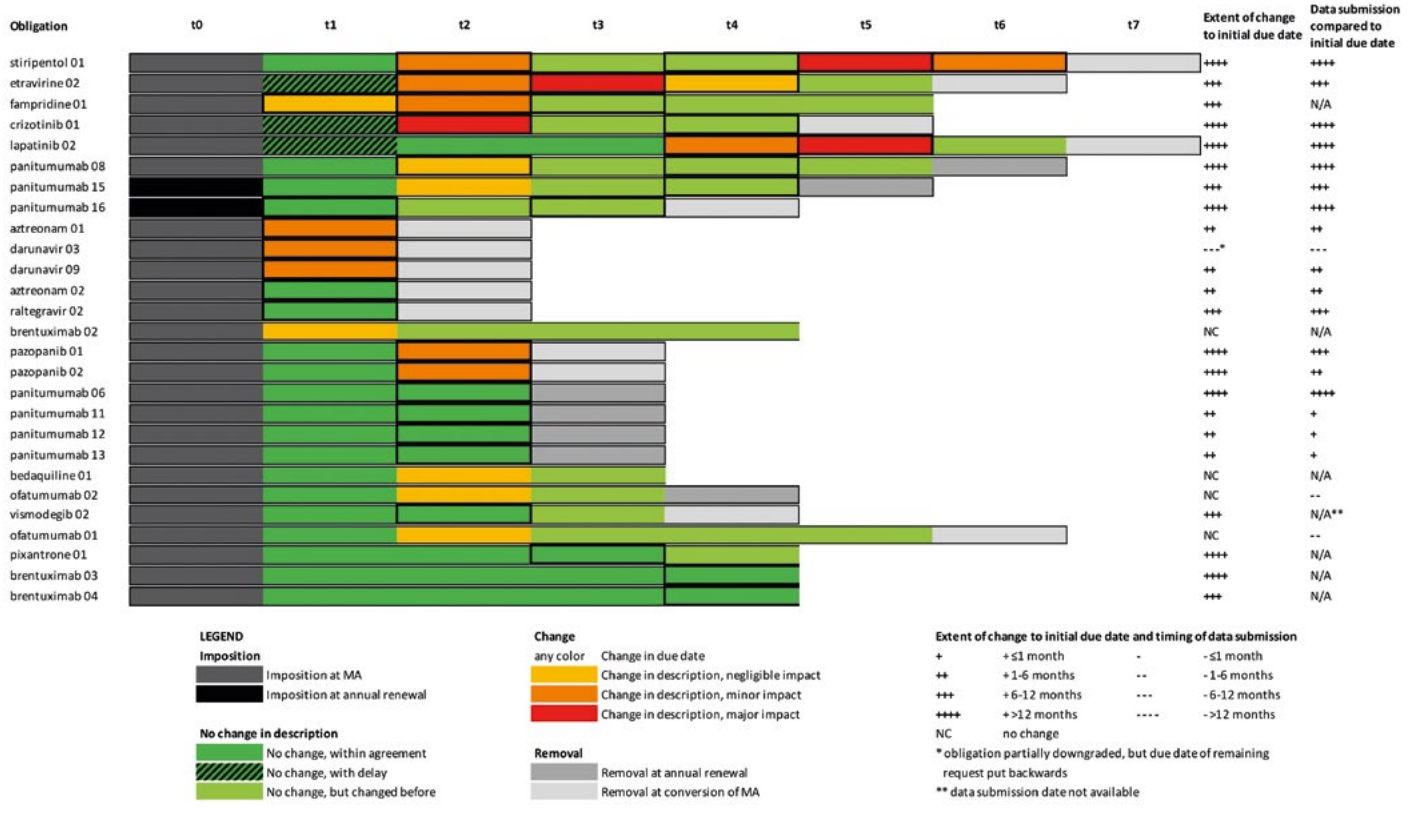

Figure 1 Visualisation of changes made to specific obligations and overview of timing of data submission for all changed obligations (n=27)

Ordered to number of changes, timing of change, type of change and time at risk of change; further listed by alphabet. MA, marketing authorization; N/A, not applicable

All four obligation changes assessed as having major impact were imposed between 2007 and 2012 for small molecule medicines (crizotinib, etravirine, lapatinib and stiripentol) for which alternatives were available. All obligations addressed a clinical uncertainty identified at time of MA. The initially requested activity concerned an interventional phase III study, which in three out of four needed to be initiated after authorization. With regard to changes, two studies were downgraded from an initially requested randomized clinical trial to a retrospective observational study, one study was discontinued and replaced by data from three ongoing studies and for one study an additional detailed safety analysis was requested following an assessment of interim results.

Timing of data submission

Because the data submission date was not available for one obligation, we assessed the timing of data submission for 47 obligations that were removed because they were considered fulfilled. The timeframe to data submission as initially set by the EMA was on median 394 days (IQR 159–759 days). Data were submitted on median 2 days after the initial due date (IQR –25 to +125 days). Overall, for 55% (n = 26/47) of the obligations, data were submitted after the initial due date, with 23% (n = 11/47) submitted more than half a year later. Strikingly, the three obligations with the longest time to data submission (5–6 years) all underwent changes that had a major impact on the initially requested activity. For all changed obligations, the timing of data submission is depicted in Figure 1.

Of the 47 obligations, for 18 obligations the initial due date was adjusted at least once. When including these updated due dates in the analysis, data were submitted on median 14 days before the updated due date (IQR –73 to –1 days). For 23% (n = 11/47) of the obligations data were submitted after the updated due date. For nine of these obligations this happened within two weeks and for two obligations after 92 and 292 days, respectively (both for panitumumab).

Factors associated with change to obligations

For all 69 obligations we further explored potential factors for change by calculating risk ratios (RRs; Table 1). Based on our chosen cutoff points, we identified 11 drug-related, procedure-related, and obligation-related factors that were associated with change to obligations. The drug-related factors associated with change were drug type (biological or advanced therapeutic medicinal product (ATMP) vs. small molecule; 50% vs. 33% changed; RR = 1.5) and US Food and Drug Administration

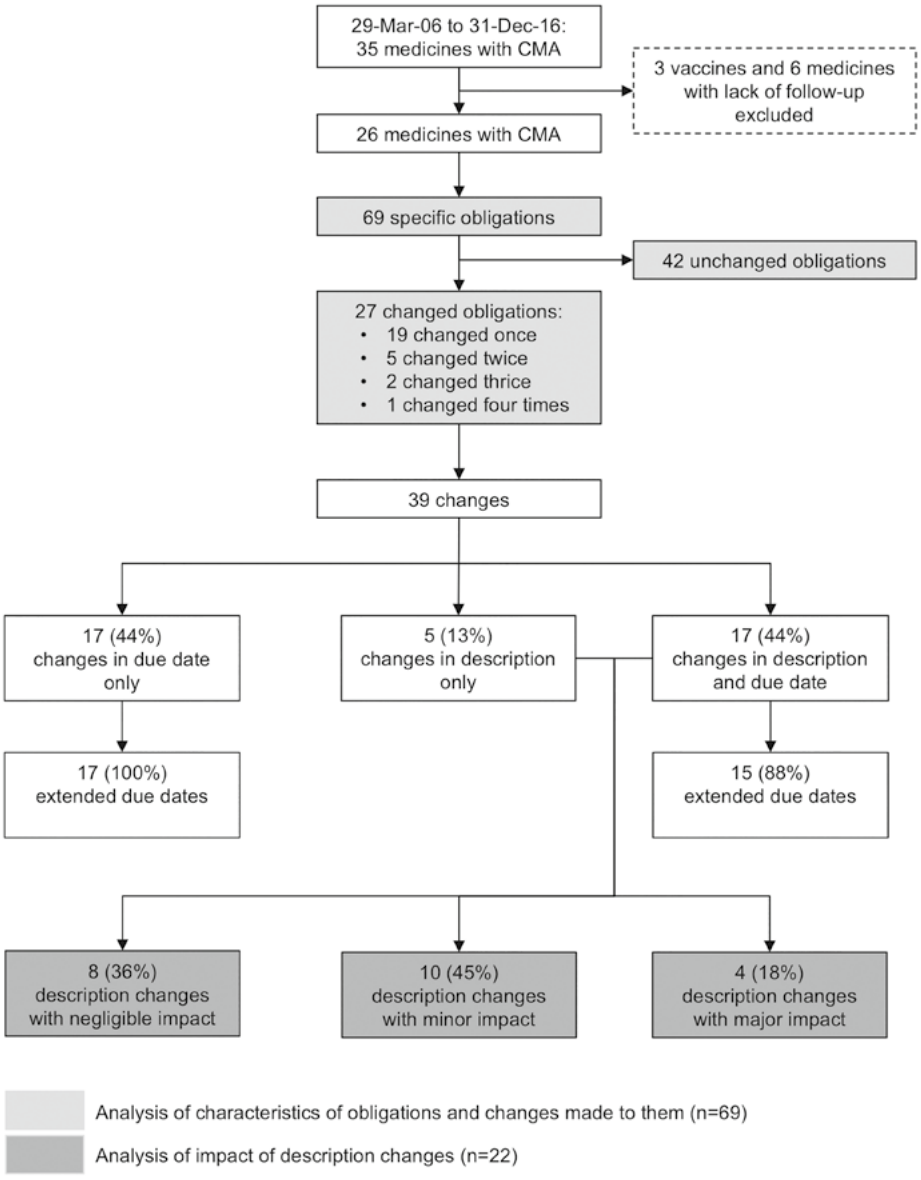

Figure 2 Flowchart showing the process of identification of obligations and changes
CMA, conditional marketing authorization

(FDA) approval (no approval vs. regular approval; 29% vs. 47% changed; RR = 0.61). The procedure-related factors associated with change were prospective use of CMA pathway (yes vs. no; 27% vs. 47% changed; RR = 0.58), accelerated assessment during the MA procedure (yes vs. no; 25% vs. 40% changed; RR = 0.63), adherence to scientific advice or protocol assistance (yes vs. no; 47% vs. 32% changed; = RR 1.5), MA procedure clock-stop time (i.e., the portion of the approval process during which the company prepares answers to questions posed by regulators; >160 days vs. ≤160 days; 46% vs. 31% changed; RR = 1.5) and MA procedure calendar time (i.e., the full length of the approval process including time for re-examination, where applicable; >1 year vs. ≤1 year; 47% vs. 27% changed; RR = 1.7). The obligation-related factors associated with change were addressed uncertainty (other vs. clinical effect; 20% vs. 42% changed; RR = 0.47), study status (new study vs. ongoing study; 61% vs. 29% changed; RR = 2.1), study design (observational vs. interventional; 67% vs. 38% changed; RR = 1.8), and development phase addressed by obligation (early clinical vs. late clinical; 13% vs. 49% changed; RR = 0.27).

Discussion

The aim of this study was to characterize specific obligations imposed on the CMA of medicines licensed by the EMA, examine changes to their description and due dates after initial authorization, determine timing of data submission relative to due dates and drug-related, procedure-related, and obligation-related factors associated with change. The results indicate that a relatively large proportion of obligations (27/69; 39%) was changed at least once between their imposition and removal or the end of follow-up. The majority of these changes concerned at least a change in due date (34/39) necessary to account for delays. In line with previous research,[6, 8] we found that for 11 obligations, data were submitted more than half a year later, reflecting substantial delays in data availability. Additionally, four changes to the description of obligations had a major impact on the initially requested activities, severely affecting the data that would become available.

Various studies have interpreted results like our study by focusing on whether companies indeed honor postmarketing commitments,[1-5, 7, 10-12] with three of these studies focusing specifically on the CMA pathway.[6, 8, 9] Our study contributes to the findings of these studies by demonstrating that the majority of obligations attached to CMAs are honored. Our results also suggest that regulators make extensive use of the annual renewal procedure to assess the progress of obligations. This is evident from the observation that, in most cases, regulators make small changes to

obligation descriptions that do not have a major impact on the initially requested activity. However, we also show that due date changes do result in considerable delays in data availability. The consequences for public health of these delays might be substantial. Because these are medicines for which relatively many uncertainties exist, patients may unnecessarily be exposed to unknown risks, especially when their physician is unable to accurately assess the impact of these uncertainties.[15] The results show that these risks could have been characterized earlier if initial due dates were adhered to. A previous study by Davis et al.[16] also showed that for most oncology medicines authorized based on limited evidence regarding benefits, evidence on overall survival and quality of life was still not available after a minimum of 3.3 years after authorization. This suggests that accepted uncertainties at the time of authorization may not readily be resolved, making it difficult for physicians, patients, and other stakeholders to make informed decisions without knowledge of the added clinical value of a medicine. These findings underline that regulators should be reluctant to accept changes and additional delays, unless strictly necessary to yield relevant results.

Given that we conducted a process study that followed obligations over time, our study can also provide insights in regulatory learning which is of great importance for the CMA pathway in order to further characterize the benefit-risk profile of a medicine through regulatory interventions (specific obligations). The observed changes to obligations mostly involved alterations of details of the obligations and thereby may represent a continuous regulatory search for the right way to receive desired information, while adapting to unforeseen situations along the way. Indeed, in response to other research,[12] regulators have mentioned that changes to postauthorization studies may be necessary to adjust to, for example, advances in science or changes in clinical practice.[13] In the end, regulators are limited in foreseeing outcomes and possible issues encountered along the way. Of note, changes to obligations do not decrease over time, suggesting that adaptations during annual renewal have become an important way for regulators to steer what data becomes available in the postmarketing phase.

However, the shift of a large body of evidence generation from the preauthorization to the postauthorization phase puts pressure on regulators to make the process of conducting obligations as efficient and effective as possible in order to ensure that comprehensive data are available in a timely manner. Our study may assist in this challenge as it identified 11 factors disproportionally associated with change to obligations. These factors point toward two major conditions under which learning about a medicine's uncertainties in the postauthorization phase can be more or

less effective and efficient. Although these analyses had limited statistical power, we did observe a few patterns that support insights from previous research. First, prospectively planning a CMA following early dialogue and along with timely consideration of relevant and feasible obligations seems to contribute to receiving additional data in time, as suggested before.[8, 17] We found that this approach also results in less need to change the request along the way. This is demonstrated by a relatively small number of changes associated with: (i) an applicant's request for CMA at time of application for a MA as compared to using the CMA as a "rescue option" later in the procedure; (ii) imposition of ongoing studies as a specific obligation (by regulators) as compared to imposition of new studies; (iii) an accelerated assessment of the application; and (iv) and (v) longer review times both in terms of the answering of outstanding questions from regulators by companies and the entire duration of the approval process, also including review time by regulators. Accelerated assessment can be granted following an early request for consideration of this approach and, additionally, applicants are urged to request a presubmission meeting during which they can already present the data and Risk Management Plan that supports the application,[18] thereby necessitating prospective planning. Relatively long review times indicate that uncertainties arising from insufficiently prepared application dossiers necessitate an iterative and reactive process to establish feasibility of the CMA. This requires a considerable amount of time from both the regulators assessing the applications and the applicant providing answers to questions. These observations suggest that use of the CMA pathway should be restricted to those situations in which it is planned prospectively and following early dialogue.

Second, the level of uncertainty about benefits and risks may play an important role, as illustrated by the fact that: (i) obligations addressing a clinical uncertainty as compared to other uncertainties (e.g., pharmacokinetics, monitoring of drug resistance, collecting information on medical practice); (ii) biologicals and ATMPs as compared to small molecule medicines; (iii) late-phase clinical studies (i.e., phase III/confirmatory studies) as compared to early-phase clinical studies; and (iv) new as compared to ongoing studies were all associated with obligation change. Learning under conditions of uncertainties is less straightforward and our study suggests that it is accompanied more often by unforeseen issues. An example is the greater ease of defining and performing exact follow-up activities based on an already ongoing study (possibly even with subject recruitment already finished) as compared to a new study. The four changes in description with a major impact on the initially requested activity also support the view that the level of uncertainty may complicate the learning process: they were all phase III studies that addressed a clinical uncertainty and three were newly initiated. The results suggest that regulators should pay additional

attention to obligations that address a high level of uncertainty at MA and continue to do so throughout the drug life-cycle.

The results also raise the question whether a CMA should be granted when the level of uncertainty is substantial. The moment of approval in a drug's life-cycle and the resulting consequences for additional data generation have been a subject of concern, arguing that a window of opportunity for generating data is lost when medicines are authorized early in the life-cycle. First, obtaining comprehensive data postauthorization may be complicated by patients who do not want to participate in requested studies when a medicine is already on the market.[19] This may explain why a large proportion of obligations were delayed. Indeed, a report by the EMA suggest that the main reason for due date changes were recruitment issues and in the case of brentuximab vedotin "the context of an already registered indication" was even explicitly noted as a reason for slow recruitment.[14] Second, companies may be stimulated to perform adequate studies by the prospect of receiving a marketing authorization.[19] This view is supported by our finding that obligations were less likely to be changed when no FDA approval for the medicine was obtained, as compared to regular FDA approval. This may stimulate companies to conduct these studies thoroughly and as soon as possible, in order to obtain necessary data for FDA approval. Third, the preauthorization phase offers less complex (i.e., more structured and controlled) conditions for learning. These latter two may be less so postauthorization, resulting in an iterative process of conducting studies through continuous fine-tuning. Regulators should, therefore, carefully consider the moment of (conditional) approval and the impact of the identified uncertainties, bearing in mind that data may become available later than expected.

There are a number of limitations to our study. Although the study cohort was relatively small, we were able to identify multiple factors associated with obligation changes based on disproportionality. However, although our results add substantially to the accumulating research on this topic, we did not answer the question whether submitted data indeed solve the outstanding issues or uncertainties they address and, thus, to what extent the observed delays and changes impacted knowledge about the clinical value of these medicines. This question is of utmost importance for patients and physicians who require confirmation of the benefit-risk profile based on robust data on long-term safety and effectiveness to allow for optimally informed decision-making on treatment. Therefore, this is an important focus for future research.

In conclusion, we identified changes in 39% of the obligations imposed as a condition to a CMA, representing several changes with a major impact on the initially requested activities and partially accounting for a delay in 55% of obligations. Additionally, we identified 11 factors associated with these changes that are potentially indicative of a continuous regulatory search for ways to reduce uncertainties of conditionally authorized medicines. Although the existing regulatory framework seems sufficient to address these issues and, therefore, policy reform may not be needed, efforts to improve implementation of CMA within that framework could be pursued. To facilitate further effective and efficient regulatory learning about benefits and risks of conditionally approved medicines, regulators are advised to ensure that CMAs are prospectively planned, consider the moment of approval in a medicine's life-cycle, and pay extra attention to obligations that address a high level of uncertainty.

Methods

Selection and extraction of specific obligations

We performed a retrospective cohort study of specific obligations imposed as a condition to the CMA of medicines licensed since 2006 in the EU (i.e., when the CMA regulation came into use). Eligible medicines were identified by searching EMA annual reports and the EMA website (www.ema.europa.eu). Vaccines were excluded, because they were authorized as mockups, only to be used in emergency situations and with obligations not actively being followed up by the MA holder. Obligations for CMA medicines that were authorized for at least one year or with one annual renewal up to December 31, 2016 were included.

Specific obligations for each conditionally authorized medicine were extracted from lists of obligations provided in Annex IIC to the MA of medicines consisting of a text description and one or more due dates for data submission. We considered each demarcated piece of text in Annex IIC describing one or more postauthorization activities ("the description") with one or more due dates for data submission as a separate obligation. If more than one due date was provided for an obligation, the latest due date was considered the final due date. Included obligations were followed during each annual renewal of the CMA. Follow-up was discontinued after the obligation was removed from Annex IIC at annual renewal, after conversion, withdrawal, revocation or suspension of the CMA or at the end of the study period, December 31, 2016, whichever came first.

To extract descriptions and due dates of obligations over time, we searched European Commission (EC) decision documents and EMA documentation (Annexes IIC to the MA, minutes and assessment reports of the Committee for Medicinal Products for Human Use [CHMP]) on the MA granting, annual renewals and conversion of the selected CMA medicines. EC decisions documents and the Annexes IIC were accessed through the EC Community Register of medicinal products (http://ec.europa.eu/health/documents/community-register/html/index_en.htm). CHMP minutes and assessment reports were accessed through the EMA's internal meeting documentation system. These data were available as part of a Memorandum of Understanding between Utrecht University and the Dutch Medicines Evaluation Board. Dates of inclusion in the Annex IIC were noted, using the corresponding EC decision dates. Extracted data were cross-checked against a recent EMA report.[14] Furthermore, the obligation data submission dates were also extracted from this report.

Characterization of changes to specific obligations

We determined the state of obligations at baseline and for each moment of follow-up. Together this resulted in a categorization of obligation states in nine mutually exclusive categories describing imposition, no change, change or removal of the obligation (Table 2). The possible states of obligations over time are depicted in Figure 3. When an obligation description concerned multiple activities with separate due dates per activity and one or more but not all of these activities and associated due dates were removed, we regarded this as continuation of the obligation rather than a change and categorized it as "no change".

Description changes were further assessed by two researchers (L.B. and J.H.) as having a negligible impact on the initially requested activity (i.e., further specifications of initial obligations), a minor impact (i.e., requests for limited additional or less data, but not expected to severely affect what data will come available), or a major impact (i.e., requests that are expected to severely affect what data will come available). For those changes assessed as having a major impact we read relevant EMA documentation (e.g., European Public Assessment Reports) to provide a narrative of the regulatory decision-making process.

Timing of data submission

For each obligation for which data submission resulted in removal of the obligation because they were considered fulfilled, we established the timing of data submission relative to the due date by calculating the difference between the data submission

date and both (i) the initially imposed final due date, and (ii) the updated final due date (only in case an adjustment to the initial due date was made). If several changes to the due date had been made, the last change was used.

Table 2 Definitions for obligation states used for characterization

Obligation state	Definition
Imposition	
Imposition at MA	Obligation included in the initial Annex IIC to the conditional marketing authorization
Imposition at annual renewal	Newly identified obligation, not previously included in Annex IIC*
No change	
No change, within agreement	Obligation description and due date unchanged in Annex IIC* and: a) no data submitted and follow-up date < final due date; or, b) data submitted since previous follow-up and data submission date ≤ final due date**
No change, with delay	Obligation description and due date unchanged in Annex IIC* and: a) no data submitted and follow-up date ≥ final due date; or, b) data submitted since previous follow-up and data submission date > final due date
Change	
Change in description***	Obligation description and/or obligation due date other than the final due date changed in Annex IIC*
Change in due date	Final due date of obligation advanced or extended in Annex IIC*
Change in description and due date***	Obligation description and/or obligation due date other than the final due date changed, plus final due date either advanced or postponed in Annex IIC*
Removal	
Removal at annual renewal	Previously included obligation no longer in Annex IIC following annual renewal*
Removal at conversion of MA	Previously included obligation no longer in Annex IIC following conversion of MA*

MA, marketing authorization
* Annex IIC following annual renewal or conversion compared to the Annex IIC at the last moment of follow-up, i.e. annual renewal or MA. Other procedures not taken into account.
** The due date refers to the data submission. There is a delay between data submission and assessment of the data followed by removal of the obligation from Annex IIC. Therefore, an obligation can be considered to be within the agreed timeline because data was submitted on time while it is maintained in Annex IIC since the data have not yet been assessed.
*** Changes in obligation description are assessed as having a negligible, minor or major impact on the initially requested activities.

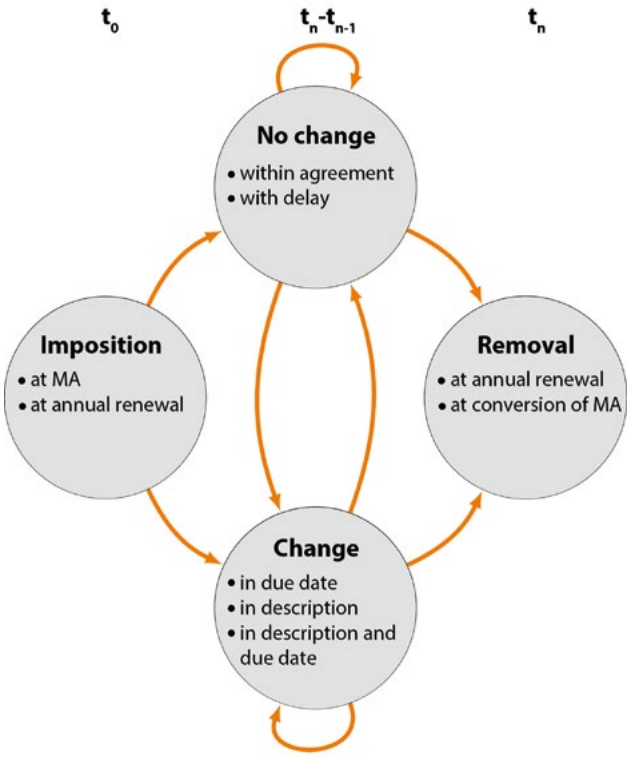

Figure 3 Dynamics in obligation states over time

The arrows indicate changes in obligation states following the assessment of progress and results of obligations during annual renewal. MA, marketing authorization

Potential factors associated with change to specific obligations

We extracted several prespecified drug-related, procedure-related and obligation-related factors mainly based on previous research on the CMA procedure,[8, 17] to assess associations with change to obligations (Table S3). For some procedure-related factors, these studies showed that a more complicated procedure was associated with more issues postauthorization.

EC decision documents and EMA documentation were used to extract most data on these factors. FDA documentation was used to extract data on whether the FDA approved the medicines. In addition, data from a recent EMA report[14] was used to cross-check extracted data and to extract the number of patients studied before MA application and data on the provision of and adherence to scientific advice and/or protocol assistance. We included three categorical factors concerning the duration of the MA procedure (i.e., the time between submission of the dossier and the opinion

of the CHMP), according to the "types" of time that can be distinguished. The first two factors concern "active time", during which the regulators initially assess the dossier and agree on questions to be asked, and "clock-stop time", during which the company prepares answers to questions posed by regulators. Additionally, in case of a negative CHMP opinion, a company may request a re-examination procedure that is not subject to clock-stop time. The third factor concerns the calendar time that combines both the active and clock-stop time, and, where relevant, the re-examination time. Furthermore, the MA applicant size was determined through the employee headcount and total revenue in the year of approval, using the Scrip 100 League Tables 2006–2016 (https://scrip.pharmamedtechbi.com/scrip100/home) or, alternatively, a company's annual report. Companies were considered a small or medium-sized enterprise if they employed fewer than 250 people and their total revenue did not exceed 50 million euros, in line with a recommendation by the EC,[20] or if no information could be identified. Other companies were considered "big pharma".

Data analysis

We described obligations, the number, type and timing of changes made to them and the timing of data submission. RRs and 95% confidence intervals were calculated using the Wald method to assess the association between potential factors and change to obligations, for which we used a cutoff of ≤0.66 or ≥1.5. Because the cohort of obligations studied is not a subset but the complete population and the absolute number of obligations is small, significance testing was deemed less relevant. All calculations were performed using R version 3.4.2 and RStudio Desktop version 1.1.383.

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Supplementary material

Box S1 The Conditional Marketing Authorisation pathway in the EU[1]

The conditional marketing authorisation regulation laid down in Commission Regulation (EC) No 507/2006 aims to provide timely access to medicines that address an unmet medical need in a) diseases that are considered "seriously debilitating or life-threatening", b) emergency situations, or c) orphan diseases. Medicines are considered to cover an unmet medical need when a) no satisfactory alternative ("method of diagnosis, prevention or treatment") is authorised, or b) if a "major therapeutic advantage" is achieved as compared to medicines already authorised. The regulation stipulates that in these situations, less comprehensive data than normally would be required, in case the benefit-risk is positive and provided that "the immediate availability on the market of the medicine outweighs the risk inherent in the fact that additional data are still required" and "it is likely that the applicant will be in a position to provide comprehensive clinical data" (within a reasonable timeframe).

A key feature of the CMA is the limited validity of the MA of one year as compared to the conventional five years, which facilitates the yearly assessment of the benefit-risk during "annual renewal". Furthermore, to obtain "comprehensive data" in order to resolve uncertainties, specific obligations are imposed as condition to the MA (recorded in Annex IIC), that are in place to resolve the observed data gap and which are proposed by the CHMP. These obligations consist of two elements: a text description of the obligation, i.e. one or more mandatory post-authorisation activities, and one or more due dates for the submission of data generated by these activities. The activities concern either ongoing studies that should be continued or new studies that should be conducted, but can also be other requests associated with acquiring knowledge on the quality, efficacy or safety of a medicine.

The results and progress on the fulfilment of obligations are assessed periodically through the annual renewal procedure of the marketing authorisation. When the obligation is considered fulfilled, it will be removed from the MA, while the lack of or unexpected results can lead to changes in descriptions or due dates. Moreover, new obligations can also be imposed during the annual renewal of the marketing authorisation.

If all obligations are considered fulfilled and the benefit-risk is considered positive, the CMA is converted to a non-conditional MA, which is no longer subject to specific obligations and annual renewals. If the benefit-risk is considered negative, the CMA is revoked. If one or more specific obligations are not met, but no new data has been provided that changes the benefit-risk, the CMA cannot be revoked. In such a case, the European Commission could impose a financial penalty, according to Commission Regulation (EC) No 658/2007,[2] and as amended by Commission Regulation (EU) No 488/2012.[3]

Table S1 Characteristics of conditionally authorised medicines for which specific obligations were included*

INN	Trade name	Applicant	Date of authorisation	Initially approved indication	No. of obligations
ataluren	Translarna	PTC Therapeutics, Limited	31/7/2014	Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.	1
aztreonam	Cayston	Gilead Sciences International Limited	21/9/2009	Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 18 years and older. The primary support for this indication is based on two single 28-day course placebo-controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	5
bedaquiline	Sirturo	Janssen-Cilag International NV	5/3/2014	SIRTURO is indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	1
blinatumomab	Blincyto	Amgen Europe B.V.	23/11/2015	BLINCYTO is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).	1

Table S1 *Continued*

INN	Trade name	Applicant	Date of authorisation	Initially approved indication	No. of obligations
bosutinib	Bosulif	Pfizer Limited	27/3/2013	Bosulif is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	1
brentuximab vedotin	Adcetris	Takeda Global Research and Development Centre (Europe) Ltd.	25/10/2012	ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).	4
cabozantinib	Cometriq	TMC Pharma Services Ltd.	21/3/2014	COMETRIQ is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma. For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.	1
ceritinib	Zykadia	Novartis Europharm Limited	6/5/2015	Zykadia is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.	2

Table S1 *Continued*

INN	Trade name	Applicant	Date of authorisation	Initially approved indication	No. of obligations
crizotinib	Xalkori	Pfizer Limited	23/10/2012	XALKORI is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).	3
darunavir	Prezista	Janssen-Cilag International NV	12/2/2007	PREZISTA, co-administered with 100 mg ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor (PI). This indication is based on week-24 analyses of virological and immunological response from 2 controlled dose range finding Phase II trials and additional data from uncontrolled studies. In deciding to initiate treatment with PREZISTA co-administered with 100 mg ritonavir careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of PREZISTA.	9
delamanid	Deltyba	Otsuka Novel Products GmbH	28/4/2014	Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents.	2

Table S1 *Continued*

INN	Trade name	Applicant	Date of authorisation	Initially approved indication	No. of obligations
etravirine	Intelence	Janssen-Cilag International NV	28/8/2008	INTELENCE, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients. This indication is based on week 24 analyses from 2 randomised, double-blind, placebo-controlled Phase III trials in highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors, where INTELENCE was investigated in combination with an optimised background regimen (OBR) which included darunavir/ritonavir.	2
everolimus	Votubia	Novartis Europharm Limited	2/9/2011	Votubia is indicated for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery. The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.	2
ex vivo expanded autologous human corneal epithelial cells containing stem cells	Holoclar	Chiesi Farmaceutici SPA	17/2/2015	Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1 - 2 mm^2 of undamaged limbus is required for biopsy.	1

Table S1 *Continued*

INN	Trade name	Applicant	Date of authorisation	Initially approved indication	No. of obligations
fampridine	Fampyra	Biogen Idec Limited	20/7/2011	Fampyra is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7).	1
lapatinib	Tyverb	Glaxo Group Limited	10/6/2008	Tyverb, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.	2
ofatumumab	Arzerra	Glaxo Group Limited	19/4/2010	Arzerra is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab.	2
osimertinib	Tagrisso	AstraZeneca AB	2/2/2016	TAGRISSO is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC).	1
panitumumab	Vectibix	Amgen Europe B.V.	3/12/2007	Vectibix is indicated as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.	16
pazopanib	Votrient	Glaxo Group Limited	14/6/2010	Votrient is indicated for the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.	2
pixantrone dimaleate	Pixuvri	CTI Life Sciences Limited	10/5/2012	Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.	1

Table S1 *Continued*

INN	Trade name	Applicant	Date of authorisation	Initially approved indication	No. of obligations
raltegravir	Isentress	Merck Sharp & Dohme Limited	20/12/2007	ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy. This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials of 24 weeks duration in treatment-experienced patients	3
stiripentol	Diacomit	Biocodex	4/1/2007	Diacomit is indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate.	2
sunitinib	Sutent	Pfizer Limited	19/7/2006	SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. SUTENT is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy. Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC.	1

Table S1 *Continued*

INN	Trade name	Applicant	Date of authorisation	Initially approved indication	No. of obligations
vandetanib	Caprelsa	AstraZeneca AB	17/2/2012	Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.	1
vismodegib	Erivedge	Roche Registration Limited	12/7/2013	Erivedge is indicated for the treatment of adult patients with: • symptomatic metastatic basal cell carcinoma • locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.	2

INN, international nonproprietary name
* excluded medicines were: allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor and the herpes simplex I virus thymidine kinase (Zalmoxis), daratumumab (Darzalex), ixazomib (Ninlaro), obeticholic acid (Ocaliva), olaratumab (Lartruvo), pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) (Arepanrix and Humenza), pandemic influenza vaccine (H5N1) (live attenuated, nasal) (Pandemic influenza vaccine H5N1 Medimmune), venetoclax (Venclyxto).

Table S2 Description changes in specific obligations, with assessment of impact on the initially requested activities and reasons for change (n=22)

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
aztreonam 01	The applicant commits to submit the results of study GS-US-205-0110 and other available long term data *[by July 2010]*.	21/09/2009	Initial: 31/07/2010 Updated: 30/09/2010	1	Deleted: 'and other available long term data'. [minor impact]	Following submission of final results of study CP-AI-006
bedaquiline 01	The MAH will evaluate additional efficacy and safety data of bedaquiline in different treatment regimen compared to a regimen that does not include bedaquiline (confirmatory phase III study) following an agreed protocol.	05/03/2014	30/11/2021 (unchanged)	2	Interim analysis changed from W68 to W76 and due date changed to 2Q 2018 Primary analysis changed from W68 to W76 and due date changed to 4Q 2020 [negligible impact]	-
brentuximab 02	A Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500) should be performed including a sufficient number of sALCL patients (i.e. at least n=50, Study MA25101).	25/10/2012	31/12/2018 (unchanged)	1	Rephrased to 'A Non-interventional Post-Authorisation...' [negligible impact]	SO description updated to specify that the study in question should be non-interventional

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
crizotinib 01	The MAH should submit the CSR of study A8081007, *[expected in Q1 2013]*. The CSR should also include a detailed analysis of outcome on post-progression treatments in Study 1007 as well as efficacy and baseline data according to race (Caucasian/Asian) by treatment groups.	23/10/2012	Initial: 31/03/2013 Updated: 30/06/2013	2	New wording: 'The MAH is requested to update OS status of study A8081007 and provide the final data within 9 months after the required 238 OS events have been reached. The CSR should also include a detailed safety analysis.' [major impact]	- NB: request for additional detailed safety analysis regarded as having a major impact
darunavir 03	The 48 week (primary analysis) final study report from study TMC114-C214 (A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of TMC114/ RTV versus LPV/RTV in treatment-experienced HIV-1 infected subjects) should be provided and should contain an analysis assessing the effect of coadministered nevirapine and efavirenz on darunavir; in addition estimation of intra-subject variability.	12/02/2007	Initial: 30/09/2008 Updated: 28/02/2008	1	New wording: 'The data of the 48 week (primary analysis) final study report from study TMC114-C214 (A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of TMC114/RTV versus LPV/RTV in treatment-experienced HIV-1 infected subjects) should be presented within a Type II variation to extend the indication to the patient population studied, as appropriate.' [minor impact]	Removal of explicit reference to assessment of effects of nevirapine and efavirenz and of intra-subject variability, addition of reference to possible extension of indication (in view of the relevance of this information to the indication); Week 96 data downgraded to FUM since "the 96 weeks data are no longer considered relevant as a SOB within the context of this MA

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
	The week 96 final study report from study TMC114-C214 should be provided.					(highly experienced patients). Data remain of relevance for expansion of present indication."
darunavir 09	The data from the darunavir treatment arm that do not receive the candidate NNRTI (TMC125) for the two following studies should be provided: - week 24 (primary analysis) final study report from study TMC125-C206 (A Phase III randomized, double-blinded, placebo-controlled trial to investigate the efficacy, tolerability and safety of TMC125 as part of an ART including TMC114/RTV and an investigator-selected OBR in HIV-1 infected subjects with limited to no treatment options) - week 24 (primary analysis) final study report from study TMC125-C216 (A Phase III randomized, double-blinded, placebo-controlled trial to investigate the efficacy, tolerability and safety of TMC125 as part of an ART	12/02/2007	Initial: 31/10/2007 Updated: 31/01/2008	1	New wording: 'Based on the darunavir treatment arms [that do not receive the candidate NNRTI (TMC125)] of studies TMC125-C206 and -C216, the MAH should submit an integrated safety analysis of the 24 week data, and propose, if appropriate, the necessary changes to section 4.8 of the PREZISTA SPC.' [minor impact]	Reworded, requesting instead of two final study reports to provide integrated safety analysis for these 2 studies in a sub-group of study population

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
	including TMC114/RTV and an investigator-selected OBR in HIV-1 infected subjects with limited to no treatment options) should be submitted.					
etravirine 02	The applicant commits to conduct a confirmatory study with the objective to provide reassurance on the extrapolation of the study results from the two pivotal studies (DUET-1 and DUET-2) to the combined use of etravirine with boosted PIs other than darunavir/ ritonavir. To meet this objective an adequately powered clinical study should be designed to allow for a valid statistical comparison between combination therapy including etravirine + boosted PIs other than darunavir/ritonavir and standard triple therapy. The design should employ NNRTI resistance as part of the inclusion criteria, as well as individual stopping rules for non response and failure to treatment. A DSMB should be set-up.	28/08/2008	Initial: 30/06/2012 Updated: 30/06/2013	2, 3, 4 (three changes)	1. Added: 'The MAH commits to conduct a feasibility study to provide further information regarding the feasibility of conducting the currently proposed confirmatory study. Should the outcome of such a feasibility study be negative, the MAH will propose an alternative study design to confirm results from the DUET-1 & -2 studies, in line with current treatment guidelines for the target population.' [minor impact] 2. New wording: 'A study SHOULD be conducted with the objective of further charcterizing the clinical efficacy of etravirine with other boosted protease inhibitors than darunavir/r. The analysis will be based on the data from the EURESIST	Confirmatory study on the combined use of etravirine with boosted PIs other than darunavir/ ritonavir was replaced with a retrospective observational study (recommended in CHMP SA), due to slow recruitment in original study (only reason for major change provided by EMA)

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
	The applicant will provide the draft protocol of the study to the CHMP for agreement before study start. The applicant will provide regular updates on study progress within the PSURs. The final study report will be submitted for assessment whether the objective of the study has been met. The SmPC and Package Leaflet will be updated with the study results.				cohort and other appropriate sources of similar data. The final protocol for the dedicated study from the EURESIST cohort should be submitted to the CHMP for agreement prior to the start of the study. Final results for the study should be provided to the CHMP no later than 3Q2012.' [major impact] 3. New wording: 'TMC125IFD0000003 is a retrospective observational study which will be conducted to describe the antiretroviral activity of and resistance to etravirine in combination with background regimens containing boosted PI other than darunavir/ritonavir, using clinical cohort data of HIV-1 infected patients. Following agreement with the CHMP on the protocol, the final results for the study should be provided to the CHMP no later than 2Q 2013.' [negligible impact]	

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
fampridine 01	To conduct a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment. A study report is to be submitted.	20/07/2011	Initial: 30/06/2016 Updated: 31/12/2016	1, 2 (two changes)	1. New wording: 'To provide results of a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment based on a CHMP agreed protocol.' [negligible impact] 2. Added: 'An update of the progress in completing the obligation should be provided every 6 months.' [minor impact]	-

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
lapatinib 02	To conduct a Phase III randomised, controlled clinical study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-containing therapy compared with an appropriate, trastuzumab-containing control arm. *[The study protocol will be finalised and submitted to the EMEA by July 2008. The final study report for the trial will by submitted by May 2013.]*	10/06/2008	Initial: 31/05/2013 Updated: 31/12/2014	4, 5 (two changes)	1. Added: 'interim analysis report' [minor impact] 2. New wording: 'To provide comparative data on the incidence of CNS metastases from studies EGF108919 (COMPLETE), EGF105485 (TEACH) and EGF106808 (ALTTO).' [major impact]	Revised from dedicated randomised clinical study to evaluate the incidence of brain metastases (terminated due to lower than expected incidence of CNS metastases) to combination of data from 3 (ongoing) studies on incidence CNS metastases (only reason for major change provided by EMA)
ofatumumab 01	To conduct an open label, multicenter study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine refractory chronic lymphocytic leukaemia (CLL). *[The final protocol will be submitted for CHMP agreement within 3 months of conditional marketing authorisation*	19/04/2010	31/12/2014 (unchanged)	2	Rephrased: 'conduct' → 'submit' [negligible impact]	- (change not reported by EMA)

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
	date. The study report is to be submitted by December 2014, but the timing will be confirmed at the time of submission of the final protocol, when feasibility will be complete.]					
ofatumumab 02	To conduct a phase IV observational study to provide further data on the clinical efficacy and safety of ofatumumab. *[The final protocol will be submitted for CHMP agreement within 3 months of conditional marketing authorisation date.]* The time needed to recruit the target number of subjects (100) will depend on the date of availability on the market of Arzerra across EU, degree of use and on the willingness of patients and physicians to participate in the study. *[The study report is to be submitted by June 2013, but the timing may be changed at the time of submission of the final protocol.]*	19/04/2010	30/06/2013 (unchanged)	2	Rephrased: 'conduct' → 'submit' [negligible impact]	- (change not reported by EMA)

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
panitumumab 08	To submit the clinical study summary reports of SPIRITT and PRECEPT studies including the safety-efficacy analysis in relation with KRAS *[by Q2-2009]*	03/12/2007	Initial: 30/06/2009 Updated: 30/09/2012	2	PRECEPT study deleted from description. [negligible impact]	- (by EMA regarded as separate obligation and finalisation thereof)
panitumumab 15	To complete a confirmatory trial examining panitumumab monotherapy in licensed indication. In particular to - Provide a study protocol outline for this study *[by February 2009]* - Based on Rapporteur feedback on the outline to provide a final protocol to CHMP *[in April 2009]* to allow agreement of the final protocol with CHMP - Commit to start the study as soon as is possible - Agree a timeline for provision of data from the study once the design has been agreed	19/03/2009 (imposed during first AR)	Initial: 31/12/2012 Updated: 30/09/2013	2	Clarification which study should be conducted: 20080763 [negligible impact]	-

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
pazopanib 01	Submit the study report for VEG108844 (a study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/ or metastatic renal cell carcinoma) *[by February 2012]*	14/06/2010	Initial: 29/02/2012 Updated: 30/06/2013	2	New wording: 'Submit the study report for VEG108844 (a study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/ or metastatic renal cell carcinoma). This study report will contain a pooled analysis of data from study VEG108844 and VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Assian subjects with locally advanced and/ or metastatic renal cell carcinoma – a sub study of VEG108844). A discussion on the applicability of the efficacy data from VEG113078 to the European population will be provided.' [minor impact]	To require pooled data including also Study VEG113078 (pooled data already subject to a separate SO)

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
pazopanib 02	Submit a pooled analysis of data from study VEG108844 and VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma - a sub study of VEG108844). The studies should be appropriately powered to demonstrate non-inferiority with a margin of 1.22. A discussion on the applicability of the efficacy data from VEG113078 to the European population should be provided *[by June 2012]*.	14/06/2010	Initial: 30/06/2012 Updated: 30/09/2013	2	New wording: 'Submit an updated pooled analysis of the PFS data as assessed by the Investigator from study VEG108844 and VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma - a sub study of VEG108844). The studies should be appropriately powered to demonstrate non-inferiority with a margin of 1.22 with 794 PFS events per Investigator.' [minor impact]	Endpoint for pooled analysis and power calculation specified in the description of the specific obligation (due to higher than expected discontinuation rate and more than expected missing assessments)
stiripentol 01	A randomised controlled clinical trial with stiripentol in the add-on therapy using maximally safe doses of clobazam+valproate *[by 2009]* (STP 165).	04/01/2007	Initial: 31/12/2009 Updated: 31/12/2012	2, 5, 6 (three changes)	1. New wording: 'A multicentre randomised controlled trial comparing topiramate, stiripentol and clobazam as adjunctive therapy to valproate and clobazam in paediatric patients with Dravet's syndrome (SMEI) not adequately controlled	Difficulties in conduct of the study (consortium disbanded, slow approval process) + new PK data indicate that original study would unlikely address the research question

Table S2 *Continued*

Obligation	Initial wording*	Date imposed**	Final due date	Time to change (ARs)	Change(s) [assessment of impact]	Reason***
					with clobazam and valproate, and auxiliary pharmacogenetic study (STP 167).' [minor impact] 2. New wording: 'To provide robust observational study data to support the efficacy and safety of stiripentol to control clonic seizure or tonic-clonic seizure in Dravet's Syndrome over the short and longer term of at least 1 year.' [major impact] 3. New wording: 'To provide further observational data to support the intrinsic anticonvulsant activity of stiripentol, and to further support its safety and efficacy in the treatment of Dravet's syndrome.' [minor impact]	(only reason for major change provided by EMA)

AR, annual renewal
* text sections that only concern the obligation due date(s) but are formally considered part of the obligation description are shown in italic and between brackets
** also date of MA approval, unless stated otherwise
*** available from EMA,[4] with additional specification by the authors underlined

Table S3 Drug-, procedure- and obligation-related factors possibly impacting obligation changes

Factor	Categories
Drug-related	
Marketing authorisation applicant size	Big pharma
	Small and medium-sized enterprises
Drug type	Biological/ATMP vs. small molecule
Indication	Infectious disease
	Oncology
	Other
FDA approval	Regular approval
	Accelerated approval
	No approval
Size of studies delivering main/pivotal evidence at MAA	>500 patients vs. 0-500 patients
Procedure-related	
Prospective use of CMA pathway	Yes vs. no
CHMP experience with CMA pathway	Imposed in 2009-2016 vs. imposed in 2006-2008
Accelerated assessment during MA procedure	Yes vs. no
Re-examination during MA procedure	Yes vs. no
Scientific advice or protocol assistance (SA/PA) received before authorisation	Yes vs. no
Adherence to SA/PA	No
	Yes
	No advice provided
Scope of Commission Regulation (EC) No 507/2006 – Orphan designation	Yes vs. no
Scope of Commission Regulation (EC) No 507/2006 – Treatment for seriously debilitating or life-threatening disease	Yes vs. no
Argumentation for unmet medical need	Other vs. no satisfactory method of diagnosis, prevention or treatment authorised
CHMP agreement on MA	Majority vs. consensus
MA procedure active time*	≤200 days
	201-210 days
	>210 days
MA procedure clock-stop time**	>160 days vs. ≤160 days
MA procedure calendar time***	>1 year vs. ≤1 year

Table S3 *Continued*

Factor	Categories
Obligation-related	
Addressed uncertainty	Other vs. clinical effect
Study status	Ongoing study
	New study
	Other obligation (no study)
Study design	Interventional
	Observational
	Other obligation (no study)
Development phase addressed by obligation	Late clinical (phase 3)
	Early clinical
	Post-clinical

ATMP, advanced therapeutic medicinal product; FDA, Food and Drug Administration (United States); MAA, marketing authorisation application; CMA, conditional marketing authorisation; CHMP, Committee for Medicinal Products for Human Use; MA, marketing authorisation
* Active time was divided into ≤200 days, 201-210 days and >210 days, since the general MA procedure is envisaged to take up to 210 days for regulatory assessment.[5]
** Clock-stop time was divided into ≤160 days and >160 days, which translates into a total MA procedure time of around 1 year and correlates with the median amount of clock-stop time observed in this study.
***Calendar time was divided into ≤1 year and >1 year, which reflects the sum of the cut-off values that were used for the MA procedure active time and clock-stop time variables.

Supplementary references

1. European Commission. Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. *OJ* 2006;L 92:6-9.
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3. European Commission. Commission Regulation (EU) No 488/2012 of 8 June 2012 amending Regulation (EC) No 658/2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council. *OJ* 2012;L 150:68-70.
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Chapter 2.2

Comprehensive evaluation of post-approval regulatory actions during the drug lifecycle – a focus on benefits and risks

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Abstract

Background: Prior studies investigated regulatory actions that reflected a negative impact on drug risks. We aimed to evaluate occurrence of regulatory actions that reflected a negative or positive impact on benefits or risks, as well as relations between them.

Research design and methods: We followed EMA-approved innovative drugs from approval (2009-2010) until July 2020 or withdrawal to identify regulatory actions. We assessed these for impact on benefits or risks and relations between actions. Additionally, we scrutinized drug lifecycles for time-variant characteristics that may contribute to specific patterns of regulatory actions.

Results: We identified 14 letters and 361 label updates for 40 drugs. Of the label updates, 85 (24%) reflected a positive impact, mostly concerning indications, and 276 (76%) a negative impact, mostly adverse drug reactions. Many updates (54%) occurred simultaneously with other updates, also if these reflected a different impact. Furthermore, levels of patient exposure, innovativeness, needs for regulatory learning and unexpected risks may contribute to patterns of regulatory actions.

Conclusions: Almost a quarter of regulatory actions reflected a positive impact on benefits and risks. Also, simultaneous learning about benefits and risks suggests an important role for drug development in risk characterization. These findings may impact regulatory analyses and decision-making.

Introduction

Regulatory learning about drugs is an important process. At the time of initial drug approval, many uncertainties about its clinical aspects remain.[1] Knowledge is often limited to efficacy and the most common adverse events when used to treat a specific disease in a specific patient population. While a well-designed clinical trial in a restricted patient population is paramount to establishing efficacy,[2] it limits generalizability of these findings to the broader patient population. At the same time, it limits the characterization of a drug's safety profile in the broader population.[2] Also, it often follows too few patients for a too short time period to identify rare adverse events and adverse events with a long latency.[3] Thus, there is ample room for post-approval learning about benefits and risks of drugs. Indeed, efficacy in broader or completely other indications is studied years after initial approval[4] and the methods to characterize the safety profile continue to be refined.[5]

Contemporary drug regulation reflects the idea that drug development is never finished. It aims to capture and stimulate continuous knowledge accrual throughout the entire drug lifecycle, rather than a one-off learning experience at initial approval decisions.[6, 7] Regulators can stimulate this process in the post-approval phase through e.g. requests for additional studies and periodic reports of information available in company databases and scientific literature, among others. Consequently, new information comes available on a regular basis, which is then assessed in terms of their positive or negative impact on either the benefits or risks of drugs. The weighing of information on adverse effects and other potential risks against the desired, therapeutic benefits of a drug in a specific population is called benefit-risk assessment and is important to all regulatory decisions in any country.[8, 9] It may lead to post-approval regulatory actions such as the approval or refusal of a new drug or indication, the broadening or restriction of an indication, the addition of a new warning or adverse drug reaction (ADR) to the drug label, or perhaps the removal of an existing one.[10-13] In some cases, new information may question the available knowledge or suggest a critical risk not known or expected before. Then, a complete reassessment of the benefit-risk balance based on all available data may be considered, in Europe also known as a referral procedure.[14-16]

Post-approval regulatory decision-making thus universally considers both drug benefits and risks and whether new information has a positive or a negative impact on either. However, recent studies on the outcomes of regulatory decision-making mostly assessed safety-related post-approval regulatory actions, i.e. those that respond to new

information with a negative impact on drug risks. This often concerns newly identified ADRs, and the respective regulatory actions include drug label updates,[17-23] healthcare professional letters or similar notifications,[24, 25] withdrawals,[14, 26-29] or a combination thereof.[15, 16, 30-40] Of these studies, few also assessed benefit-related post-approval regulatory actions – such as amended indications – as outcomes,[15, 20, 21] let alone how they are associated with safety-related regulatory actions.[24] The few studies that focused primarily on amended indications[4] or posology changes[41, 42] did not consider other regulatory actions. Most importantly, no study comprehensively assessed relations between various regulatory actions.

We aimed to build on this previous research by assessing the type and impact of European post-approval regulatory actions that occur during the drug lifecycle (i.e., whether reflecting new information with a positive or a negative impact on benefits or risks), any relations between them, and potential characteristics that seem to play a role in their occurrence. We therefore used publicly available European regulatory action data, including changes to the marketing authorization, Direct Healthcare Professional Communications (DHPC) and all newly available clinical information in the product label – the Summary of Product Characteristics (SmPC).

Patients and methods

Study design and cohort selection

We performed a retrospective cohort study of drugs approved by the European Medicines Agency (EMA) between 1 January 2009 and 31 December 2010 that contained a new active substance and followed these up until 1 July 2020 or withdrawal from the market if that occurred earlier. This allowed 10 years of follow-up that was considered a relevant time horizon to address the aim of this study. In case of duplicate applications, i.e. drugs approved under multiple product names, we included the one with the longest time on the market. We excluded vaccines approved for the prevention of seasonal disease (e.g. influenza) because these are often marketed only temporarily, rendering them incomparable to other drugs in terms of their lifecycle and consequently changes to their marketing authorization. For the remaining drugs, European Public Assessment Reports (EPAR) at the EMA website[i] were consulted to extract baseline drug and regulatory characteristics. Confidential Periodic Safety Update Reports (PSUR) were accessed through the

[i] www.ema.europa.eu

database of the Dutch Medicines Evaluation Board to extract information about cumulative patient exposure at end of follow-up.

Data collection

For the included drugs, we accessed their EPARs and extracted all regulatory procedures that occurred between drug approval and 1 July 2020 and led to regulatory actions (Figure 1, inspired by work of Ebbers et al.[43]). For each regulatory procedure, we extracted i) a high-level description of the type of information that prompted regulatory actions, ii) the decision date, iii) the type of regulatory action(s) (Figure 1), and iv) the number of changes in case the regulatory action concerned an SmPC update. If any of iii-iv were unclear, we accessed the Union Register of medicinal products for human use[ii] to compare the SmPCs before and after the decision and extracted these data accordingly.

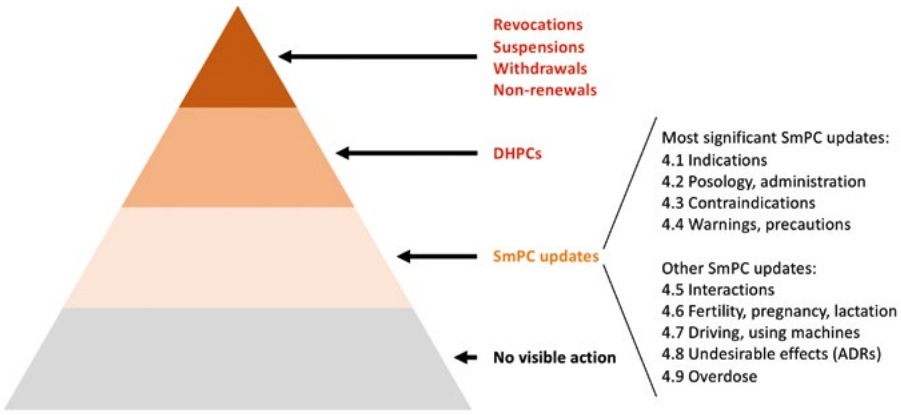

Figure 1 Potential regulatory actions, ordered according to the impact on benefits and risks
Red text indicates per definition a negative impact on benefits and risks, orange text indicates either a positive or negative impact. ADR, adverse drug reaction; DHPC, Direct Healthcare Professional Communication; SmPC, Summary of Product Characteristics

To limit our study to regulatory actions that reflected truly new information concerning benefits and risks, we only included SmPC updates that concerned topics that were not previously described in that specific section or if their description was substantially altered, e.g. updated warnings to note that fatal outcomes are possible.

[ii] http://ec.europa.eu/health/documents/community-register/html/index_en.htm

Also, we only included SmPC updates that reported in vitro or pharmacokinetic drug-drug interaction study results if these also noted implications or recommendations for clinical practice. We did not include SmPC updates that concerned (specifications of) clinical recommendations for topics already described in that specific section, confirmations of previously included information regarding expected or potential benefits and risks (e.g. concerning renally or hepatically impaired patients), study results, rewordings, clarifications, or cross-references to other SmPC sections.

Since EPARs do not provide information on DHPCs, we used European national regulatory authorities' websites to identify relevant DHPCs for the included drugs.[iii] From each DHPC, we extracted i) the DHPC date, ii) a high-level description of the type of new information it addressed (less detailed than for SmPC updates), and iii) the number of key messages it communicated. Regulatory actions due to commercial reasons were excluded.

Categorization of regulatory actions according to the impact of new information on benefits and risks

While newly available information may have a positive or negative impact on knowledge of drug benefits and risks, detailed information is often not publicly available. Instead, regulatory actions are indicative of such information since they aim to ensure an optimal benefit-risk balance. Therefore, we reviewed the content of all changes to the marketing authorization, DHPCs and SmPC updates to understand what impact on benefits and risks these regulatory actions reflected. In addition to the impact being assessed as positive or negative, it was assessed as impact on benefits, defined as impact on the population eligible to use the drug and how to use it, or impact on risks, defined as safety aspects. This resulted in the following four categories: A) positive impact on benefits, e.g., a broadening of the indication; B) positive impact on risks, e.g., a decreased frequency of a known ADR; C) negative impact on benefits, e.g., a new contraindication; and D) negative impact on risks, e.g., a new ADR (Figure 2).

To consistently assess the category that each regulatory action belonged to, we created a list of subcategories (Table S1). This occurred in an explorative and iterative fashion, by creating an initial set of subcategories that were expected to be encountered based on input from LTB, MK, JH and AKMT.

[iii] See https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/direct-healthcare-professional-communications for an overview of national regulatory authorities' web pages where information on DHPCs is published.

This already included the majority of the subcategories in Table S1. Subsequently, when these provided an insufficient basis for detailed and consistent assessment, existing subcategories were reworded or complemented by new subcategories by LTB and MK and agreed by the other authors. Examples of new subcategories were “Change in posology resulting in a reduced patient-burden” and “Change of a contraindication into recommendation”. This process was repeated until each regulatory action was categorized and the subcategories were mutually exclusive.

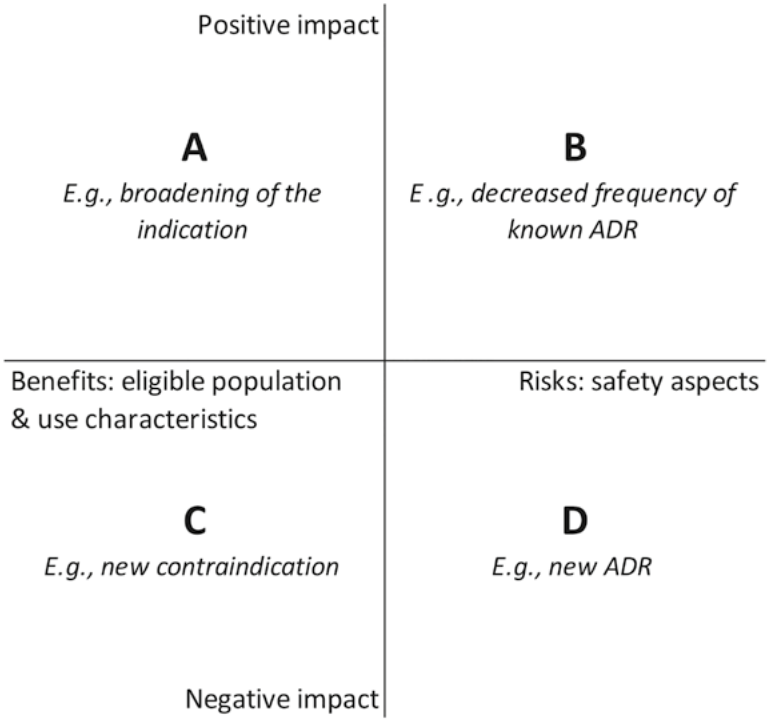

Figure 2 Categories used to assess a positive or negative impact on benefits and risks reflected by regulatory actions

ADR, adverse drug reaction

In case an SmPC update comprised several changes to the same SmPC section that were considered to reflect an impact on eligible population and use characteristics as well as safety aspects (e.g. in case of multiple new interactions listed in the respective SmPC section), we categorized this SmPC section as the former (A or C). In case changes reflected both a positive and a negative impact (this only occurred in case of multiple updates to the SmPC section on ADRs, i.e. “Undesirable effects”), we categorized the updated SmPC section according to the most often occurring category.

This way, each regulatory action was assessed by two researchers (LTB and MK). This ensured discussion about regulatory actions that were potentially difficult to categorize, which was predominantly the case for SmPC updates to the interactions section. There, we needed to establish the effect of the interaction on exposure to the drugs involved, and consequently their efficacy and/or safety (Table S1).

Data analysis

First, we used descriptive statistics to describe the cohort of drugs with regard to drug and regulatory characteristics as well as the regulatory actions that these drugs underwent during follow-up, and the type of information that prompted regulatory actions. Second, we categorized all regulatory actions according to the approach discussed above. Third, we described relations between regulatory actions, i.e. simultaneous updates within the same procedure. Last, we scrutinized individual drug lifecycles to identify time-variant characteristics that may typically play a role in specific patterns of regulatory actions, based on cohort characteristics, EPARs, previous research, and our own regulatory experience. For this analysis, we took into account the most significant regulatory actions, i.e. all but the 'other SmPC updates' listed in Figure 1.

Results

Description of the cohort

We included 40 drugs that were approved by EMA in 2009 and 2010 (Table 1). Of these, five were later withdrawn by the company – all because of commercial reasons: autologous cartilage cells (brand name ChondroCelect), catumaxomab (Removab), collagenase Clostridium histolyticum (Xiapex), ofatumumab (Arzerra) and rilonacept (Rilonacept Regeneron). The remaining drugs were followed until 1 July 2020, resulting in a median follow-up of 10.5 years (interquartile range 9.8-10.8 years).

Occurrence of regulatory actions and their impact on benefits and risks

During the study period, there were no revocations, suspensions, withdrawals (apart from the five because of commercial reasons discussed above) or non-renewals. However, we identified 14 DHPCs that had been distributed after new information with negative impact on benefits and risks had come available.

Table 1 Cohort characteristics

Characteristic	Drugs (*N* = 40)	
Drug characteristics		
Drug type		
Small molecule	24	60%
Biological/ATMP	16	40%
Therapeutic area		
Cancer treatment	6	15%
Cardiovascular treatment	4	10%
Immunosuppressive treatment	5	13%
Musculoskeletal disorder treatment	4	10%
Other treatment[a]	21	53%
Regulatory characteristics		
Approval pathway		
Standard approval	34	85%
Approval under exceptional circumstances	3	8%
Conditional approval	3	8%
Orphan designation at approval	9	23%
Other characteristics		
Cumulative patient exposure at end of follow-up		
Median patient-years (interquartile range)	132,215 (19,317-1,166,667)	

ATMP, advanced therapy medicinal product
[a] Multiple categories consisting of three or fewer drugs, e.g. antibacterial vaccines, sex hormones and related treatment.

Of these, one mainly had a negative impact on the eligible population and use characteristics, i.e. it communicated restrictions of the indication and new contraindications for dronedarone (Multaq) following a referral procedure. In addition, it communicated new warnings with regard to liver injury, lung toxicity and cardiovascular risk. Another DHPC also for dronedarone communicated that an increased cardiovascular risk had been observed in a study in a non-approved indication, which did not lead to an SmPC update but informed the start of the referral procedure. The remaining 12 DHPCs communicated (clinical recommendations for) one or two safety issues. Of these, another also concerned dronedarone. Six concerned denosumab (Prolia), ofatumumab and tolvaptan (Samsca) – two for each product. Five concerned epoetin theta (Eporatio), pazopanib (Votrient), regadenoson (Rapiscan), saxagliptin (Onglyza), and vernakalant (Brinavess) – one for each product. These 12 DHPCs often led to an update of SmPC sections concerning posology and administration, warnings and precautions and/or ADRs. However, these SmPC

updates were not all included in our study because some concerned (specifications of) clinical recommendations for topics already described in that SmPC section.

We also identified 266 regulatory procedures during which 361 SmPC sections had been updated with new information concerning benefits and risks. Of these 361 updates, 276 were considered to reflect a negative impact on benefits and risks (76%) and 85 to reflect a positive impact (24%). The updates most frequently concerned the ADR section (155, 43%), followed by the warnings and precautions section (85, 24%). For these sections, the majority of updates was considered to reflect a negative impact because it concerned new ADRs or increased frequencies of previously known ADRs (152/155, 98%), or new warnings or precautions (75/85, 88%), respectively. Another frequently updated SmPC section was the indications section (50, 14%), for which the majority of updates was considered to reflect a positive impact because it concerned new or broadened indications (48/50, 96%). Furthermore, while most updates to SmPC sections implemented one change to that specific section (252, 70%), in 109 instances (30%) two or more changes were implemented. These latter mostly concerned the ADR (81/109, 74%) and the warnings and precautions sections (18/109, 17%). A complete overview of all regulatory actions (DHPCs and updated SmPC sections) and their categorization according to impact on benefits and risks is provided in Table 2. In addition, an overview of the type of information that prompted the regulatory actions is provided in Table S2, according to the impact on benefits and risks.

Relations between SmPC updates

Looking closer into the occurrence of the 361 SmPC updates, we observed that during 85 of 266 regulatory procedures (32%) multiple SmPC sections were updated simultaneously. During the majority of these procedures (68, 80%), two SmPC sections were updated simultaneously, while during 17 procedures (20%), three or more SmPC sections were updated. In total, 194 of 361 updates to SmPC sections (54%) occurred simultaneously with at least one other SmPC section. Of these, 44 reflected a positive impact on benefits and risks and 150 reflected a negative impact, i.e. 52% and 54%, respectively, of all updated SmPC sections that reflected a positive or negative impact. Figure 3 illustrates for each SmPC section the number and proportion of updates that occurred simultaneously with updates to other sections, the impact reflected by these updates and the relations between the sections.

Table 2 Overview of regulatory actions that reflected a positive or negative impact on benefits and risks

Type of regulatory action	Positive impact Benefits (A)	Risks (B)	Negative impact Benefits (C)	Risks (D)	Total (*N* = 375)	
DHPCs	**–**	**–**	**1**	**13**	**14**	**4%**
SmPC updates	**73**	**12**	**14**	**262**	**361**	**96%**
Indications	48	–	2	–	*50*	*14%*[a]
Posology, administration	16	3	2	4	*25*	*7%*[a]
Contraindications	2	–	5	–	*7*	*2%*[a]
Warnings, precautions	4	6	1	74	*85*	*24%*[a]
Interactions	3	–	4	22	*29*	*8%*[a]
Fertility, pregnancy, lactation	–	–	–	3	*3*	*1%*[a]
Driving, using machines	–	–	–	5	*5*	*1%*[a]
Undesirable effects (ADRs)	–	3	–	152	*155*	*43%*[a]
Overdose	–	–	–	2	*2*	*1%*[a]

ADR, adverse drug reaction; DHPC, Direct Healthcare Professional Communication; SmPC, Summary of Product Characteristics
[a] Percentage of all 361 SmPC updates

Of the 85 regulatory procedures that led to simultaneous updates to SmPC sections, 55 (65%) concerned updates that only reflected a negative impact. Of these, 30 procedures led to a simultaneous update to the warnings and precautions section and the ADR section – the most commonly observed combination. The procedure that led to the most SmPC updates was the referral for dronedarone discussed earlier, which led to restrictions of the indication, new contraindications, new warnings in the posology and administration as well as the warnings and precautions section, and new ADRs.

The remaining 30 procedures (35%) concerned simultaneous updates that either reflected only a positive impact on benefits and risks, or a combination of positive and negative impact. Apart from one procedure during which interactions and a warning about interactions were removed for ulipristal acetate (ellaOne), all these procedures were initiated by study results that supported a new or broadened indication or an update of posology and/or administration characteristics. While 2 procedures only concerned these aspects, 27 procedures also led to changes in ADRs, warnings and precautions and/or other risk-related SmPC sections, indicating an important role for further post-approval drug development in characterizing drug risk profiles.

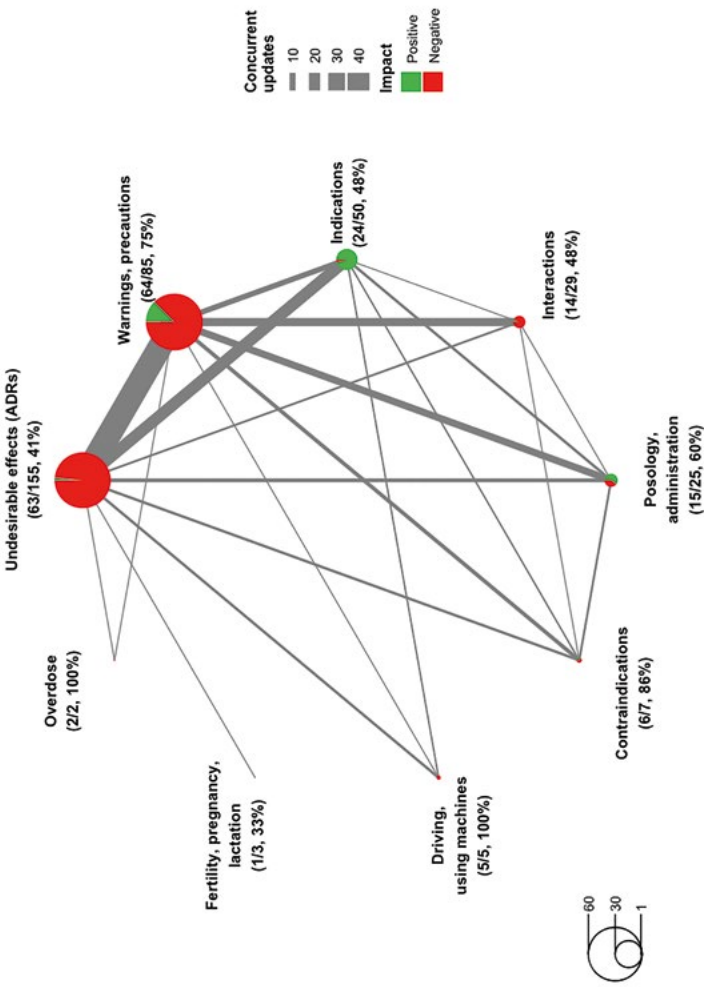

Figure 3 Overview of updates to SmPC sections during the same regulatory procedure (194/361)
Numbers, percentages, the width of the connections and the size of the circles indicate for each SmPC section the updates that occurred simultaneously with an update to one or more other section(s). ADR, adverse drug reaction; SmPC, Summary of Product Characteristics

This does not always have to become more negative, e.g. a new indication for liraglutide (Victoza) also led to a less restrictive warning regarding patients with congestive heart failure, and the broadening of the indication of prucalopride (Resolor) to use in men led to removal of a warning that use in men was not recommended due to a lack of efficacy and safety data. Similarly, a new indication for golimumab (Simponi) led to multiple ADR frequencies being decreased based on the new study data. Lastly, such procedures may even positively impact contraindications, as illustrated by moderate hepatic impairment no longer being contraindicated based on study data supporting a new indication for ticagrelor (Brilique).

Identification and characterization of typical drug lifecycles

In Figure 4, we plotted all 40 drug lifecycles according to the most significant regulatory actions (Figure 1) that reflected positive (vertical axis) versus negative (horizontal axis) impact on benefits and risks. We identified several typical drug lifecycles that seem to undergo specific patterns of regulatory actions. These are characterized by levels of post-approval patient exposure, innovativeness, need for further regulatory learning and unexpected risks. First, the level of post-approval patient exposure seems to play an important role in the occurrence of regulatory actions, thereby facilitating further development or learning about a drug. Of the 17 drugs that underwent up to two regulatory actions, eight (47%) had one or more specific characteristics that are often suggestive of low patient exposure, i.e. orphan designation (5/9 orphan drugs), market withdrawal (4/5 withdrawn drugs – all except ofatumumab, which was withdrawn to be remarketed in another disease area[44, 45]), and approval under exceptional circumstances (2/3 exceptionally approved drugs). The latter approval pathway is applicable only when little evidence is available at approval and not expected to be supplemented post-approval. The patient exposure data from PSURs support these observations: of the 13 drugs (33%) with the lowest patient exposure, 11 underwent a maximum of two regulatory actions, including those discussed earlier.

Second, the level of drug innovativeness also seems to play a role in the occurrence of regulatory actions, in various ways. For instance, five of the remaining six drugs that also underwent up to two regulatory actions but were exposed to substantially more patients, were of a drug class that had been available for many years. These are asenapine (Sycrest, an atypical antipsychotic), bazedoxifene (Conbriza, a selective estrogen receptor modulator), epoetin theta, indacaterol (Onbrez Breezhaler, a long-acting inhaled β_2-agonist), and silodosin (Urorec, an α1-adrenoceptor antagonist).

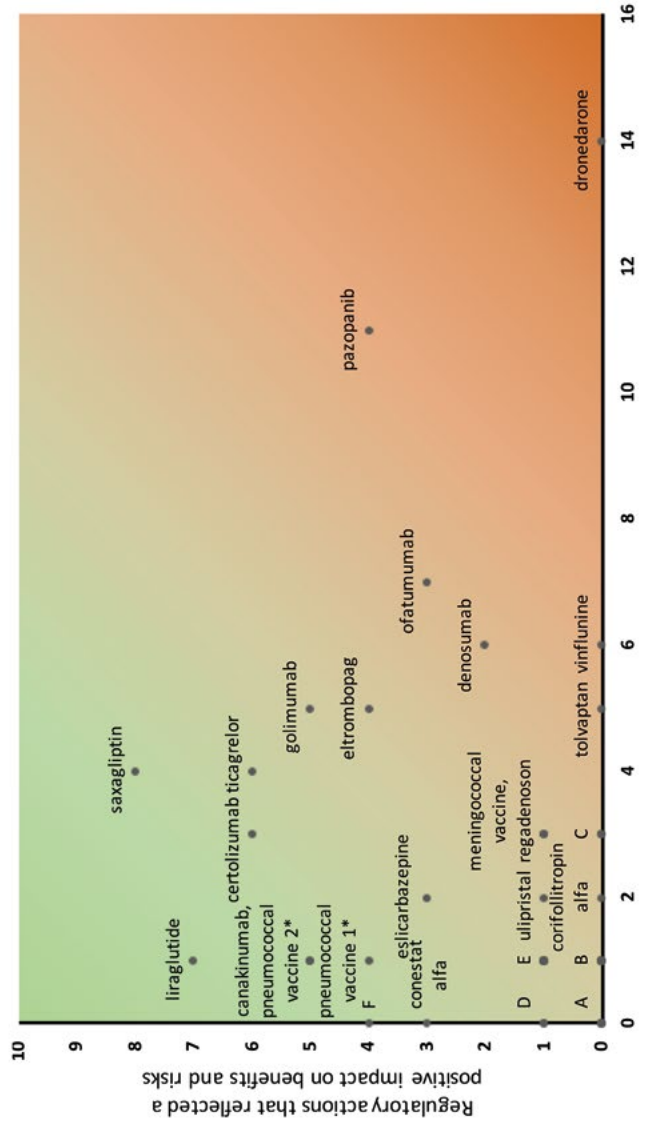

Figure 4 Characterization of drug lifecycles according to most significant regulatory actions that reflected a positive versus negative impact on benefits and risks

A: besilesomab, rilonacept, silodosin, velaglucerase alfa; B: amifampridine, autologous cartilage cells, epoetin theta, indacaterol, vernakalant; C: gefitinib, pirfenidone; D: bazedoxifene, catumaxomab; E: asenapine, aztreonam, collagenase Clostridium histolyticum, plerixafor, roflumilast; F: prucalopride

* pneumococcal vaccine 1 indicates Prevenar 13, pneumococcal vaccine 2 indicates Synflorix

This reflects limited innovativeness and relevant knowledge about efficacy and safety may have already been available or expected and addressed in the SmPC at initial approval. In contrast, higher innovativeness may be reflected by further post-approval drug development, including conditional approval as a special case, and initiate many regulatory actions. These include drugs for which multiple truly new indications are approved after initial approval as well as drugs for which the initial indication is progressively broadened toward 'blockbuster' status. The first group includes for example the anti-inflammatory monoclonal antibodies canakinumab (Ilaris), certolizumab (Cimzia) and golimumab. Canakinumab's initial approval under exceptional circumstances was – highly exceptional – later converted to a standard approval when comprehensive evidence had come available. This was due to evidence supporting three new indications in gouty arthritis, systemic juvenile idiopathic arthritis and periodic fever syndromes, as well as two extensions of existing indications. Similarly, for certolizumab and golimumab, also various new and extended indications were approved, four and five, respectively. The second group includes for example the antidiabetics liraglutide and saxagliptin. These both saw their initial indications progressively broadened to new combination regimens, lines of treatment and age groups. In line with our general findings discussed earlier, the further drug development of these five drugs also enabled further characterization of safety profiles, with several warnings added to their SmPCs – most after new or extended indications were approved. These drugs' lifecycles confirm that relevant regulatory learning is conditional on sufficient patient exposure. However, the relatively limited number of regulatory actions reflecting a negative impact on benefits and risks suggests that baseline uncertainty at initial approval was quite low. This is different for the drugs that received conditional approval, i.e. ofatumumab and pazopanib, indicating that less comprehensive evidence was available at initial approval. While further post-approval drug development ultimately led to extensions of the indication and other SmPC updates that reflect a positive impact, it also led to various warnings as well as DHPCs. This supports the expectation that baseline uncertainty is much higher for drugs that received conditional instead of standard approval, and underscores the need for 'regulator-induced learning' through obligations to generate further evidence post-approval.

Last, the frequent occurrence of risks without clear factors that drive their occurrence may define another type of drug lifecycle. This constitutes extensive unexpected post-approval characterization of the drug risk-profile without significant drug development efforts, up to the point that the initial approval decision may be reconsidered. One may describe these as potential regulatory type I errors. For example, for dronedarone, three DHPCs were distributed (21% of all DHPCs sent

for this cohort), the indication was restricted to last-line treatment and a cautionary note concerning use by the elderly, contraindications and new warnings were added. It was the only drug in our cohort that underwent a referral for safety reasons, and we did not identify any regulatory actions that reflected a positive impact on benefits and risks. Although the benefit-risk balance in the broader initial indication was thus considered negative, it is currently considered a valuable therapeutic option in a strictly limited setting – mainly because its safety profile is still better than that of the more efficacious alternative drug amiodarone.[46]

Discussion

We aimed to perform an in-depth evaluation of regulatory actions during the drug lifecycle, taking into account regulatory actions that reflected positive and negative impact on benefits and risks, and the relations between them. During more than ten years of follow-up of 40 innovative medicines, 14 DHPCs were distributed that reflected a negative impact on benefits and risks. Also, 361 SmPC sections were updated, of which 24% reflected a positive impact and 76% a negative impact on benefits and risks. Of these updates, 54% occurred simultaneously with at least one update to another SmPC section. Lastly, we found that levels of post-approval patient exposure, innovativeness, needs for further regulatory learning and unexpected risks may play a role in the occurrence of specific patterns of regulatory actions during a drug lifecycle.

Our findings that almost one-fourth of SmPC updates reflected a positive impact on benefits and risks and that more than half were updated simultaneously are important, for several reasons. First, the former highlights that safety-related regulatory actions may also reflect a positive impact on risks, as exemplified by 12 regulatory actions in our study such as removed warnings and ADRs. We encountered one other study that previously reported a similar finding,[19] while many others only reported safety-related regulatory actions that reflect a negative impact. Second, they highlight the relative importance of regulatory actions that reflect a positive impact on benefits. These 73 regulatory actions formed one-fifth of all regulatory actions and mostly concerned new or broadened indications or an update of posology and/or administration characteristics. These were especially important given their frequent role in the further characterization of risks, with 27 leading to changes in ADRs, warnings and precautions and other risk-related sections, including changes that reflected a positive impact on risks. One previous study reported a similar finding.[24]

These findings are of relevance to researchers and regulators, but also to healthcare professionals and patients. First, they may prompt researchers to investigate a broader range of regulatory outcomes than is often studied as well as relations between them, or discuss their findings in this broader context. As a consequence, such studies may better reflect regulatory practice and inform their public; other researchers, clinicians and regulators. Second, these findings may prompt regulators to stimulate simultaneous learning about benefits and risks. Although regulators typically have a greater influence on the generation of risk-related evidence, e.g. through requests for monitoring in PSURs and post-authorization safety studies (PASS),[47] they may influence the generation of benefit-related evidence through post-authorization efficacy studies (PAES). These include so-called 'specific obligations' for e.g. conditionally[48] and exceptionally[49] approved drugs, but may also be requested for other drugs.[50] Such PAESs also form an opportunity for further characterization of risks. Similarly, when companies request scientific advice on how to study a new or broadened indication, new pharmaceutical form or new method of administration, further characterization of risks can also be stimulated. Lastly, our findings confirm that by reporting their observations during clinical practice and daily use, healthcare providers and patients play an important role in the continuous regulatory learning process about drug risks, but also about benefits.

The drug lifecycle characteristics post-approval patient exposure,[24, 35] innovativeness, [24, 34, 39] and need for further regulatory learning[19, 32, 40] have also previously been highlighted as factors that are associated with regulatory actions. They may help regulators to plan regulatory measures, including those discussed above. Currently, these characteristics are used to e.g. define the European PSUR submission frequency. By default, once a drug is marketed in Europe, PSURs are submitted every six months for two years, then every year for two years, and then every three years.[51] However, regulators may deviate from this schedule using a risk-based approach that comprises, among others, the following criteria: "size of the safety database and exposure to the medicinal product", "new product for which there is limited safety information available", "significant changes to the product (e.g. new indication (...), new pharmaceutical form or route of administration (...))", "medicinal products subjected to additional monitoring".[52] This last group of medicines also includes those that received conditional approval or approval under exceptional circumstances.[53] Our findings support these criteria, which could potentially also be used to define the need for other regulatory tools, such as the electronic Reaction Monitoring Report (eRMR) used for signal detection.[54] Moreover, where regulators play an active role in further learning about benefits through e.g. PAESs, similar criteria could help to define the need for simultaneous characterization of the safety profile.

Our study was the first to comprehensively assess all regulatory actions that occurred during a long period of follow-up of EMA-approved innovative drugs, and assess relations between them. The findings can improve the methodology and interpretation of future studies that evaluate regulatory decision-making, and regulatory actions specifically. While manual extraction and categorization of the data were highly resource intensive, future studies could employ data science methods to perform these tasks. In addition, our findings may help regulators to plan and implement regulatory measures. However, our study also had several limitations. First, we assessed the occurrence of regulatory actions for a relatively small sample of 40 innovative drugs that were approved relatively long ago. Although the results provide important insights in regulatory decision-making that are relevant for researchers and regulators in general, our specific findings may not be generalizable to every cohort of drugs. Future studies may thus use and perhaps expand our categorization and analyses for other drugs. Second, we performed an assessment of European post-approval regulatory actions for innovative drugs. We do not expect that these are substantially different in other jurisdictions such as the United States. However, regulatory actions in one jurisdiction may play a role in the occurrence of regulatory actions in other jurisdictions. Future studies may thus employ a multi-jurisdiction perspective to evaluate these relations. Third, our unit of analysis comprised the number of regulatory actions that were encountered during each regulatory procedure, including DHPCs, rather than the precise number of issues addressed during each regulatory procedure. This mainly affected the ADR section that underwent most updates involving two or more changes. However, we considered that counting these changes as separate updates would skew our analysis of simultaneously occurring SmPC updates, which we found most important to assess in detail. Fourth, EPARs often provided limited to no details about specific information that led to regulatory actions, which required us to interpret reflected impact on benefits or risks. Specifically, we may have categorized regulatory actions as reflecting negative impact on benefits since they concerned the eligible population and use characteristics, while it would have been more correct to categorize these as reflecting negative impact on risks since they formally occurred due to safety issues. However, these concern only 15 regulatory actions that definitely reflected a negative impact, whether on benefits or risks, and thus did not impact any other results.

Conclusions

In conclusion, we identified 375 regulatory actions – 14 DHPCs and 361 SmPC updates – that occurred for 40 EMA-approved innovative drugs during more than ten years of follow-up. Of the SmPC updates, 24% reflected a positive and 76% a negative impact on benefits and risks. Moreover, simultaneous learning about benefits and risks suggests an important role for drug development in characterization of risks. Lastly, we found that the drug lifecycle characteristics post-approval patient exposure, innovativeness, need for further regulatory learning and unexpected risks play a role in the occurrence of specific patterns of regulatory actions. These findings may support the methodology and interpretation of future comprehensive regulatory analyses, and impact regulatory decision-making by stimulating simultaneous regulatory learning about benefits and risks. Also, they may help to define the need for further evidence generation.

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Supplementary material

Table S1 Categories used to assess regulatory actions according to impacted benefits and risks

Positive impact on benefits and risks
Benefits, i.e. eligible population and use characteristics (category A)
Addition of a new indication
Modification of an approved indication
Change in posology resulting in a reduced patient-burden while maintaining the same total dose, e.g. reduced dosing frequency/increased dosing interval, reduced infusion time/ increased infusion rate
Change in posology: lower dose while maintaining same/comparable efficacy
Change of (notion of) a contraindication into recommendation
Removal of need for a booster dose
Widening of applicability, e.g. renally or hepatically impaired patients, administration through tube
Removal of a contraindication
Removal of a warning concerning unknown efficacy/effectiveness or expected lack of efficacy/ effectiveness in a specific patient population, because of the availability of evidence that either demonstrates efficacy or refutes the expectancies of lack of efficacy
Risks, i.e. safety aspects (category B)
Refutal of expectancy of decreased safety (no/less dose restriction needed in renally or hepatically impaired patients)
Removal of a refuted warning concerning expected situations of decreased safety
Decreased frequency of an ADR
Negative impact on benefits and risks
Benefits, i.e. eligible population and use characteristics (category C)
Restriction of an indication
Reduced applicability of an indication, e.g. only monotherapy
Addition of a drug-drug interaction (PK or PD) causing a decrease in exposure/efficacy of the current drug
Addition of a contraindication
Addition of a warning concerning situations of decreased effectiveness
Risks, i.e. safety aspects (category D)
Addition of a precaution for use/recommendation to prevent the occurrence of a previously unknown risk, i.e. not yet listed in that section
Removal of a warning because of concurrent upgrade to contraindication
Addition of a warning concerning situations of decreased safety
Strengthening of a warning concerning situations of decreased safety

Table S1 *Continued*

Risks, i.e. safety aspects (category D)
Addition of a drug-drug interaction (PK or PD) causing an increase in exposure to and thereby (theoretically) (the worsening of) an ADR of the current drug, i.e. direct risk of current drug
Addition of a drug-drug interaction (PK or PD) causing a decrease in exposure/efficacy of another drug, i.e. indirect risk of current drug
Addition of a drug-drug interaction (PK) causing an increase in exposure to and thereby (theoretically) (the worsening of) an ADR of another drug, i.e. indirect risk of current drug
Strengthening of the wording of an interaction, e.g. change from recommendation to contraindication
Addition of a recommendation concerning (longer) abstinence of breastfeeding
Addition of a notion concerning hindered ability to drive because of an ADR
Addition of an ADR
Increased frequency of an ADR

ADR, adverse drug reaction; PD, pharmacodynamic; PK, pharmacokinetic

Table S2 High-level description of the type of information that prompted regulatory actions

Type of information	**Positive impact (A & B)**		**Negative impact (C & D)**	
DHPCs	***N* = 0**		***N* = 14**	
New study results	N/A		3	21%
New post-approval experience data[a]	N/A		10	71%
Re-evaluation of all available data (referral procedure)	N/A		1	7%
SmPC updates	***N* = 85**		***N* = 276**	
New study results	**81**	**95%**	**83**	**30%**
Company application for new or modified indication	55	65%	28	10%
Company application for new pharmaceutical form	1	1%	0	0%
Other study results[b]	25	29%	55	20%
New post-approval experience data	**2**	**2%**	**123**	**45%**
Periodic safety update reports	1	1%	28	10%
Other post-approval experience data[a]	1	1%	95	34%
Other new data[c]	**0**	**0%**	**3**	**1%**
Re-evaluation of all available data (referral procedure)	**0**	**0%**	**6**	**2%**
Unclear	**2**	**2%**	**61**	**22%**

DHPC, Direct Healthcare Professional Communication; SmPC, Summary of Product Characteristics

[a] E.g. spontaneous, clinical trial and literature reports of adverse events

[b] Sometimes combined with post-approval experience data (n=4) or literature data (n=1)

[c] E.g. data modelling

Chapter 2.3

Associations between the level of complexity of the European Medicines Agency assessment process and post-approval regulatory actions

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Abstract

Purpose: Identification of factors associated with post-approval drug regulatory actions may help to predict such actions. We assessed whether level of complexity of the European assessment process could be a factor.

Methods: We followed 40 innovative drugs up until 10 years post-approval and identified regulatory actions that reflected positive or negative impact on benefits and risks. Level of complexity comprised a composite of procedure duration, whether consensus was reached, concerns regarding trials and negative initial opinion. We fitted recurrent time-to-event models based on likelihood and estimated adjusted intensity rate ratios (aIRR) and 95% confidence intervals (CI) to compare levels of complexity adjusted for pre-approval patient exposure.

Results: Of 375 regulatory actions, comprising healthcare professional letters and label changes, 85 reflected positive impact and 290 reflected negative impact on benefits and risks. Level of complexity of the assessment process was low for 11 and high for 29 drugs. Overall, complexity appeared associated with regulatory actions that reflected positive impact, high versus low complexity aIRR 0.69 (95% CI 0.35-1.33), but not with those that reflected negative impact, aIRR 1.01 (95% CI 0.56-1.80). However, high complexity was associated with an increased risk of both types of regulatory actions up to 39 months post-approval, aIRRs 6.12 (95% CI 0.93-40.47) and 3.51 (95% CI 1.01-12.16), but a decreased risk beyond, aIRRs 0.47 (95% CI 0.22-0.99) and 0.54 (95% 0.31-0.93).

Conclusions: Earlier occurrence of regulatory actions may indicate that drugs for which the assessment process was highly complex were more actively monitored during early lifecycle stages.

Introduction

In the 1960s, the thalidomide disaster caused the widespread establishment of formal national drug regulatory authorities that – for the first time – assessed a drug's safety and efficacy prior to its approval.[1-4] Nonetheless, serious safety issues continued to occur, more recently concerning among others the drugs rofecoxib (2004) and rosiglitazone (2007).[1, 3, 4] Around the same time, enhanced regulatory 'pharmacovigilance' practices including the Risk Management Plan by the European Medicines Agency (EMA)[5] and the Risk Evaluation and Mitigation Strategy by the United States (US) Food and Drug Administration (FDA)[6] were established to proactively monitor and address safety issues throughout the drug lifecycle.[7] Along with the early identification and characterization of safety issues, these measures aimed to prevent or minimize the occurrence of safety issues or minimize their severity. Importantly, by then, drug regulation also involved a more structured approach towards the weighing of these safety issues and uncertainties against drug benefits.[8] As a result, pharmacovigilance has become common regulatory practice,[9] which is likely to continue to evolve in the future.[10]

The occurrence of post-approval drug safety issues has frequently been investigated, often to identify factors associated with their occurrence. Such factors would allow better prediction of the occurrence of safety issues as well as understanding of the regulatory context in which they are more likely to occur. This may enable earlier identification or perhaps even prevention of safety issues. Recent studies mostly focused at so-called safety-related regulatory actions that addressed safety issues, which include drug label updates,[11-17] healthcare professional letters,[18, 19] drug withdrawals,[20-24] or combinations of these.[25-37] Only two studies investigated all types of safety-related regulatory actions for FDA approved drugs but did not consider all drug label sections.[25, 27] This was recognized by others, who subsequently studied all potentially safety-related drug label sections and drug withdrawals for FDA approved drugs, but not healthcare professional letters.[31, 33] Moreover, only one study reported label updates that reflected improved safety profiles, e.g. less severe or frequent adverse events.[13] Furthermore, few studies investigated drug benefit-related regulatory actions, e.g. restricted or extended indications.[14, 15, 32, 38] Only when studying all these regulatory actions combined – whether safety or benefit-related, positive or negative – one may estimate how the drug benefit-risk balance is changing over time.

Factors that were explored in these studies were mostly drug, clinical development or regulatory characteristics, including drug type, drug class, therapeutic area, orphan designation, whether pivotal trials were randomized and controlled, number of patients included in pivotal trials, review time and approval type. So far, one study investigated whether EMA review time was associated with safety-related regulatory actions. It found no evidence of such association, but suggested a potential association for the total procedure duration, i.e. including company response time.[39]

The EMA assessment process is inherently more complex than that of the FDA given the involvement of representatives from 29 countries who generally strive to take decisions in full agreement – by consensus. We considered that a longer procedure may reflect greater complexity of the assessment process, especially when EMA's approval decision is not taken by consensus but by majority vote. Longer regulatory time and majority vote expectedly reflect greater complexity due to persistent uncertainties about clinical effects, as do re-examination procedures after initially refused applications. Additionally, we considered that concerns about the methodological robustness of early and confirmatory trials may further enhance the complexity of the assessment process. Therefore, we aimed to study whether a composite measure of these aspects that reflect complexity of EMA's assessment process was associated with post-approval regulatory actions. We hypothesized that a higher level of complexity was associated with more regulatory actions that reflected a negative impact on benefits and risks but not with those that reflected a positive impact.

Methods

Study design and cohort characteristics

We performed a retrospective cohort study of drugs with new active substances that were approved by EMA in 2009-2010, and followed these up until 1 July 2020 or market withdrawal. We excluded duplicate applications and vaccines for the prevention of seasonal disease that are often marketed for a limited time period. For the remaining drugs, we extracted baseline drug characteristics – including the number of patients exposed prior to approval – from EMA's European Public Assessment Reports (EPAR) and annual reports at www.ema.europa.eu and literature.[40]

Assessment of level of complexity of the drug assessment process

We assessed the level of complexity of the initial drug assessment process based on four characteristics: whether the procedure was extended, whether approval decisions were made by consensus or majority vote, whether significant concerns regarding the methodological robustness of early or confirmatory clinical trials had been expressed and whether it concerned a re-examination procedure after an initially refused application. When none of these applied or only the procedure duration was extended, the level of complexity was considered low. Otherwise, it was considered high. We considered the procedure to be extended when it was longer than a year in total, in line with the average duration as reported by EMA.[41] Whether significant concerns regarding methodological robustness of trials had been expressed by EMA was extracted previously from confidential EMA reports through a memorandum of understanding with the Dutch Medicines Evaluation Board.[42] Information regarding other characteristics was extracted from EPARs and EMA's annual reports.

Identification of regulatory actions that reflected impact on benefits and risks

We identified all relevant regulatory actions that occurred during follow-up, i.e. revocations, suspensions, withdrawals or non-renewals of the marketing authorisation; Direct Healthcare Professional Communications (DHPC); and changes to clinical sections (4.1-4.9) of the European drug label, the Summary of Product Characteristics (SmPC). Except for DHPCs, all regulatory actions were identified through EPARs. DHPCs were identified at websites of national regulatory authorities. Where possible, we also determined whether the data that led to regulatory actions originated from post-approval studies or other sources. We then included the regulatory actions that were considered to reflect impact on benefits or risks, i.e. those that responded to or conveyed information about previously unknown issues such as new (restrictions of) indications or new warnings, or that strengthened previous regulatory actions such as updates of existing warnings to note the possibility of fatal outcomes. We excluded withdrawals due to commercial reasons and changes to the SmPC that noted newly available evidence without discussing relevance or implications for clinical practice. Lastly, we examined the content of regulatory actions to determine how the information that had prompted the regulatory actions had impacted benefits and risks. For example, regulatory actions were considered to reflect a positive impact on benefits or risks if the eligible population and administration characteristics were broadened, e.g. a new indication, or safety aspects were less negative than previously thought, e.g. a removed warning. Conversely, they were considered to reflect a negative impact when the

eligible population and administration characteristics were narrowed, e.g. a new contraindication, or new safety aspects were identified, e.g. a new adverse effect (Table S1).

Data analysis

First, we employed descriptive statistics to describe the cohort of drugs according to baseline drug characteristics, and the relevant regulatory actions that occurred for these drugs. Second, we fitted recurrent time-to-event models – which allow for multiple events per drug – to assess associations between a high versus low level of complexity of the drug assessment process and occurrence of regulatory actions. These models estimate the 'intensity rate ratio' (IRR), which is comparable to the hazard ratio for time-to-first-event analyses, along with its 95% confidence interval (CI). IRRs and 95% CIs were estimated separately for regulatory actions that reflected positive versus negative impact on benefits and risks, and both unadjusted and adjusted (aIRR) for the number of patients exposed to these drugs prior to approval. We included pre-approval exposure to control for a potential effect of the extent of experience with – and thereby knowledge of – a drug at time of approval on the chance for regulatory actions post-approval.

To account for potential interrelatedness of simultaneously occurring regulatory actions for the same drug, we performed the analyses for multiple outcome clusters. These clusters consisted of increasing numbers of regulatory actions according to their level of regulatory impact on the marketing authorization, as proposed previously by Ebbers *et al.* (2012)[43] and similar to analyses performed by Pinnow *et al.* (2018)[31] (Table 1). We used the cluster that included major changes to the marketing authorization, DHPCs and changes to the most important SmPC sections, i.e. the indications, posology, contraindications, and warnings and precautions sections, to perform our main analyses. In addition, we used the other outcome clusters to perform secondary analyses. We visualised intensity rates over time and plotted scaled Schoenfeld residuals to test the proportional hazards assumption, and performed likelihood-based model fitting to identify the best fitting model for our data.

Table 1 Outcome clusters used for the recurrent time-to-event analyses

Regulatory actions	Positive impact on benefits and risks (*N*)	Negative impact on benefits and risks (*N*)
MA revocation, suspension, withdrawal or non-renewal	N/A	0
As previous cluster + DHPCs	N/A	14
As previous cluster + changes to SmPC sections 4.1-4.4	**79**	**102**
As previous cluster + changes to SmPC sections 4.5-4.9	85	290

The outcome cluster printed in bold was used for the main analyses. DHPC, direct healthcare professional communication; MA, marketing authorization; SmPC, summary of product characteristics. SmPC sections: 4.1, indications; 4.2, posology; 4.3, contraindications; 4.4, warnings and precautions; 4.5, interactions; 4.6, fertility, pregnancy and lactation; 4.7, driving and using machines; 4.8, adverse effects; 4.9, overdose

Results

Cohort description and occurrence of regulatory actions

Of the drugs approved by EMA in 2009-2010, 40 were eligible for inclusion in our study. We assessed the level of complexity of their assessment process as low for 11 drugs and high for 29 drugs. Table 2 provides an overview of their characteristics. Five drugs were withdrawn post-approval for commercial reasons: autologous cartilage cells (ChondroCelect), catumaxomab (Removab), collagenase Clostridium histolyticum (Xiapex), ofatumumab (Arzerra) and rilonacept (Rilonacept Regeneron). The other 35 drugs were followed up until the end of the study, 1 July 2020, which resulted in a median follow-up of 10.5 years. During follow-up, we identified 14 DHPCs – that all reflected a negative impact on benefits and risks – and 361 changes to SmPC sections. Of these changes, 85 (24%) reflected a positive impact and 276 (76%) reflected a negative impact on benefits or risks. An overview of the number of regulatory actions for each group of drugs in our study and the source of the underlying data is provided in Table S2.

Regulatory actions that reflected positive impact on benefits and risks

For the main analyses, 79 regulatory actions were available that reflected a positive impact on benefits or risks (Table 1). During complete follow-up, fewer of these regulatory actions seemed to occur for drugs for which the level of complexity of the

drug assessment process was high than for those for which it was low: 0.18 versus 0.24 events per year, IRR 0.76 (95% CI 0.39-1.48) and aIRR 0.69 (95% CI 0.35-1.33). While these confidence intervals include one, the point estimates consistently suggest an association. However, graphical data exploration indicated that the proportional hazards assumption was clearly violated (Figure S1a). This was confirmed by likelihood-based model fitting that suggested two different patterns of associations up to versus beyond 37-39 months post-approval. We used 39 months as a cut-off point, since it was also required for the other analyses (see below). Up to 39 months, high versus low complexity seemed associated with a higher risk of regulatory actions that reflected a positive impact: 0.19 versus 0.03 events per year, aIRR 6.12 (95% CI 0.93-40.47). Conversely, beyond 39 months, it was associated with a lower risk: 0.18 versus 0.36 events per year, aIRR 0.47 (95% CI 0.22-0.99) (Figure 1). These results were confirmed by the secondary analysis that included all 85 regulatory actions that reflected a positive impact (Table S3).

Table 2 Cohort characteristics

Characteristic	**Low complexity of the assessment process (*N* = 11 drugs)**	**High complexity of the assessment process (*N* = 29 drugs)**
Drug characteristics		
Drug type		
Small molecule	5 (45%)	19 (66%)
Biological/ATMP	6 (55%)	10 (34%)
Therapeutic area		
Cancer treatment	0 (0%)	6 (21%)
Cardiovascular treatment	1 (9%)	3 (10%)
Immunosuppressive treatment	3 (27%)	2 (7%)
Musculoskeletal disorder treatment	2 (18%)	1 (3%)
Sex hormones and related treatment	0 (0%)	3 (10%)
Vaccines (meningococcal/pneumococcal)	1 (9%)	2 (7%)
Other treatment[a]	4 (44%)	12 (41%)
Assessment process characteristics		
Extended procedure duration	1 (9%)	15 (52%)
Median days (interquartile range)	323 (271-344)	386 (330-456)
Approval decision not by consensus	0 (0%)	6 (21%)
Concerns regarding early trials	0 (0%)	14 (48%)
Concerns regarding confirmatory trials	0 (0%)	23 (79%)
Re-examination procedure	0 (0%)	1 (3%)

Table 2 *Continued*

Characteristic	Low complexity of the assessment process (*N* = 11 drugs)	High complexity of the assessment process (*N* = 29 drugs)
Other characteristics		
Number of patients exposed prior to approval		
Median (interquartile range)	1082 (271-3940)	1855 (1088-4042)
Orphan designation at approval	5 (45%)	4 (14%)
Type of approval		
Standard approval	9 (82%)	25 (86%)
Conditional approval	0 (0%)	3 (10%)
Approval under exceptional circumstances	2 (18%)	1 (3%)

ATMP, advanced therapy medicinal product
[a] Remaining areas represent ≤2 drugs, e.g. antidiabetics, neurological treatment

Regulatory actions that reflected negative impact on benefits and risks

In contrast, the level of complexity seemed not associated with the 102 regulatory actions that reflected a negative impact on benefits or risks (Table 1): 0.26 versus 0.24 events per year, IRR 1.11 (95% CI 0.56-2.17) and aIRR 1.01 (95% CI 0.56-1.80). However, also for these analyses the proportional hazards assumption was clearly violated (Figure S1b) and likelihood-based model fitting suggested different patterns of association up to versus beyond 39 months post-approval. Up to 39 months, high versus low complexity was associated with a higher risk of regulatory actions that reflected a negative impact: 0.44 versus 0.11 events per year, aIRR 3.51 (95% CI 1.01-12.16). Again, beyond 39 months, it was associated with a lower risk: 0.18 versus 0.31 events per year, aIRR 0.54 (95% 0.31-0.93) (Figure 1). These results were confirmed by the secondary analysis that included all 290 regulatory actions that reflected a negative impact (Table S3). The secondary analysis that included only the 14 DHPCs suggested a consistently increased risk of DHPCs for drugs with a high versus low level of complexity of the drug assessment process, although this was associated with substantial uncertainty due to the small sample size: aIRR 1.95 (95% CI 0.30-12.84). Again, the majority of these had occurred in the first 39 months – eight, of which seven for drugs with a high level of complexity of the assessment process – but the proportional hazards assumption seemed met.

	Event rate low complexity	Event rate high complexity	aIRR (95% CI)
Positive impact			
Overall	0.24/year	0.18/year	0.69 (0.35-1.33)
≤39 months	0.03/year	0.19/year	6.12 (0.93-40.47)
>39 months	0.36/year	0.18/year	0.47 (0.22-0.99)
Negative impact			
Overall	0.24/year	0.26/year	1.01 (0.56-1.80)
≤39 months	0.11/year	0.44/year	3.51 (1.01-12.16)
>39 months	0.31/year	0.18/year	0.54 (0.31-0.93)

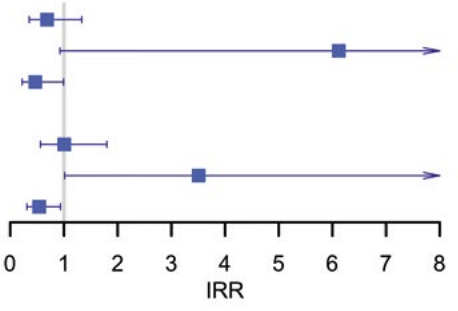

Figure 1 Forest plots for the main analyses[a], separately for regulatory actions that reflected a positive and negative impact on benefits and risks

[a] Main analyses included direct healthcare professional communications and label changes concerning indications, posology, contraindications, and warnings and precautions

Discussion

In this retrospective cohort study, a higher level of complexity of the drug assessment process seemed associated with fewer regulatory actions that reflected a positive impact on benefits and risks but not with regulatory actions that reflected a negative impact. This was in contrast to our hypothesis that a higher level of complexity would be associated with more regulatory actions that reflected a negative impact but not with those that reflected a positive impact. However, further analyses indicated that in the first 39 months post-approval, drugs with a high level of complexity of the assessment process were at increased risk for both types of regulatory actions, but afterwards at lower risk.

As for regulatory actions that reflected a negative impact on benefits and risks, the analyses and data visualization indicated that high versus low level of complexity was associated with a 3.5-fold increased risk in the first 39 months and an almost twofold decreased risk thereafter – up to 11 years and three months post-approval. These results suggest that for drugs with a high level of complexity of the assessment process, characterization of negative drug aspects was concentrated early in the drug lifecycle. In contrast, for drugs with a low level of complexity, this characterization process started later and continued at a more constant rate throughout the drug lifecycle. An explanation for these findings may be that drugs for which the assessment process was more complex were monitored more actively through pharmacovigilance activities. These may include for example long-term extensions of pivotal trials, post-approval safety studies, or follow-up questionnaires or reviews in periodic safety update reports for specific adverse reactions.[44] This is not an unlikely explanation, given that the European Risk Management Plan was already in use at the time of approval of the drugs in our cohort[45, 46] and further pharmacovigilance legislation soon followed.[44, 47] Perhaps after such initial active monitoring period, these drugs had been characterized sufficiently, while for the other drugs characterization occurred more gradually. If so, our study suggests that over a time horizon of ten years, these approaches did ultimately not differ in the extent of characterization but that active monitoring sped up characterization, which could be useful for any drug. Unfortunately, the information provided in EPARs about the source of the data that led to regulatory actions was too limited to establish whether e.g. post-approval study results or post-marketing experience data had been collected as a consequence of more active monitoring.

Alternatively, the decrease in occurrence of these regulatory actions after the initial 39 months may have been a consequence of decreased patient exposure to drugs with a high level of complexity of the assessment process.[18, 30] Such decrease in patient exposure may occur due to treatment choices made by patients and their physicians in clinical practice. However, alternatively, it may be a consequence of prior impactful regulatory actions, including restrictions of the indication to a smaller patient population or new contraindications,[18, 48] which are typically communicated by DHPCs.[48, 49] This may have been the case in our study, where 12 of the 14 DHPCs had been distributed for drugs for which the level of complexity was high, and mostly within the first 39 months.

As for regulatory actions that reflected a positive impact on benefits and risks, the analyses and data visualization indicated that high versus low level of complexity was associated with a 6-fold increased risk in the first 39 months and an almost twofold decreased risk thereafter. Thus, also characterization of positive aspects seemed to have started earlier for these drugs. An explanation may be that the issues that caused the assessment process to be complex were (partially) addressed by granting a restricted indication. Further post-approval studies could then have supported extended indications relatively early in the drug lifecycle. Such approach is typical for conditionally approved drugs[50] and not uncommon for cancer drugs,[51, 52] which were all part of the group of drugs for which the assessment process was considered to be highly complex. However, these drugs seemed also about 31% less likely to undergo regulatory actions that reflected a positive impact during complete follow-up. This may very well be related to regulatory actions that led to decreased patient exposure, as discussed above.

In general, our findings illustrate that when studying factors that are potentially associated with outcomes of regulatory decision-making, it is imperative to consider timing aspects, including the duration of follow-up, to allow nuanced conclusions about the existence of associations.

Important strengths of our study are that we: i) studied a composite of relevant complexity aspects that are specific for the European drug assessment process, ii) followed-up a cohort of drugs for more than ten years, iii) in addition to safety-related regulatory actions, identified a broader group of actions stratified according to their impact on the benefit-risk profile, and iv) assessed associations using recurrent time-to-event models rather than time-to-first-event models. Limitations, however, are that: i) the cohort of drugs is relatively old, although many characteristics are similar to present-day approved drugs, ii) we were unable to assess whether regulatory

actions had occurred as a consequence of pharmacovigilance activities, and iii) despite the long-term follow-up, we identified relatively few regulatory actions yielding broad confidence intervals.

In conclusion, for drugs with a high level of complexity of the assessment process, post-approval regulatory actions seemed to occur earlier than for those with a low level of complexity. This may be a result of purposefully planned and executed regulatory interventions, which may be useful for any drug. Furthermore, it is imperative for future studies to consider timing aspects when conducting research on factors associated with outcomes of regulatory decision-making.

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Supplementary material

Table S1 Methodology of categorization of regulatory actions according to impact on benefits and risks

Regulatory actions that reflected a positive impact on benefits or risks
Addition of a new indication
Modification of an approved indication
Change in posology resulting in a reduced patient-burden while maintaining the same total dose, e.g. reduced dosing frequency/increased dosing interval, reduced infusion time/ increased infusion rate
Change in posology: lower dose while maintaining same/comparable efficacy
Change of (notion of) a contraindication into recommendation
Removal of need for a booster dose
Widening of applicability, e.g. renally or hepatically impaired patients, administration through tube
Removal of a contraindication
Removal of a warning concerning unknown efficacy/effectiveness or expected lack of efficacy/ effectiveness in a specific patient population, because of the availability of evidence that either demonstrates efficacy or refutes the expectancies of lack of efficacy
Refutal of expectancy of decreased safety (no/less dose restriction needed in renally or hepatically impaired patients)
Removal of a refuted warning concerning expected situations of decreased safety
Decreased frequency of an ADR
Regulatory actions that reflected a negative impact on benefits or risks
Restriction of an indication
Reduced applicability of an indication, e.g. only monotherapy
Addition of a drug-drug interaction (PK or PD) causing a decrease in exposure/efficacy of the current drug
Addition of a contraindication
Addition of a warning concerning situations of decreased effectiveness
Addition of a precaution for use/recommendation to prevent the occurrence of a previously unknown risk, i.e. not yet listed in that section
Removal of a warning because of concurrent upgrade to contraindication
Addition of a warning concerning situations of decreased safety
Strengthening of a warning concerning situations of decreased safety
Addition of a drug-drug interaction (PK or PD) causing an increase in exposure to and thereby (theoretically) (the worsening of) an ADR of the current drug, i.e. direct risk of current drug

Table S1 *Continued*

Regulatory actions that reflected a negative impact on benefits or risks
Addition of a drug-drug interaction (PK or PD) causing a decrease in exposure/efficacy of another drug, i.e. indirect risk of current drug
Addition of a drug-drug interaction (PK) causing an increase in exposure to and thereby (theoretically) (the worsening of) an ADR of another drug, i.e. indirect risk of current drug
Strengthening of the wording of an interaction, e.g. change from recommendation to contraindication
Addition of a recommendation concerning (longer) abstinence of breastfeeding
Addition of a notion concerning hindered ability to drive because of an ADR
Addition of an ADR
Increased frequency of an ADR

ADR, adverse drug reaction; PD, pharmacodynamic; PK, pharmacokinetic

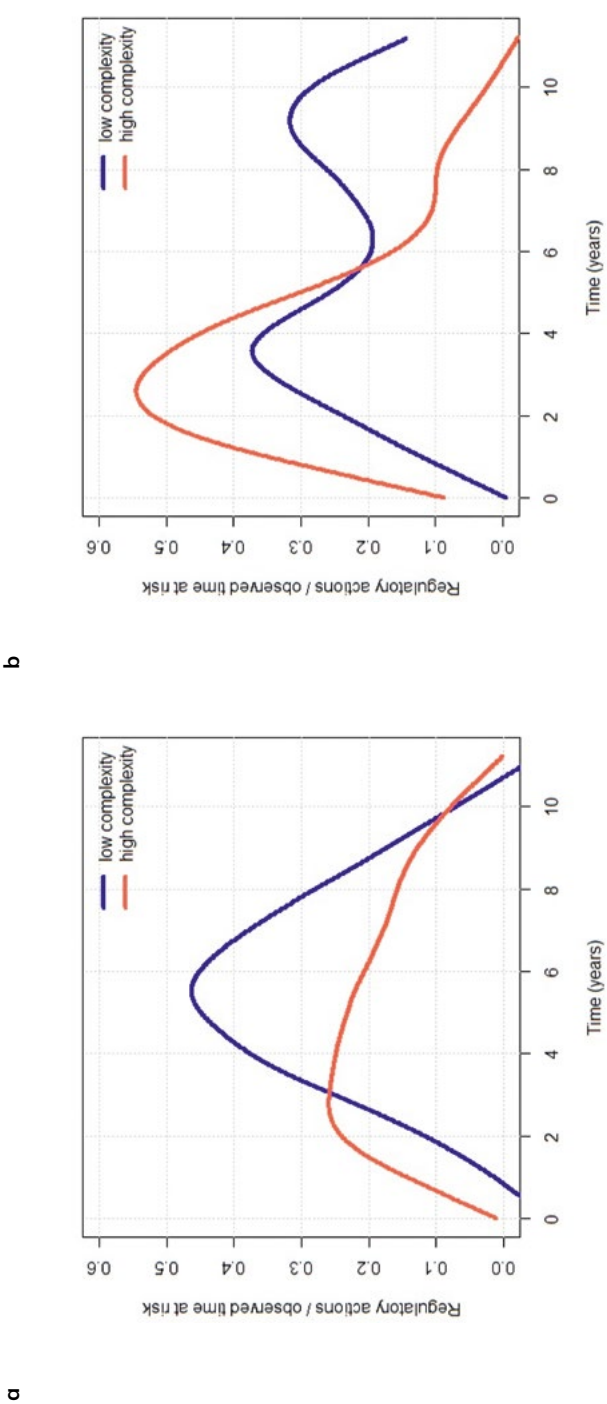

Figure S1 Curves representing intensity rates of regulatory actions that reflected a positive (**a**) and negative (**b**) impact on benefits and risks, for low and high complexity of the drug assessment process

Table S2 Overview of regulatory actions and source of underlying data

Type of regulatory action and data source	Complexity of the assessment process			
	Low (*N* = 11 drugs)		High (*N* = 29 drugs)	
Positive impact on benefits and risks				
Changes to SmPC	**28**		**57**	
Post-approval study results	25	89%	56	98%
Post-marketing experience data	1	4%	1	2%
Unclear	2	7%	0	0%
Negative impact on benefits and risks				
DHPCs	**2**		**12**	
Post-approval study results	1	50%	2	17%
Post-marketing experience data	1	50%	9	75%
Re-evaluation of all available data (referral procedure)	0	0%	1	8%
Changes to SmPC	**79**		**197**	
Post-approval study results	32	41%	51	26%
Post-marketing experience data	29	37%	94	48%
Other data, e.g. modelling	1	1%	2	1%
Re-evaluation of all available data (referral procedure)	0	0%	6	3%
Unclear	17	22%	44	22%

DHPC, direct healthcare professional communication; SmPC, Summary of Product Characteristics

Table S3 Adjusted intensity rate ratios[a] and 95% confidence intervals for secondary analyses that included all relevant regulatory actions

Complexity	≤39 months	>39 months
Positive impact on benefits and risks (*N* = 85)		
Low	Ref.	Ref.
High	6.08 (0.92-40.24)	0.44 (0.23-0.85)
Negative impact on benefits and risks (*N* = 290)		
Low	Ref.	Ref.
High	2.79 (1.50-5.16)	0.46 (0.29-0.73)

[a] Adjusted for pre-approval patient exposure

Chapter 3

Impact of evidence generation for regulatory decision-making on downstream decision-makers

Alles stroomt
Zelfs steen verwordt tot stof
dat waait met alle winden mee
Tot elke zekerheid verweert

Het is de stroming zelf die blijft
De niet te stuiten dorst naar meer
Die overeind staat door de tijd
-is wat de wetenschap ons leert

– Stucwerk Dichtkunst

Chapter 3.1

Associations between uncertainties identified by the European Medicines Agency and national decision-making on reimbursement by HTA agencies

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Abstract

We aimed to determine whether uncertainties identified by the European Medicines Agency (EMA) were associated with negative relative effectiveness assessments (REA) and negative overall reimbursement recommendations by national health technology assessment (HTA) agencies. Therefore, we identified all HTA reports from HAS (France), NICE (England), SMC (Scotland) and ZIN (the Netherlands) for a cohort of innovative medicines that EMA had approved in 2009-2010 (excluding vaccines). Uncertainty regarding pivotal trial methodology, clinical outcomes and their clinical relevance were combined to reflect a low, medium or high level of uncertainty. We assessed associations by calculating risk ratios (RR) and 95% confidence intervals (CI), and agreement between REA and overall reimbursement recommendation outcomes. We identified 36 medicines for which 121 reimbursement recommendations had been issued by the HTA agencies between September 2009 and July 2018. High vs. low uncertainty was associated with an increased risk for negative REAs and negative overall reimbursement recommendations: RRs 1.9 (95% CI 0.9-3.9) and 1.6 (95% CI 0.7-3.5), respectively, which was supported by further sensitivity analyses. We identified a lack of agreement between 33 (27%) REA and overall reimbursement recommendation outcomes, which were mostly restricted recommendations that followed on negative REAs in case of low or medium uncertainty. In conclusion, high uncertainty identified by EMA was negatively associated with REAs and overall reimbursement recommendations. To reduce uncertainty and ultimately facilitate efficient patient access, regulators, HTA agencies and other stakeholders should discuss how uncertainties should be weighed and addressed early in the drug life cycle of innovative treatments.

Introduction

In Europe, patient access to costly innovative medicines often requires a positive reimbursement recommendation by a national health technology assessment (HTA) agency.[1, 2] HTA agencies provide recommendations based on a relative effectiveness assessment (REA), and, depending on the agency, other considerations such as a cost-effectiveness assessment (CEA) and budget impact analysis (BIA).[3] For these assessments, HTA agencies depend on evidence submitted to them by medicine manufacturers. However, since HTA decision-making on reimbursement is preceded by regulatory decision-making on market approval in the drug life cycle, evidentiary standards set by regulators such as the European Medicines Agency (EMA) influence the amount and type of data and (un)certainty available to downstream decision-makers such as HTA agencies.[4]

When deciding on market approval, medicine regulators assess the benefit-risk balance of a medicine based on its quality, safety and efficacy.[5] These decisions always involve some level of uncertainty, which is inherent to the underlying data and the relative weights that are, explicitly or implicitly, given to different safety and efficacy outcomes.[5, 6] Moreover, when considering patient access to medicines, regulators weigh the need for more data against potential risks associated with remaining uncertainties and, in some cases, against an unmet medical need in the studied patient population.[7]

Whether factors that represent a higher level of uncertainty in regulatory decisions are associated with HTA outcomes has recently been studied, with varying results. Some studies assessed the association between such factors and REA outcomes,[8] while most focused on overall reimbursement recommendation outcomes.[8-13] With regard to REAs, negative outcomes may be expected when regulatory benefit-risk decisions are made with a high level of uncertainty since these decisions are informed by largely the same clinical data.[14] In contrast, such uncertainty may have less of an impact on overall reimbursement recommendations because, depending on the HTA agency, these recommendations may also be informed by additional assessments such as CEA and BIA.[3, 15] HTA agencies may then weigh the uncertainties associated with clinical assessment outcomes against CEA and BIA outcomes and considerations such as unmet medical need. Thus, to better understand the role of upstream uncertainty in the HTA decision-making process, it is important to study its impact on both REA and overall reimbursement recommendation outcomes.

Moreover, previous studies focused on one specific disease-related, clinical or regulatory factor that represented uncertainty in regulatory decision-making, i.e. presence of (ultra-)orphan status for medicines,[9, 10] uncontrolled clinical trials supporting regulatory approval[8, 11] and use of early access pathways.[12, 13] However, a more diverse set of regulatory uncertainty aspects may be more in line with the HTA perspective on relative effectiveness, e.g. uncertainty regarding the methodology of pivotal clinical trials, uncertainty regarding the clinical outcome demonstrated by these trials and uncertainty regarding the clinical relevance of these outcomes.

For the current study, we hypothesised that a higher level of these uncertainty aspects identified by EMA during regulatory assessment would be associated with negative REAs since the data underlying these assessments are roughly similar. However, we expected that the level of uncertainty would be less strongly associated with overall reimbursement recommendation outcomes, since also other aspects are taken into account. Therefore, the aim of this study was to determine whether a higher level of uncertainty identified by EMA was associated with negative REAs and negative overall reimbursement recommendations by national HTA agencies.

Methods

Study design and inclusion criteria for medicines and HTA agencies

We performed a retrospective cohort study consisting of all innovative medicines, i.e. products containing new active substances, that were approved by EMA between 1 January 2009 and 31 December 2010. This cohort was chosen for two reasons: i) for these medicines, confidential, non-publicly available data on EMA's uncertainty regarding pivotal clinical trial data (methods, clinical outcome and clinical relevance) had previously been obtained through a Memorandum of Understanding with the Dutch Medicines Evaluation Board,[16] which formed a unique opportunity to study this association, and ii) substantial follow-up time was considered necessary to allow for the availability of the HTA decision-making outcomes. We excluded vaccines because their product and clinical use characteristics require HTA assessment processes that are substantially different from the assessment processes for other medicines.

Consecutively, we determined whether the following four HTA agencies had assessed the initially approved indications of the remaining medicines: the Haute Autorité de Santé (HAS, responsible for France), the National Institute for Health and Care Excellence (NICE, responsible for England and Wales in the United Kingdom), the

Scottish Medicine Consortium (SMC, responsible for Scotland in the United Kingdom), and the Zorginstituut Nederland (ZIN, responsible for the Netherlands). These agencies were selected based on five criteria that we also used in previous studies: [8, 12] i) the agency had to be responsible for making reimbursement recommendations in an European jurisdiction during the study period, ii) recommendation reports had to be publicly available, iii) recommendations had to play an official role in the final reimbursement decision-making process, iv) the agency had to be the primary institute with legal capacity in making reimbursement recommendations within the jurisdiction, v) the report had to be in a language understood by the researchers (LTB, RAV, NWLP), i.e. Dutch, English, French or German. We excluded medicines that had not been assessed by any of the above agencies.

Data extraction: EMA uncertainty aspects and HTA reimbursement recommendations

For the included medicines, we first assessed the level of uncertainty identified by EMA during the regulatory assessment, based on three uncertainty aspects. First, uncertainty regarding the methodology of pivotal clinical trials was considered present when so-called "major objections" concerning the study design, choice of endpoints, patient population studied, trial duration and statistical analyses had been expressed during the pre-approval review process.[17] Second, uncertainty regarding the clinical outcome demonstrated by pivotal clinical trials was considered present when uncertainty regarding the statistical significance of the primary outcome remained at the time of approval and/or serious safety concerns had been raised. Third, uncertainty regarding the clinical relevance of the clinical outcomes was considered present when none of the following applied at the time of approval: a large effect size, important medical need and compelling clinical benefit. These data were previously extracted from public and confidential EMA assessment reports and assessed, with substantial agreement reached between the primary data collection and a blinded independent review of a randomly selected sample.[16] The level of composite uncertainty was scored as low when none of these uncertainty aspects were considered present, medium when one aspect was considered present and high when two or three aspects were considered present.

Second, we identified the first reimbursement recommendation report for each medicines' initial EMA approved indication(s) ("medicine-indication combination"). This was done for all four HTA agencies noted above and up to 30 November 2020. We disregarded recommendation reports that were not based on data ('non-submissions') and excluded reassessments. When HTA agencies had split EMA approved indications

into sub-indications for which they issued separate reimbursement recommendations, we regarded these as unique medicine-indication combinations. From the included reports we extracted the date of recommendation, REA outcome, and overall reimbursement recommendation outcome for each relevant medicine-indication combination. We assessed REA outcomes as positive or negative, and overall reimbursement recommendation outcomes as unrestricted positive, restricted positive or negative, in line with previous research.[8, 12] Relative effectiveness that was higher than or comparable to a comparator was considered a positive REA outcome, while lower effectiveness – including in case of a lack of data – was considered a negative REA outcome. Overall reimbursement recommendations were considered restricted in case of reimbursement for a smaller indication than initially approved by EMA or lower reimbursement than the price requested by the company.[8, 12] Data extraction was performed by NWLP for the full cohort and validated by LTB for a random 10% sample of medicines, based on which we calculated the percentage of agreement and Cohen's kappa for interrater agreement.[18] Data that did not correspond were discussed until consensus was reached.

Data analysis

We initially characterised the cohort using descriptive statistics. We then performed two main analyses to assess associations between a higher level of composite uncertainty (medium vs. low and high vs. low) identified by EMA and HTA outcomes, by calculating risk ratios (RR) and Wald 95% confidence intervals (CI). First, we assessed the association with negative REAs. Second, we assessed the association with negative overall reimbursement recommendations. For the latter analysis, restricted positive and unrestricted positive overall reimbursement recommendations were aggregated. The analyses were performed irrespective of HTA agency that issued the recommendations. However, to provide insight in agency-specific associations, we visualised the overall and agency-specific distributions of outcomes. Also, we performed sensitivity analyses by restricting the two main analyses to medicine-indication combinations for which all agencies issued reimbursement recommendations. This was done to avoid that the analyses would be affected by variation due to differences between HTA agencies in medicine-indication combinations they assessed.

Furthermore, to provide insight in the most important uncertainty aspects driving potential associations, we performed six ancillary analyses to assess associations between each individual uncertainty aspect and negative REAs and negative overall

reimbursement recommendations. For these, we also performed sensitivity analyses as described above.

Additionally, we performed sensitivity analyses to substantiate our assumption that pre-approval major objections concerning the methodological robustness of pivotal clinical trials would reflect remaining methodological uncertainty. We therefore reviewed the major objections and how these were addressed by the companies, and considered whether a higher level of methodological uncertainty in line with the major objections remained at time of approval. In doing so, we followed a conservative approach and only considered the level of uncertainty to remain higher if companies were unable to submit the requested data pre-approval and thus committed to submit further data post-approval. If an indication was restricted pending the submission of data post-approval, we considered that the level of methodological uncertainty was lowered. We then recategorized the level of composite uncertainty and replicated both the main analyses and the ancillary analyses involving methodological uncertainty to assess whether any changes in the categorization of uncertainty affected the results.

Lastly, we assessed the proportion of medicine-indication combinations for which the REA and overall reimbursement recommendation outcomes did not correspond. That is, when an unrestricted or restricted positive overall reimbursement recommendation was issued while the REA was negative, or a negative overall reimbursement recommendation while the REA was positive. We also assessed whether this proportion differed depending on the level of uncertainty identified by EMA.

Results

Cohort characteristics: medicines, HTA agencies and reimbursement recommendations

Between 1 January 2009 and 31 December 2010, 45 innovative medicines were approved by EMA. Of these, we excluded nine medicines: eight vaccines and one medicine which initial indication had not been assessed by any included HTA agency (rilonacept, brand name Rilonacept Regeneron). We included the remaining 36 medicines (see Table 1 for some summary characteristics). A detailed overview of the included medicines and their indications as initially approved by EMA is available in Table S1. We identified uncertainty regarding the methodology of pivotal clinical trials for 22 medicines, uncertainty regarding the clinical outcome for six, and uncertainty regarding clinical relevance for ten.[16]

Table 1 Characteristics of the included medicines (n=36) approved by EMA in 2009-2010

Characteristic	Level of composite uncertainty		
	Low (n=9)	Medium (n=18)	High (n=9)
Biological or ATMP	5 (56%)	8 (44%)	0 (0%)
Initial approved indication			
Cancer treatment	1 (11%)	3 (17%)	2 (22%)
Cardiovascular treatment	2 (22%)	1 (6%)	1 (11%)
Immunosuppressive treatment	1 (11%)	3 (17%)	0 (0%)
Musculo-skeletal disorder treatment	2 (22%)	1 (6%)	0 (0%)
Other treatment[1]	3 (33%)	10 (56%)	6 (67%)
Type of market approval			
Regular approval	7 (78%)	15 (83%)	9 (100%)
Conditional approval[2]	0 (0%)	3 (17%)	0 (0%)
Exceptional approval[2]	2 (22%)	0 (0%)	0 (0%)
Orphan status at approval	3 (33%)	4 (22%)	1 (6%)
At least one indication assessed by			
HAS (France)	9 (100%)	18 (100%)	9 (100%)
NICE (England & Wales)	4 (44%)	8 (44%)	4 (44%)
SMC (Scotland)	6 (67%)	13 (72%)	7 (78%)
ZIN (the Netherlands)	7 (78%)	11 (61%)	9 (100%)
Time between EMA approval and HTA recommendation (median, range)			
HAS (France)	240 days (86-567)	242 days (104-1631)	380 days (62-1210)
NICE (England & Wales)	774 days (154-2340)	529 days (146-1854)	412 days (272-569)
SMC (Scotland)	332 days (126-926)	245 days (81-2808)	186 days (32-386)
ZIN (the Netherlands)	395 days (171-1387)	399 days (130-1653)	200 days (130-1146)

ATMP, advanced therapeutic medicinal product; EMA, European Medicines Agency; HAS, Haute Autorité de Santé; HTA, Health Technology Assessment; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; ZIN, Zorginstituut Nederland
[1] E.g. antidiabetics, blood-related treatment, diagnostic agents, psychopharmacological treatment, respiratory treatment, sex hormones and related treatment. All ≤3 medicines in total.
[2] Conditional approval or approval under exceptional circumstances, i.e. regulatory pathways that aim at providing (early) access to medicines that address a high unmet medical need[19]

The 36 medicines were approved by EMA with one or more initial indication(s) – 40 in total –, and some were further split by HTA agencies into two sub-indications. In total, this led to 45 unique medicine-indication combinations for which HTA agencies could have issued reimbursement recommendations. However, not all agencies

assessed all medicine-indication combinations, and we therefore ultimately included 121 reimbursement recommendations that had been issued between September 2009 and July 2018. The process of identification of medicines, HTA agencies and reimbursement recommendations is shown in Figure 1. The data validation yielded a 93% agreement rate with a Kappa of 0.88, indicating excellent agreement.

Table 2 Associations between level of composite uncertainty and negative REAs and overall reimbursement recommendations

Level of composite uncertainty	Primary analysis (n=121)	RR (95% CI)	Sensitivity analysis (n=68)[1]	RR (95% CI)
Negative REA				
Low	7/28 (25%)	Ref.	4/12 (33%)	Ref.
Medium	27/63 (43%)	1.7 (0.9-3.5)	17/39 (44%)	1.3 (0.5-3.1)
High	14/30 (47%)	1.9 (0.9-3.9)	12/17 (71%)	2.1 (0.9-5.0)
Negative overall reimbursement recommendation[2]				
Low	7/28 (25%)	Ref.	3/12 (25%)	Ref.
Medium	16/63 (25%)	1.0 (0.5-2.2)	8/39 (21%)	0.8 (0.3-2.6)
High	12/30 (40%)	1.6 (0.7-3.5)	10/17 (59%)	2.4 (0.8-6.8)

CI, confidence interval; REA, relative effectiveness assessment; RR, risk ratio
[1] Restricted to medicine-indication combinations for which all HTA agencies issued reimbursement recommendations
[2] For this analysis, the alternative non-negative outcome consisted of restricted and unrestricted positive overall reimbursement recommendations

Relative effectiveness assessments

Of the 121 REAs, 48 (40%) were negative and 73 (60%) were positive. The distribution of these outcomes is presented in Figure 2a; separately for medicine-indication combinations associated with a low, medium and high level of composite uncertainty identified by EMA, and both overall as well as for each individual HTA agency. RRs for a negative REA were 1.7 (95% CI 0.9-3.5; medium vs. low uncertainty) and 1.9 (95% CI 0.9-3.9; high vs. low uncertainty) (Table 2), which, given the relatively small sample, is suggestive of an association between level of uncertainty and decision-making on REAs by HTA agencies. The sensitivity analysis that was restricted to medicine-indication combinations for which all four HTA agencies issued reimbursement recommendations (see Figure 3a) supported the existence of an increased RR for high vs. low uncertainty: RR 2.1 (95% CI 0.9-5.0). This result indicates a slightly more pronounced association given the higher point estimate and higher lower bound of the CI. However, it did not support the existence of an increased RR for medium vs. low uncertainty: 1.3 (95% CI 0.5-3.1) (Table 2). The most important uncertainty

aspect driving the association seemed to be uncertainty regarding the methodology of pivotal clinical trials: 1.6 (95% CI 1.0-2.7) (see Figure S1a and Table S2).

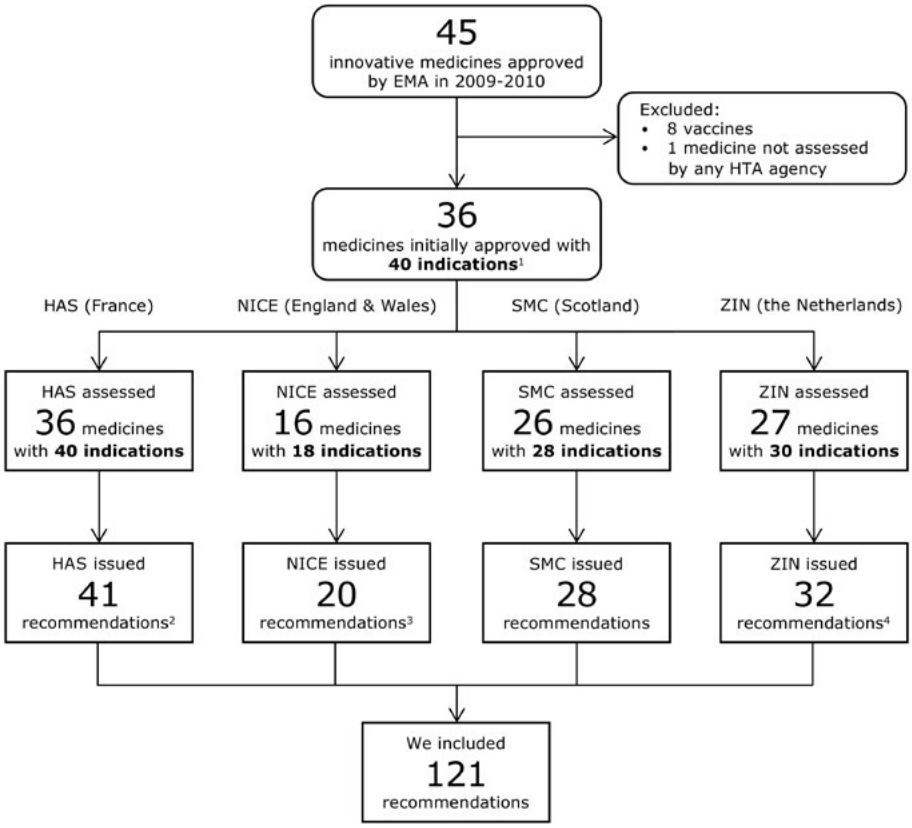

Figure 1 Flowchart of medicines included in the study cohort and medicine-indication combinations for which HTA outcomes were extracted

EMA, European Medicines Agency; HAS, Haute Autorité de Santé; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; ZIN, Zorginstituut Nederland

[1] epoetin theta (Eporatio) and denosumab (Prolia) were initially approved for two indications, golimumab (Simponi) was initially approved for three indications (see Table S1)

[2] HAS further split one EMA approved indication into two subindications, which resulted in two separate recommendations

[3] NICE further split two EMA approved indications into two subindications each, which resulted in four separate recommendations

[4] ZIN further split two EMA approved indications into two subindications each, which resulted in four separate recommendations

Overall reimbursement recommendations

Of the 121 overall reimbursement recommendations, 35 (29%) were negative, 71 were positive but restricted (59%) and 15 (12%) were positive and unrestricted. The distribution of these outcomes is presented in Figure 2b; separately for medicine-indication combinations associated with a low, medium and high level of composite uncertainty identified by EMA, and both overall as well as for each individual HTA agency. RRs for a negative overall reimbursement recommendation were 1.0 (95% CI 0.5-2.2; medium vs. low uncertainty) and 1.6 (95% CI 0.7-3.5; high vs. low uncertainty) (Table 2), which suggests a potential association only for a high vs. low level of composite uncertainty. These findings were both supported by the sensitivity analysis (see Figure 3b): RR 0.8 (95% CI 0.3-2.6), indicating no association for medium vs. low uncertainty, and RR 2.4 (95% CI 0.8-6.8), indicating that a high level of uncertainty led to more negative overall recommendations by HTA agencies (Table 2). The most important uncertainty aspect driving the potential association seemed to be uncertainty regarding the clinical outcome: 1.7 (95% CI 1.0-3.0) (see Figure S1b and Table S2).

Review of major objections and sensitivity analyses

We considered that a higher level of methodological uncertainty remained for at least 11 of the 22 medicines for which major objections had been expressed during the pre-approval review process, because of commitments to provide additional data post-approval. For nine of these medicines, all data were to be obtained from new or ongoing studies that had not been part of the approval dossier. For one, only preliminary data of one of two requested studies had been part of the approval dossier. For another, requested long-term efficacy and safety data of the pivotal trial had to be provided post-approval. The analyses based on this alternative categorization supported the main and ancillary analyses, indicating the same trends and no substantial changes in point estimates considering the relatively broad confidence intervals (Table S3).

For the other 11 medicines, major objections had been resolved through (a combination of) restricted indications, labelling, additional analyses or narrative justifications. However, also for these medicines we often noted that at approval, EMA had flagged important remaining limitations in the data that resolved major objections, which may affect HTA decision-making. These included non-preferred comparators, the uncontrolled nature of additional studies, indirect comparisons and inability to demonstrate non-inferiority.

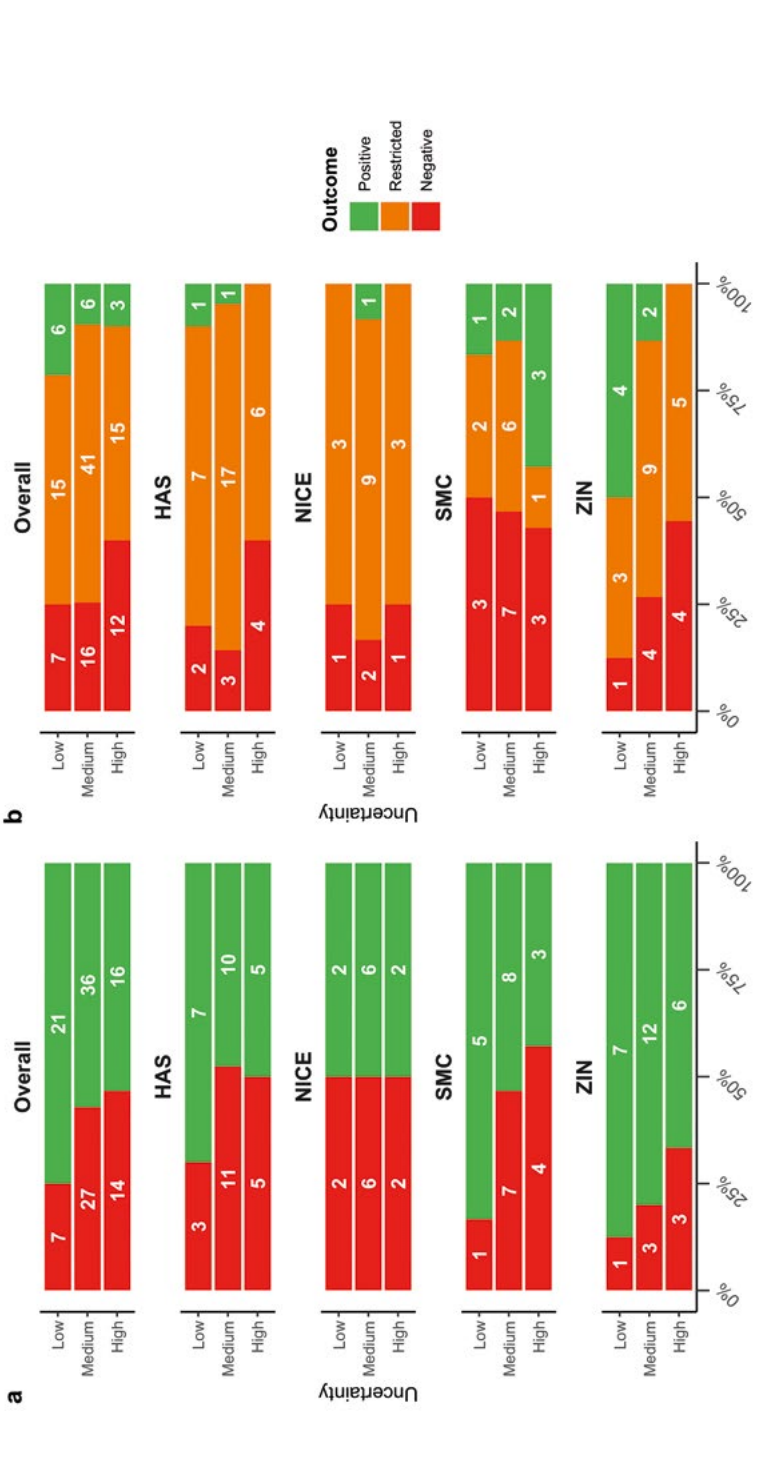

Figure 2 REA (**a**) and overall reimbursement recommendation (**b**) outcomes for all medicine-indication combinations (n=121) stratified by level of composite uncertainty, overall and per HTA agency

HAS, Haute Autorité de Santé (France); NICE, National Institute for Health and Care Excellence (England and Wales, United Kingdom); SMC, Scottish Medicines Consortium (Scotland, United Kingdom); ZIN, Zorginstituut Nederland (the Netherlands)

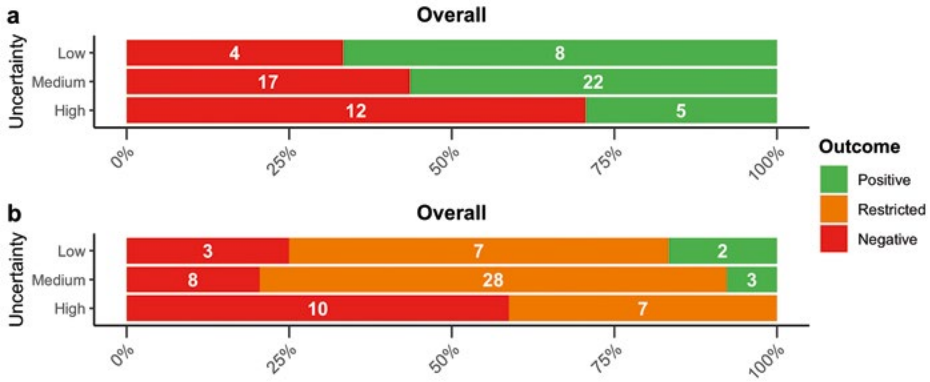

Figure 3 REA (**a**) and overall reimbursement recommendation (**b**) outcomes for medicine-indication combinations for which all four HTA agencies issued reimbursement recommendations (n=68), stratified by level of composite uncertainty

HAS, Haute Autorité de Santé (France); NICE, National Institute for Health and Care Excellence (England and Wales, United Kingdom); SMC, Scottish Medicines Consortium (Scotland, United Kingdom); ZIN, Zorginstituut Nederland (the Netherlands)

Discrepancies between REA and corresponding overall reimbursement recommendation outcomes per medicine-indication combination

REA and overall reimbursement recommendation outcomes did not correspond for 33 of the 121 medicine-indication combinations (27%). This occurred most frequently for medicine-indication combinations with a negative REA: 23 of 48 negative REAs (48%) were followed by a positive overall reimbursement recommendation. Of these, 22 (96%) were restricted positive overall reimbursement recommendations. In case of a negative REA, medicine-indication combinations with a high level of composite uncertainty seemed less likely than those with a low or medium level to receive a (restricted) positive overall reimbursement recommendation: 4/14 (29%) vs. 3/7 (43%) and 16/27 (59%), respectively. In contrast, only 10 of 73 positive REAs (14%) were followed by a negative overall reimbursement recommendation and this occurred equally often for low (3/21, 14%), medium (5/36, 14%) and high 2/16, 13%) level of composite uncertainty.

Discussion

Our study suggests that a high vs. a low level of composite uncertainty identified by EMA was associated with a 1.9-fold increased risk of negative REAs and 1.6-fold increased risk of negative overall reimbursement recommendations by HTA agencies. Our sensitivity analysis restricted to medicine-indication combinations for which all

agencies issued reimbursement recommendations showed stronger associations and strengthened our main findings.

These associations for medicine-indication combinations with a high level of composite uncertainty may at least be partly explained by similarities in clinical data that inform benefit-risk assessments and REAs.[14] In addition, similarities in how regulators and HTA agencies assess relevant uncertainties in these data may also play a role.[20] HTA agencies may obtain information on relevant uncertainties either indirectly through the regulator's assessment – as evidenced by the many references to EMA's public assessment reports that we identified in HTA reports and the fact that some HTA agencies explicitly require these reports to be submitted[21] - or by performing their own assessment of the data. However, while regulators may decide to grant approval and address remaining uncertainties through requests for further post-approval evidence generation, HTA agencies have to come to a decision based on the then available data including uncertainties. Moreover, regulators are potentially more inclined to do so in case of uncertainties that are of less relevance to them as they are to HTA agencies – such as use of a non-preferred comparator[20, 22] or surrogate rather than clinical outcomes in clinical trials – which may result in negative REAs as we show in our study.

In contrast, we identified a weaker association between a medium level of composite uncertainty and negative REAs that largely disappeared in the sensitivity analysis and no association with negative overall reimbursement recommendations. One of the reasons for this was that a large proportion of negative REAs was translated into a positive overall reimbursement recommendation – of which most (96%) were restricted. This occurred most often for medicine-indication combinations with a medium level of composite uncertainty; more than twice as often as for those with a high level of composite uncertainty and 1.4 times as often as for those with a low level. These clinical and/or economic restrictions may be one way for HTA agencies to address a remaining – but acceptable – level of uncertainty while allowing access to medicines.

The lack of an association with negative HTA outcomes for medicine-indication combinations with a medium level of composite uncertainty could further be explained by other factors that may be taken into account during reimbursement decision-making, such as unmet medical need[23] and price-related aspects such as CEA and BIA.[3] These may cause a medium level of composite uncertainty to be weighed differently and considered acceptable while a high level of uncertainty is not. The importance of unmet medical need in HTA decision-making has been highlighted by others that studied uncertainty associated with medicines that had

been approved based on data from uncontrolled trials[11, 24] or through early access pathways.[12] Both uncontrolled trials and approval through early access pathways are typical characteristics of medicines that address an unmet medical need,[25-27] and may also have played a role in our study. Although only few medicines had been approved through early access pathways (14%), all three that were conditionally approved – indicating that uncertainties had to be addressed post-approval – were associated with a medium level of uncertainty and mostly received positive (but restricted) overall reimbursement recommendations. In addition, most medicines indicated for cancer treatment – which often address a high unmet medical need and may be approved based on uncontrolled trials[28] – were associated with a higher level of uncertainty identified by EMA. However, also other indications may be associated with an unmet medical need. For example, dronedarone (Multaq) was associated with one of the highest levels of uncertainty – scoring negative on all uncertainty aspects – and all HTA agencies considered that its relative effectiveness in preventing atrial fibrillation recurrence was negative. Nonetheless, NICE and SMC issued a positive – but restricted – reimbursement recommendation to allow for the availability of a treatment option with a better side-effect profile, which was regarded an unmet medical need by patients and health care providers.[29, 30]

Importantly, while the different HTA agencies request broadly similar evidence for their REAs,[31] they differ in the extent to which they take aspects such as CEA, BIA and unmet medical need into account.[15, 32-34] Differences in the content and the processes of these assessments between agencies may explain discrepancies in reimbursement recommendation outcomes between them that have previously been reported.[8, 13, 33-35] In our current study, agency-specific distributions of overall reimbursement recommendation outcomes indicate an association between a higher level of uncertainty and negative outcomes for HAS and ZIN, but not for NICE and SMC. A potential explanation may be the extent to which CEA is taken into account by agencies. NICE and SMC perform a comprehensive CEA for every recommendation and may perform pricing negotiations prior to issuing a reimbursement recommendation. In contrast, HAS does not perform CEAs in most cases and ZIN applies a risk-based approach to considering CEAs while pricing negotiations fall outside their mandate.[15] Moreover, NICE's assessment process is very extensive and includes a review of the company submission as well as additional data – for which they are known to sometimes wait – by an external 'Evidence Review Group'.[36] This may reduce uncertainty and thus lead to less negative outcomes – also of their REAs, as evidenced by the agency-specific data. Conversely, HTA outcomes for NICE constitute final reimbursement decisions while HTA outcomes of other organisations can comprise recommendations to a

subsequently deciding authority that may still wish to negotiate prices, for example the Minister of Health in the Netherlands.[3] These differences between agencies may also explain the differences in time from market approval to issue of reimbursement recommendation that we observed.

To prevent that uncertainties adversely impact patient access to innovative medicines, it is imperative to reduce overall uncertainty through multi-stakeholder discussions about relevant uncertainties and how they should be weighed and addressed. In addition, these may also stimulate further alignment on specific evidence needs for decision-making between regulators and HTA agencies. Currently ongoing initiatives that facilitate such dialogues – often early in the drug life cycle – are therefore of great importance. These include e.g. collaboration between EMA and the European Network for Health Technology Assessment (EUnetHTA),[37, 38] the EMA PRIority MEdicines (PRIME) scheme,[39] and other (inter)national initiatives.[40-43] These are of great relevance to overcome the current barriers to efficient patient access to new innovative medicines, including the impact of remaining uncertainties after regulatory approval.[44]

An important strength of our study is that it studied associations between a comprehensive measure of uncertainties identified during regulatory assessment and subsequent HTA decision-making outcomes. Moreover, we substantiated our assumption that major objections would reflect remaining methodological uncertainty since i) the results of the sensitivity analyses based on a conservative assessment of remaining methodological uncertainty were in line with our other findings, and ii) we flagged important caveats that may affect HTA decision-making for many of the other medicines for which major objections had been expressed. Furthermore, our study provided insights in HTA agency-specific associations for such uncertainty, that appeared in line with known differences in activities and mandates between agencies. However, it also has several limitations. First, while the major objections reflect a diverse set of methodological aspects of the regulatory assessment of clinical data that is largely in line with the HTA REA, they may not always capture the uncertainty aspects that are relevant to HTA agencies, e.g. choice of comparator and non-inferiority rather than superiority study designs.[20, 22] We can thus not exclude the role of any other methodological uncertainties. Second, we assessed a cohort of medicines that was approved by EMA several years ago. However, the broad type of medicines and indications were largely similar to those currently approved,[45] consisting of a fair share of biologicals and even one cell-based therapy and with cancer treatment already being the major indication area. Nevertheless, recent approvals are likely associated with even more uncertainty, e.g. because they are more often based on single-arm studies that include small numbers of patients.[46]

Therefore, if anything, a more negative impact on HTA decision-making outcomes can be expected. Third, differences in the type of medicines assessed by each HTA agency as well as differences in assessment methods, responsibilities and mandates may have caused variation in assessment outcomes between HTA agencies that affected our results. However, we have addressed this by performing sensitivity analyses restricted to medicine-indication combinations that had been assessed by all agencies and these strengthened our main analyses by indicating even more pronounced results. Fourth, because of the small number of medicine-indication combinations per agency, we were not able to estimate with sufficient precision agency-specific associations and discrepancies between REA and corresponding overall reimbursement recommendation outcomes. Also, due to the relatively small sample of recommendations, we may not have been able to identify associations that actually exist. We have tried to lower the impact of this limitation by performing several sensitivity analyses on a restricted cohort and assessing and discussing any resulting shift in point estimates. Of note, the fact that our results consistently suggest a 'dose-dependent' association between uncertainty and negative HTA outcomes, i.e. the highest uncertainty was associated with the highest risk of negative outcomes, further support our findings. Fifth, we only included data from four HTA agencies, mostly because of a lack of publicly available HTA recommendation reports from other agencies. Considering the organisational and mandate-related differences between agencies, this limits the generalisability of our findings to HTA decision-making in Europe in general.

Conclusions

A high level of composite uncertainty identified by EMA seemed to be negatively associated with REAs and overall reimbursement recommendations by HTA agencies in Europe. To reduce uncertainty, current and future initiatives for multi-stakeholder interaction early in the drug life cycle must include discussions about relevant uncertainties and how they should be weighed and addressed. Ultimately, this will facilitate efficient patient access to new innovative treatments.

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Supplementary material

Table S1 Detailed characteristics of the included medicines (n=36) approved by EMA in 2009-2010

Generic name	Brand name(s)[1]	Indication(s) initially approved by EMA (high level description)
amifampridine	Firdapse	Lambert-Eaton myasthenic syndrome
asenapine	Sycrest	Manic episodes associated with bipolar 1 disorder
aztreonam	Cayston	Pulmonary infections in patients with cystic fibrosis
bazedoxifene	Conbriza	Postmenopausal osteoporosis
besilesomab	Scintimun	Scintigraphic imaging (diagnostic use)
canakinumab	Ilaris	Cryopyrin-Associated Periodic Syndromes
catumaxomab	Removab	Malignant ascites in patients with EpCAM positive carcinomas
certolizumab pegol	Cimzia	i) Rheumatoid arthritis, ii) psoriatic arthritis, iii) ankylosing spondylitis (3 indications)
characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	ChondroCelect	Cartilage defects of the knee
collagenase Clostridium histolyticum	Xiapex	Dupuytren's contracture
conestat alfa	Ruconest	Hereditary angioedema
corifollitropin alfa	Elonva	Controlled ovarian stimulation
denosumab	Prolia	i) Postmenopausal osteoporosis, ii) bone loss associated with hormone ablation in men with prostate cancer (2 indications)
dronedarone	Multaq	Atrial fibrillation
eltrombopag	Revolade	Chronic immune (idiopathic) thrombocytopenic purpura
epoetin theta	Eporatio	Symptomatic anaemia: i) associated with chronic renal failure, ii) in patients with non-myeloid malignancies (2 indications)

Table S1 *Continued*

Generic name	Brand name(s)[1]	Indication(s) initially approved by EMA (high level description)
eslicarbazepine acetate	Exalief / Zebinix	Partial-onset seizures with or without secondary generalisation
gefitinib	Iressa	Non-small cell lung cancer
golimumab	Simponi	Rheumatoid arthritis
indacaterol	Onbrez Breezhaler / Oslif Breezhaler / Hirobriz Breezhaler	Chronic obstructive pulmonary disease
liraglutide	Victoza	Type 2 diabetes mellitus
ofatumumab	Arzerra	Chronic lymphocytic leukaemia
pazopanib	Votrient	Renal cell carcinoma
pirfenidone	Esbriet	Idiopathic pulmonary fibrosis
plerixafor	Mozobil	Mobilisation of haematopoietic stem cells for autologous transplantation in patients with lymphoma and multiple myeloma
prucalopride	Resolor	Chronic constipation
regadenoson	Rapiscan	Radionuclide myocardial perfusion imaging (diagnostic use)
roflumilast	Daxas	Chronic obstructive pulmonary disease
saxagliptin	Onglyza	Type 2 diabetes mellitus
silodosin	Urorec / Silodyx	Benign prostatic hyperplasia
ticagrelor	Brilique	Prevention of atherothrombotic events in patients with acute coronary syndromes or a history of myocardial infarction
tolvaptan	Samsca	Hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion
ulipristal acetate	ellaOne	Emergency contraception
velaglucerase alfa	Vpriv	Type 1 Gaucher disease
vernakalant hydrochloride	Brinavess	Atrial fibrillation
vinflunine	Javlor	Transitional cell carcinoma of the urothelial tract

EMA, European Medicines Agency

[1] Some medicines were approved with multiple brand names, i.e. so-called 'duplicate authorisations'

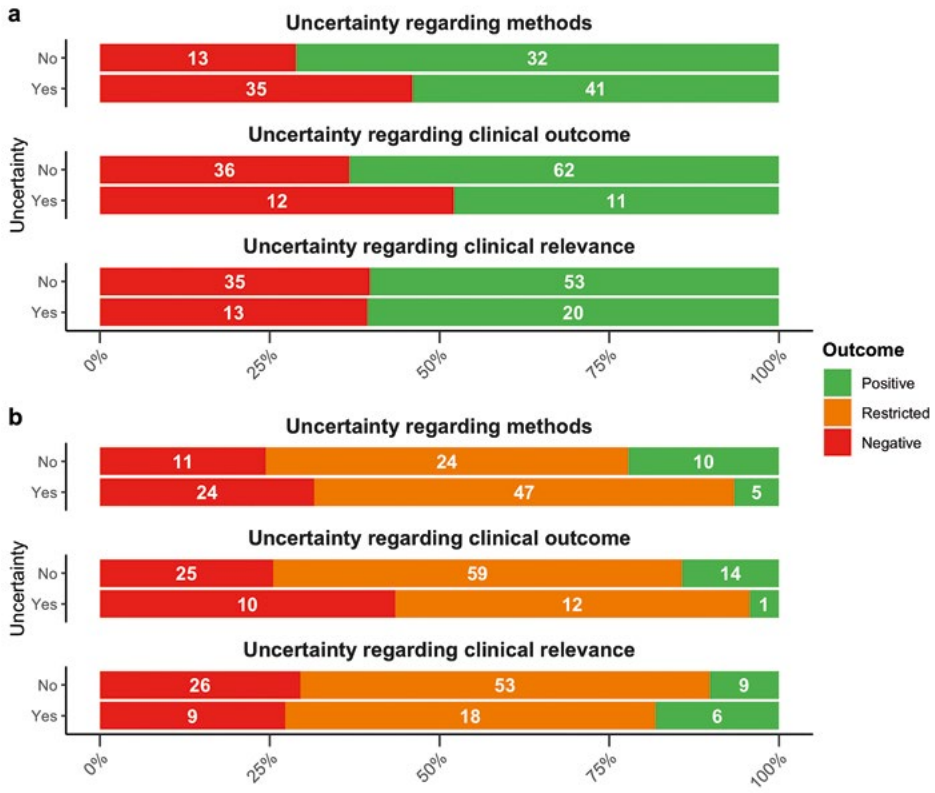

Figure S1 REA **(a)** and overall reimbursement recommendation **(b)** outcomes for medicine-indication combinations, separately for each individual uncertainty aspect

Table S2 Associations between individual uncertainty aspects and negative REAs and overall reimbursement recommendations

	Primary analysis (n=121)	RR (95% CI)	Sensitivity analysis (n=68)[1]	RR (95% CI)
Negative REA				
Uncertainty regarding methodology of pivotal clinical trials				
No	13/45 (29%)	Ref.	6/20 (30%)	Ref.
Yes	35/76 (46%)	1.6 (1.0-2.7)	27/48 (56%)	1.9 (0.9-3.8)
Uncertainty regarding clinical outcome				
No	36/98 (37%)	Ref.	24/51 (47%)	Ref.
Yes	12/23 (52%)	1.4 (0.9-2.3)	9/17 (53%)	1.1 (0.7-1.9)
Uncertainty regarding clinical relevance				
No	35/88 (38%)	Ref.	23/51 (45%)	Ref.
Yes	13/33 (39%)	1.0 (0.6-1.6)	10/17 (59%)	1.3 (0.8-2.2)
Negative overall reimbursement recommendation[2]				
Uncertainty regarding methodology of pivotal clinical trials				
No	11/45 (24%)	Ref.	6/20 (30%)	Ref.
Yes	24/76 (32%)	1.3 (0.7-2.4)	15/48 (31%)	1.0 (0.5-2.3)
Uncertainty regarding clinical outcome				
No	25/98 (26%)	Ref.	12/51 (24%)	Ref.
Yes	10/23 (43%)	1.7 (1.0-3.0)	9/17 (53%)	2.3 (1.2-4.4)
Uncertainty regarding clinical relevance				
No	26/88 (30%)	Ref.	14/51 (27%)	Ref.
Yes	9/33 (27%)	0.92 (0.5-1.8)	7/17 (41%)	1.5 (0.7-3.1)

CI, confidence interval; REA, relative effectiveness assessment; RR, risk ratio

[1] Restricted to medicine-indication combinations for which all HTA agencies issued reimbursement recommendations

[2] For this analysis, the alternative non-negative outcome consisted of restricted and unrestricted positive overall reimbursement recommendations

Table S3 Sensitivity analyses to assess the assumption of remaining methodological uncertainty, for the main analyses involving composite uncertainty and the ancillary analyses involving methodological uncertainty

	Full sample (n=121)	RR (95% CI)	Restricted sample (n=68)[1]	RR (95% CI)
Negative REA				
Composite uncertainty				
Low	16/49 (33%)	Ref.	10/25 (40%)	Ref.
Medium	22/53 (42%)	1.3 (0.8-2.1)	14/30 (47%)	1.2 (0.6-2.2)
High	10/19 (53%)	1.6 (0.9-2.9)	9/13 (69%)	1.7 (0.9-3.2)
Uncertainty regarding methodology of pivotal clinical trials				
No	27/82 (33%)	Ref.	16/42 (38%)	Ref.
Yes	21/39 (54%)	1.6 (1.1-2.5)	17/26 (65%)	1.7 (1.1-2.8)
Negative overall reimbursement recommendation[2]				
Composite uncertainty				
Low	12/49 (24%)	Ref.	5/25 (20%)	Ref.
Medium	15/53 (28%)	1.2 (0.6-2.2)	9/30 (30%)	1.5 (0.6-3.9)
High	8/19 (42%)	1.7 (0.8-3.5)	7/13 (54%)	2.7 (1.1-6.8)
Uncertainty regarding methodology of pivotal clinical trials				
No	21/82 (26%)	Ref.	12/42 (29%)	Ref.
Yes	14/39 (36%)	1.4 (0.8-2.5)	9/26 (35%)	1.2 (0.6-2.5)

CI, confidence interval; REA, relative effectiveness assessment; RR, risk ratio

[1] Restricted to medicine-indication combinations for which all HTA agencies issued reimbursement recommendations

[2] For this analysis, the alternative non-negative outcome consisted of restricted and unrestricted positive overall reimbursement recommendations

Chapter 3.2

The role of regulator-imposed post-approval studies in health technology assessments for conditionally approved drugs

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Abstract

Background: The European Medicines Agency (EMA) aims to resolve uncertainties associated with conditionally approved drugs by imposing post-approval studies. Results from these studies may be relevant for health technology assessment (HTA) organizations. This study investigated the role of regulator-imposed post-approval studies within HTA.

Methods: For all conditionally approved drugs up to December 2018, regulator-imposed post-approval studies were identified from EMA's public assessment reports. The availability for and inclusion of study results in relative effectiveness (re)assessments were analyzed for 4 European HTA organizations: NICE (National Institute for Health and Care Excellence, England/Wales), HAS (Haute Autorité de Santé, France), ZIN (Zorginstituut Nederland, the Netherlands) and the European Network for Health Technology Assessment (EUnetHTA, Europe). When study results became available between an HTA organization's initial assessment and reassessment, it was evaluated whether and how they affected the assessment and its outcome.

Results: For 36 conditionally approved drugs, 98 post-approval studies were imposed. In total, 81 initial relative effectiveness assessments (REAs) and 13 reassessments were available, with numbers of drugs (re)assessed varying greatly between jurisdictions. Study results were available for 16 initial REAs (20%) and included in 14 (88%), and available for 10 reassessments (77%) and included in all (100%). Five reassessments had an outcome different from the initial REA, with 4 (2 positive and 2 negative changes) relating directly to the new study results. Reassessments often cited the inability of post-approval studies to resolve the concerns reported in the initial REA.

Conclusion: Results from regulator-imposed post-approval studies for conditionally approved drugs were not often used in REAs by HTA organizations, because they were often not yet available at the time of initial assessment and because reassessments were scarce. When available, results from post-approval studies were almost always used within HTA, and they have led to changes in conclusions about drugs' relative effectiveness. Post-approval studies can be relevant within HTA but the current lack of alignment between regulators and HTA organizations limits their potential.

Background

To enable timely access to innovative drugs, the European Medicines Agency (EMA) can conditionally approve drugs based on a less comprehensive evidence package when immediate availability of the drug outweighs the risks due to the less comprehensive evidence package.[1,2] Importantly, the benefit-risk balance still needs to be judged positive, but more uncertainty may be considered acceptable in light of the drug's potential to address unmet medical needs. What constitutes a 'less comprehensive evidence package' is to some extent clarified by EMA guidelines and can be related to small sample sizes, surrogate primary endpoints, short follow-up times, and limited safety data, amongst others.[1] Indeed, research has shown that the evidence package available at approval for drugs with a conditional marketing authorization (CMA) is less comprehensive compared to drugs approved with a standard marketing authorization. A lower percentage of drugs has an evidence package including randomized, controlled and/or blinded studies. Fewer patients are included in the pivotal studies for conditionally approved drugs and fewer studies include clinical primary endpoints.[3-5] To address these remaining uncertainties and to ensure that more comprehensive evidence is ultimately available, the EMA obligates manufacturers to perform post-approval studies called 'specific obligations' (SOBs).

However, after approval patient access to innovative drugs can remain limited in case of negative reimbursement decisions. To inform decisions regarding a drug's optimal reimbursement status and level, health technology assessment (HTA) organizations evaluate the benefits of drugs compared to jurisdiction-specific alternative treatments.[6] These evaluations include relative effectiveness assessments (REAs), together with other HTA considerations. Since the evaluation of efficacy – and, to a lesser extent, safety – by regulators has similarities to REAs performed by HTA organizations, both organizations exhibit similar preferences regarding evidence suitable for their assessments.[7-12] Nevertheless, the acceptance of less comprehensive evidence for CMA drugs by regulators may not be acceptable for reimbursement decision-making by HTA organizations.[13] Ideally, regulators and HTA organizations would coordinate their post-approval evidence needs so that results from SOBs can inform HTA reassessments. It is currently unclear to what extent post-approval evidence has informed HTA decision-making.

Eighty-seven percent of CMA drugs approved between 2006 and 2016 did not receive unrestricted positive reimbursement recommendations.[14] Negative reimbursement recommendations lead to patient access being delayed, limited or entirely absent,

depending on the jurisdiction. For this reason, regulators and HTA organizations have emphasized the relevance of alignment of their processes and evaluations.[15] Although some HTA organizations have processes in place to conditionally reimburse drugs, these processes are currently not aligned with the EMA conditional approval pathway. Considering that SOBs are in place to ensure comprehensive evidence becoming available, their results could affect reimbursement recommendations and subsequent patient access. However, the execution of SOBs takes time.[16, 17] Thus, results from SOBs may be particularly relevant for HTA reassessments as opposed to initial evaluations. The extent to which results of post-approval studies inform HTA recommendations has never been studied. Thus, this study investigated if results from regulator-imposed post-approval studies (ie, SOBs) for conditionally approved drugs were used by HTA organizations within REAs and if so, how these studies have affected the assessments.

Methods

Included drugs and jurisdictions

A retrospective analysis of EMA and HTA reports was performed. All drugs conditionally approved between March 2006 (the start date of the CMA scheme) and December 2018 were included. Included HTA organizations were major European HTA jurisdictions that systematically publish full initial HTA reports and reassessment reports on their websites in a language understood by the investigators, being: England + Wales (National Institute for Health and Care Excellence, NICE), France (Haute Autorité de Santé, HAS), the Netherlands (Zorginstituut Nederland, ZIN) and the European Network for Health Technology Assessment (EUnetHTA). HTA reports were retrieved by searching agencies' websites for the drug generic and brand name and were included until June 2019, to allow time for HTA decision-making after drug approval. Vaccines were excluded because HTA organizations assess vaccines differently from other drugs.

Data extraction

To investigate the role of SOBs in REAs, data was extracted for regulatory evaluations and HTA initial assessments and reassessments. We recorded general characteristics of drugs including drug name, indication, therapeutic category, orphan status at conditional approval, CMA date (European Commission decision), marketing authorization conversion date (if applicable), and whether the drug had undergone

accelerated assessment by the EMA. Drug regulatory data on pivotal observational and interventional studies submitted for approval and to fulfil post-approval SOBs were retrieved from the European public assessment reports. The number of pivotal studies evaluated for approval of the drug and the included primary endpoints within these pivotal studies were recorded. Primary endpoints were categorized as surrogate or clinical efficacy endpoints, or safety endpoints based on the information provided by the European public assessment report and on previous literature describing the type of endpoints in pivotal studies for conditionally approved drugs.[18]

Considering post-approval studies, all SOBs were extracted from EMA documents following previously published procedures.[17] The number of SOBs per drug and their original due dates and final submission dates (if applicable) were recorded. The objective of the SOB (addressing, efficacy, safety or other), type of obligation (clinical trial or other) and its status at approval were also recorded. Again, the primary endpoints for those SOBs entailing clinical trials were categorized as surrogate, clinical or safety.

Data on HTA considerations and conclusions regarding relative effectiveness were retrieved from published HTA reports – including initial assessments as well as reassessments – each matching the initial CMA indication. HTA recommendations that were not substantiated by a consideration of the clinical evidence were excluded (eg, a negative recommendation because no dossier was submitted by the manufacturer). When the CMA concerned multiple indications that were considered separately by HTA organizations, all were included independently. The same approach was applied when HTA organizations split a single indication into recommendations for 2 or more subpopulations. From HTA reports, the dates of the initial assessment and reassessments were recorded, as well as the outcome of the REA and whether the assessments included a discussion of the (lack of) results from completed SOBs.

Data analysis

First, descriptive statistics were used to describe drug, pivotal study and SOB characteristics. Second, based on the dates of included HTA reports, SOB results were categorized as being available for HTA organizations (y/n) in initial REAs as well as in reassessments and it was analyzed whether available SOB results were included by HTA organizations. For initial REAs, the proportions of positive and negative recommendations were compared between those REAs including SOB results and those not including SOB results. To that end, the outcomes of the REAs were categorized into lesser effectiveness, equal effectiveness and higher

effectiveness compared to jurisdiction-specific alternative treatments, in line with previous work.[19, 20] When REAs did not include SOBs even though they were already available at the time of HTA decision, it was assessed whether the REA process was already ongoing when SOB results became available. If so, these indications were categorized as having no SOBs available yet.

Finally, the contributing role of SOB results was assessed by investigating the initial and reassessment REA reports for those drugs that had initial assessments that did not include results from SOBs while the reassessments did. HTA organizations' major concerns on the clinical evidence were extracted from the reports' summary statements. From the reassessment reports, statements were extracted about SOB results affecting the assessments and/or assessment outcomes by resolving or not resolving any or all of the major concerns. Major concerns were – in line with previous work – classified into categories related to the trial validity, the patient population, comparative effects, and the relevance of the endpoints and the drug's effect size on those endpoints.[21-23] Possible changes to REA outcomes were assessed based on the REA categories used within each jurisdiction.

Results

Characteristics of included drugs, pivotal studies and specific obligations

Forty drugs have been conditionally approved between January 2006 and December 2018. Three of them were vaccines, and one of them was not assessed by any HTA organization, giving a final cohort of 36 drugs. Table 1 shows characteristics of these drugs and associated pivotal studies and SOBs. The majority of drugs (53%) were approved based on a single pivotal study. In total, 59 pivotal trials supported the drug approvals. The EMA imposed 98 SOBs for the 36 included drugs. For 17 drugs (47%), only 1 SOB was imposed.

Inclusion of health technology assessment reports

Figure 1 shows the inclusion flowchart of HTA reports for all 36 drugs. In total, 94 HTA recommendations were included, of which 81 were initial assessments and 13 were reassessments. HAS evaluated all drugs, but all other jurisdictions evaluated only a part of the cohort. NICE evaluated 23 drugs, ZIN 16 and EUnetHTA only 1 drug. There was a second report from EUnetHTA (for pazopanib), but the report emphasized that it was not suited for decision-making as it was used to test the EUnetHTA core model.

Table 1 Drug and trial characteristics of the 36 included drugs

Characteristic	*N (%)*
Drug characteristics	
Therapeutic category (based on ATC code)	
Alimentary tract and metabolism	1 (3)
Systemic hormonal preparations	1 (3)
Anti-infectives	6 (17)
Antineoplastic agents	23 (64)
Musculo-skeletal system	2 (6)
Nervous system	2 (6)
Sensory organs	1 (3)
Orphan designation at conditional approval	22 (61)
Converted to standard marketing authorization at 31-12-2018	19 (53)
Number of pivotal trials per drug	
1	19 (53)
2	11 (31)
3	6 (17)
Number of drugs with at least one study with a clinical primary endpoint at conditional approval	1 (3)
Number of SOBs per drug	
1	17 (47)
2	9 (25)
3	2 (6)
4	4 (11)
5	2 (6)
≥6	2 (6)
Number of drugs with SOBs with clinical primary endpoints	9 (25)
Characteristics of pivotal trials	
Total number of pivotal trials	59
Endpoints included in pivotal trials	
Clinical primary endpoints	1 (2)
Surrogate primary endpoints	56 (95)
Safety endpoints	2 (3)
Characteristics of SOBs	
Total number of SOBs	98
SOBs fulfilled at 31-12-2018	77 (79)

Table 1 *Continued*

Characteristic	*N (%)*
SOB is meant to provide insight in	
Efficacy	5 (5)
Efficacy and safety	75 (77)
Safety	8 (8)
Other	10 (10)
Type of SOB	
Clinical trial (final analysis)	66 (67)
Clinical trial (interim analysis)	11 (11)
Other	21 (21)
Status of clinical trials as SOBs at approval (N = 77)	
Already ongoing	50 (65)
New study	27 (35)
Endpoints included in clinical trials as SOBs (N = 77)	
Clinical primary endpoints	13 (17)
Surrogate primary endpoints	57 (74)
Safety primary endpoints	7 (9)

ATC code, anatomical therapeutic chemical code; SOB, specific obligation

It was therefore excluded from this study. In one occasion NICE split the indication into 2 recommendations. This was the case for 4 drugs for HAS. Reassessments were available for 3 indications (13%) for NICE, 9 (23%) for HAS and for 1 indication (6%) for ZIN. Figure S1 shows the outcomes of the initial REAs of the included HTA organizations.

Availability and inclusion of specific obligations in REAs

Figure 2 shows a flowchart of the inclusion of SOBs in initial REAs and in reassessments. SOB results were available for 16 (20%) of 81 initial REAs. Of these 16, 14 (88%) included the available SOB results. SOB results were available for 10 (77%) of all 13 reassessments. All 10 (100%) included those SOB results. Overall, SOBs were included in 24 of 26 cases where they were available (92%). For one of the 10 reassessments that included SOB results the initial assessment already included those results. The availability and inclusion of SOBs in REAs is graphically presented in Figure 3. It shows for all 36 drugs the major events within regulation (conditional and standard marketing authorization, SOB completion dates) and HTA (assessments and reassessments). For HTA events, the figure also indicates whether

the EMA SOBs were considered in the assessment (yes/no, if available). Nineteen drugs had their CMA converted to a standard marketing authorization. For 4 of these drugs, an HTA reassessment existed that was not already ongoing at the time of conversion (3 from HAS and 1 from ZIN). All 4 included the available SOB results.

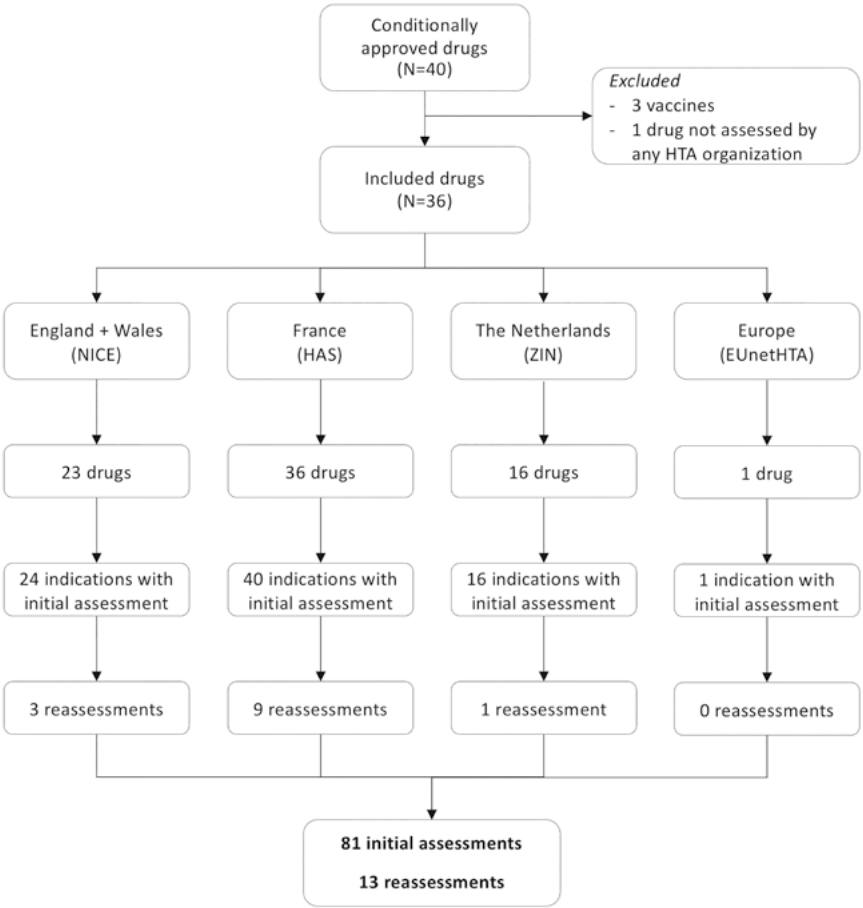

Figure 1 Inclusion flowchart for the REAs of all included HTA organizations

EUnetHTA, European Network for Health Technology Assessment; HAS, Haute Autorité de Santé; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; REA, relative effectiveness assessment; ZIN, Zorginstituut Nederland

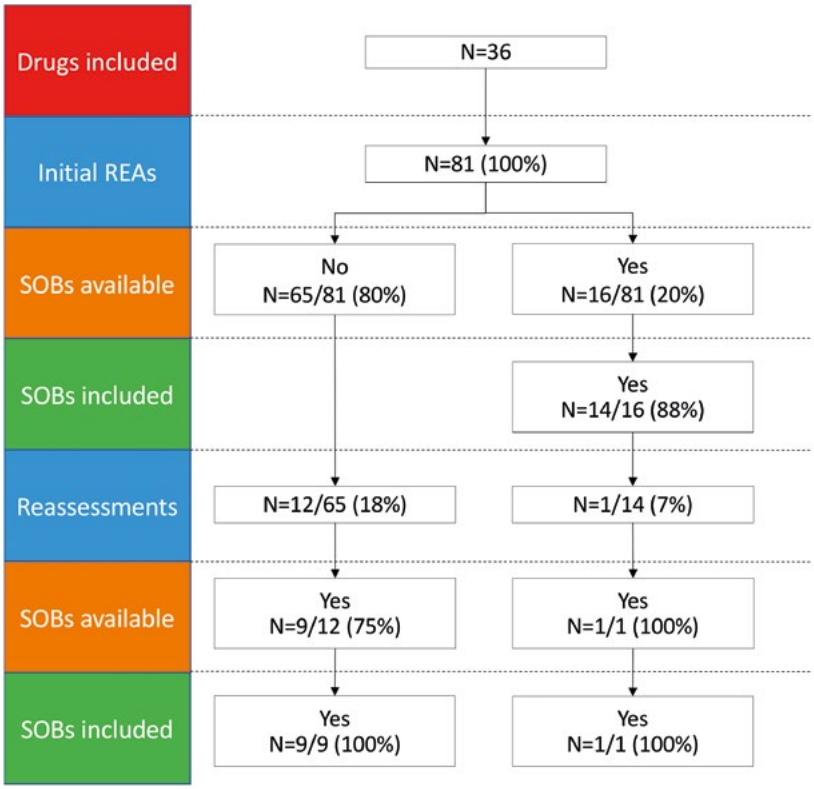

Figure 2 Availability for and inclusion of SOBs in initial and subsequent REAs
REA, relative effectiveness assessment; SOB, specific obligation

The median time from CMA to standard marketing authorization was 1095 days (N = 19, IQR = 572-1909) The median time from CMA to initial HTA recommendation was 520 days for NICE (N = 23, IQR = 245-1416), 219 days for HAS (N = 36, IQR = 144-410), 249 days for ZIN (N = 16, IQR = 110- 523), and 372 days for EUnetHTA (N = 1). The median time from conversion to a standard marketing authorization to reassessment was 176 days for HAS (N = 3, IQR = 142-1132) and 283 days for ZIN (N = 1).

Outcomes of the initial REAs seemed similar between the drugs for which SOB results were available and included (N = 14) and those for which they were either available but not included or not available at all (N = 67); 10/14 (71%) versus 43/67 (64%) were positive and 2/14 (14%) versus 11/67 (16%) were negative, see Figure S2.

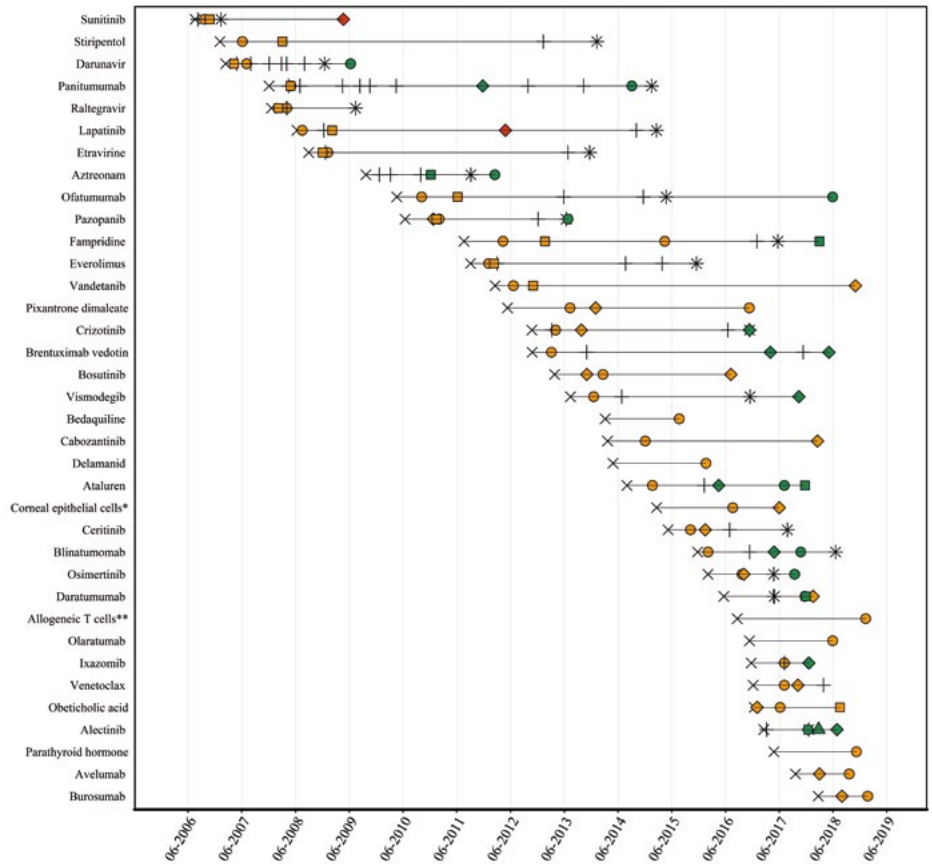

Figure 3 Timeline of drug regulatory decisions and HTAs for conditionally approved drugs

The colors indicate whether results from SOBs were considered during HTA. CMA, conditional marketing authorization; EUnetHTA, European Network for Health Technology Assessment; HAS, Haute Autorité de Santé; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; SMA, standard marketing authorization; SOB, specific obligation; ZIN, Zorginstituut Nederland

* Ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar®)

** Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) (Zalmoxis®)

HAS performed nine reassessments, NICE three, and ZIN only one.

Role of specific obligation results in relative effectiveness assessments

To assess the role of results from SOBs on REA reassessments, dossiers were analyzed for drugs for which the initial REA did not include results from SOBs while the reassessment did. As shown in Figure 2, of all 13 reassessments, nine met this criterion. Table 2 shows the initial assessment and reassessment outcomes for all nine drugs and the main concerns that impacted the result of the REA. Higher relative benefit at reassessment versus initial assessment was established for 2 drugs: osimertinib (Tagrisso®) and pazopanib (Votrient®), by HAS. In each case a lack of established comparative effects was the main factor impacting the initial assessment. Therefore, non-inferiority could not yet be established for pazopanib and superiority not for osimertinib. The results from the imposed SOBs established non-inferiority for pazopanib and superiority — although only minor — for osimertinib.

Lower relative benefit at reassessment versus initial assessment was established for 3 drugs: ataluren (Translarna®), blinatumomab (Blincyto®) and ofatumumab (Arzerra®), by HAS. For ataluren, the initial assessment explicitly stated that even though there were major concerns, the drug was given the benefit of the doubt due to a lack of alternatives. The SOB results did not resolve the concerns of HAS. For blinatumomab, the prospective benefit for a patient population with a medical need was established as moderate awaiting a comparative trial. The SOB resolved this lack, but the effects were judged as less impressive than expected, resulting in a conclusion of minor benefit. For ofatumumab, the SOB did not resolve any of the major concerns, but in the meantime alternative treatments had been approved for the same indication which led to downgrading of the benefit of ofatumumab.

Equal relative benefit at reassessment versus initial assessment was established for 4 drugs: crizotinib (Xalkori®) by NICE, darunavir (Prezista®) and panitumumab (Vectibix®) by HAS, and fampridine (Fampyra®) by ZIN. For 2 (crizotinib and darunavir), the concerns were not regarded as major, resulting in positive REA conclusions in the initial assessments. The SOB results, based on longer follow-up of the pivotal trials at approval, did not change that. Notably, the NICE reassessment of crizotinib considered the longer follow-up of overall survival data, but used this mostly to update the cost-effectiveness model. For the other 2 drugs (panitumumab and fampridine), it was explicitly mentioned that the SOB results did not resolve the major concerns even though for both drugs the SOBs included a newly initiated study.

Table 2 Initial and reassessment REA outcomes and main critique points of HTA organizations for the 9 drugs for which SOB results became available between the initial assessment and the reassessment

	Drug	HTA organization	Assessment	Relative benefit	Trial validity	Population	Comparator	Effect size/ endpoints
Higher	Osimertinib	HAS	Primary	Absent				
			Reassessment	Minor				
	Pazopanib	HAS	Primary	Insufficient				
			Reassessment	Absent				
Lower	Ataluren	HAS	Primary	Minor				
			Reassessment	Absent				
	Blinatumomab	HAS	Primary	Moderate				
			Reassessment	Minor				
	Ofatumumab	HAS	Primary	Absent				
			Reassessment	Insufficient				
No change	Crizotinib	NICE	Primary	Positive				
			Reassessment	Positive				
	Darunavir	HAS	Primary	Moderate				
			Reassessment	Moderate				
	Fampridine	ZIN	Primary	Negative				
			Reassessment	Negative				
	Panitumumab	HAS	Primary	Absent				
			Reassessment	Absent				

HAS, Haute Autorité de Santé (France); HTA, health technology assessment; NICE, National Institute for Health and Care Excellence (England, Wales); REA, relative effectiveness assessment; SOB, specific obligation; ZIN, Zorginstituut Nederland (the Netherlands). HAS categories that equal a positive REA (higher effect) are minor, moderate and substantial benefit. Absent for HAS means equal effectiveness and insufficient means a negative REA (less effective). The red color means a negative impact of this aspect on the REA and the green color a positive impact. Grey stands for this aspect not being discussed as a main critique point.

Discussion

This study aimed to investigate if results from regulator-imposed post-approval studies (ie, SOBs) for conditionally approved drugs were used by HTA organizations within REAs and if so, how these studies have affected reassessments. Our findings indicate that HTA organizations almost always included results of SOBs for conditionally approved drugs in their assessments, if those results were available at the time of assessment. However, these were only available in a minority of cases, because most initial REAs were performed before any results from SOBs were available. Furthermore, because HTA reassessments were relatively uncommon, most results from SOBs that became available after the initial HTA recommendation were not used within any REA.

In those cases where SOB results became available between the initial assessment and a reassessment, they had variable effects on HTA recommendations. In 4 cases (44%), SOB results directly led to reassessment conclusions that were different from the initial REA. A lack of established comparative effects was most often the major concern resolved by SOBs. In each case these concerns were resolved through newly initiated studies rather than continuations or extensions of pivotal trials. Depending on how convincing the effect sizes were in the SOB results in relation to what was hypothesized in the initial REA, the relative benefit was either upgraded or downgraded in the reassessment. In the other 5 cases, SOB results did not change the REA. In 2 cases this was because there were no major concerns to be solved by the SOB and in the other 3 cases the SOB results did not adequately resolve the major concerns from the initial REA. For one of those 3 cases, the reassessment REA outcome was nonetheless different from the initial REA, due to factors independent of the assessed drug or the SOB results.

Implications

The lack of initial REAs that included SOB study results was expected given the sequence and timing of regulatory evaluations and HTAs in the drug lifecycle: most initial REAs are already finished by the time any post-approval study results become available. Current initiatives between the 2 stakeholders regarding data sharing and parallel evaluations will likely further shorten the timing between regulatory evaluations and HTA.[15, 24] To ensure incorporation of relevant post-approval study results in HTA decisions, a more systematic approach to reassessments by HTA organizations could therefore be appropriate. Currently, there is a clear misalignment

between both stakeholders regarding post-approval processes. Regulators review the CMA annually and aim to ultimately convert the CMA status to a standard marketing authorization, while HTA reassessments of relative effectiveness are scarce and rarely timed after the moment of conversion to standard marketing authorization.

Our results also indicate that large differences are present in the (re)assessment procedures of the included HTA organizations. HAS aims to evaluate all drugs, while NICE and ZIN have risk-based selection procedures to decide which drugs they will assess. HAS has a procedure for reassessments that dictates reassessments every 5 years, or when new evidence warrants it. However, the reassessments performed by HAS for our cohort of drugs often included only an assessment of the actual benefit (to determine whether the drug should remain on the positive reimbursement list), while no reevaluation of relative effectiveness was performed. Therefore we could not include these reassessments in our analysis. Similarly, NICE can set a date for reassessment during the initial evaluation when this is warranted, or, if no date is set, checks for new evidence every 5 years. Again, for the drugs included in our analysis often NICE screened the evidence and found a reassessment was not necessary. ZIN can reevaluate drugs, and had a reassessment procedure for a selection of (expensive) inpatient drugs from 2006-2014. No systematic reassessment procedure currently exists and reassessments are rare. Reassessments can also be requested by manufacturers, but because many initial REAs are already positive, there may not be many. Indeed, in our study, for most indications for which a reassessment was performed, the initial REA indicated a lack of or little added benefit. There might also be an underreporting of reassessments when REA outcomes remain unchanged. Other factors, for example capacity restraints, may also contribute to the scarcity of reassessments. Further development of targeted reassessment processes – in line with the timing of evidence development and conversion of conditional to standard marketing authorization – for all HTA organizations can facilitate alignment between HTA reassessments and the CMA process of the EMA. Though EUnetHTA assessments for conditionally approved drugs were found to be extremely rare, EUnetHTA has evaluated some CMA drugs approved after the inclusion timeframe of this study (eg, polatuzumab vedotin and crizanlizumab). Besides joint assessments, EUnetHTA may play an important role in the standardization of reassessment processes throughout Europe. A good starting point may be the EUnetHTA report on the criteria to select and prioritize health technologies for additional evidence generation. Full alignment on reassessment processes is nevertheless unlikely for the near future because reassessments may also be triggered by cost aspects or by revisions to national confidential pricing arrangements or treatment guidelines.

The changes in HTA recommendations as a consequence of the availability of results from SOBs indicate that post-approval evidence can be relevant for HTA organizations. However, our study also indicates that in some cases worries about the quality or relevance of SOB results limited their impact. Lack of study quality or inadequacies in the patient populations, comparators or endpoints have been shown to result in evidence not being helpful for the assessment of relative effectiveness.[22] Previous studies have also highlighted that data requirements from HTA organizations often go beyond requests made by the EMA.[25] Early agreement between regulators and HTA organizations regarding appropriate post-approval study requests could lead to study results that are more helpful for HTA organizations.[26] It has already been shown that regulators and HTA organizations can agree on the most appropriate characteristics for pre-approval studies.[27, 28] Possibly, a similar coordinated approach throughout the entire drug lifecycle could facilitate post-approval evidence generation. However, firm conclusions about the potential impact of post-approval study results are impossible due to the small number of HTA reassessments.

The adequate and timely completion of post-approval studies can be another area for coordination. Research has shown that SOBs are often delayed, changed, or not finished at all.[16, 17] Coordination between regulators and HTA organizations regarding timing and content of (re)evaluations could provide incentives for timely finishing SOBs. Such coordination requires HTA organizations to be free to vary their timing of reassessments.

This study focused solely on REAs, but HTA organizations have repeatedly emphasized that the limited evidence associated with conditionally approved drugs does not justify their high prices.[29, 30] Post-approval studies could influence the cost-effectiveness estimate as well as the uncertainty in that estimate by providing more information regarding the drug's relative effects. Indeed, the availability of more long-term results within the crizotinib reassessment of NICE together with a renegotiation of the drug price led to the overall reimbursement recommendation going from negative to positive, even though the REA had been positive from the beginning. Already, many HTA organizations individually experiment with conditional financing schemes, but the results are mixed and their implementation is uncoordinated across countries.[31] European coordination between regulators and HTA organizations could result in a joint definition of the necessary evidence to turn a conditional approval and conditional, limited reimbursement into a standard approval and full reimbursement.

Limitations

Precise descriptions of SOBs are often not (publicly) available at the time of marketing authorization, which means that sometimes we could not determine some characteristics of these studies such as the type of endpoint included. Additionally, SOBs are sometimes changed or added in annual renewal procedures of the CMA.[17] These alterations are not explicitly reported in the public domain which means that we may have missed some SOBs. Our inclusion criteria led to a selection of HTA organizations that do not necessarily represent all HTA organizations in Europe. Most HTA organizations did not systematically publish their full dossiers in a language understood by the investigators. For these reasons, some major jurisdictions were excluded from our study (eg, Germany, Italy and Spain) and our results cannot readily be extrapolated to these or other jurisdictions. Last, for the timeline in Figure 3, we identified decision dates or, when these were not reported, dossier publication dates, which are arguably a bit later than the actual decision dates.

Conclusion

Results from post-approval studies for conditionally approved drugs are not often used in REAs by HTA organizations, mostly because they are not yet available at the time of assessment. However, when they are available they are almost always used, and they have led to changes in the conclusions about drugs' relative effectiveness. Coordination of the post-approval evidence needs between regulators and HTA organizations, increased oversight over the finishing of post-approval studies, and a more systematic approach to reassessments by HTA organizations may facilitate appropriate patient access to conditionally approved drugs.

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Supplementary material

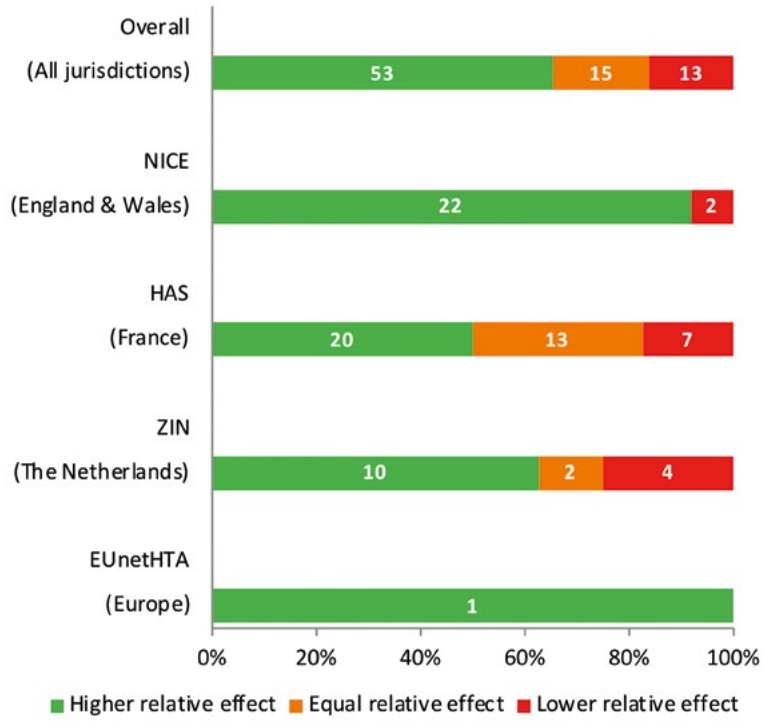

Figure S1 Primary relative effectiveness assessment outcomes (N=81) for the included drugs (N=36), excluding not assessed drugs

NICE split an indication into two recommendations in one case and HAS in four cases

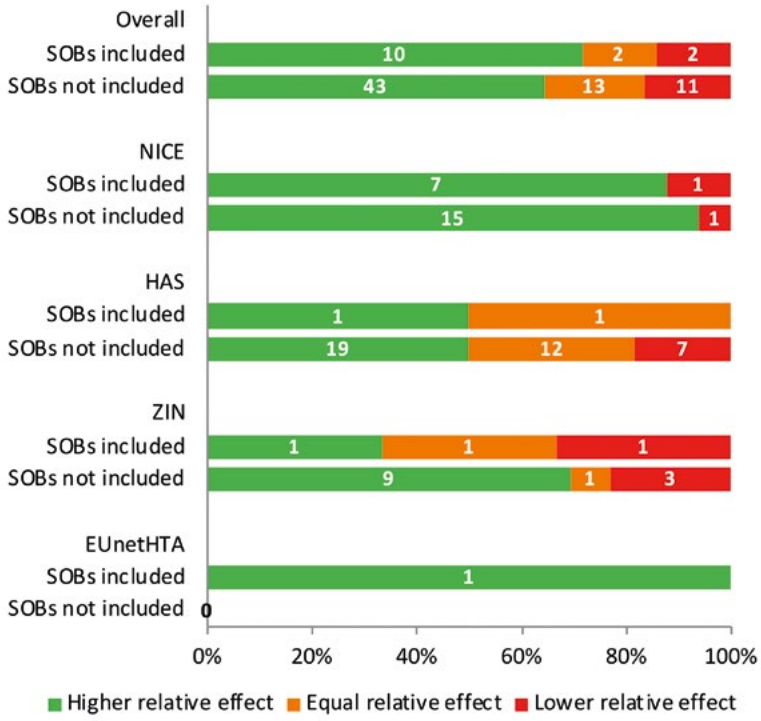

Figure S2 Outcomes of the initial relative effectiveness assessments with specific obligation results that were available and included versus relative effectiveness assessments that did not include specific obligations because they were either not available or not included

SOB, specific obligation

Chapter 3.3

Pre-approval and post-approval availability of evidence and clinical benefit of conditionally approved cancer drugs in Europe: a comparison with standard approved cancer drugs

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Abstract

Aim: Cancer drugs are increasingly approved through expedited regulatory pathways including the European conditional marketing authorization (CMA). Whether, when taking CMA post-approval confirmatory trials into account, the level of evidence and clinical benefit between CMA and standard approved (SMA) drugs differs remains unknown.

Methods: We identified all CMA cancer indications converted to SMA in 2006-2020 and compared these to similar SMA indications with regard to pivotal trial and CMA post-approval confirmatory trial design, outcomes and demonstrated clinical benefit (per the European Society for Medical Oncology Magnitude of Clinical Benefit Scale). We tested for differences in clinical benefit and whether substantial clinical benefit was demonstrated. To account for the clinical benefit of unconverted CMA indications, we performed sensitivity analyses.

Results: We included 15 CMA and 15 SMA cancer indications. The approval of 11 SMA (73%) and four CMA indications (27%) was supported by a controlled trial. Improved overall survival (OS) was demonstrated for four SMA indications (27%). Improved quality of life (QoL) was demonstrated for three SMA (20%) and one CMA indication (7%). Of subsequent CMA post-approval confirmatory trials, 11 were controlled (79%), one demonstrated improved OS (7%) and five improved QoL (36%). After conversion, CMA indications were associated with similar clinical benefit (p=0.31) and substantial clinical benefit as SMA indications (risk ratio 1.4, 95% confidence interval 0.57-3.4).

Conclusion: While CMA cancer indications are associated with less comprehensive evidence than SMA indications at approval, availability of evidence and demonstrated clinical benefit are similar after conversion from CMA to SMA.

Introduction

Cancer contributes substantially to the global disease burden, ranking third among the major causes of disability-adjusted life years.[1] Moreover, it is the primary cause of premature death in highly developed countries.[2] Although new cancer drug treatments continuously become available, a high unmet medical need for additional and more effective treatments remains.

To address unmet medical needs, drug regulatory authorities commonly use expedited regulatory pathways for approval of promising cancer drugs. These include the conditional marketing authorization (CMA) pathway of the European Medicines Agency (EMA) and the accelerated approval (AA) pathway of the United States Food and Drug Administration (US FDA).[3, 4] Expedited pathways allow approval based on less comprehensive evidence than normally required, leaving important uncertainties about efficacy and safety to be addressed by post-approval confirmatory trials. Thereafter, a standard marketing authorization (SMA) may be granted.[5]

While physicians may expect that newly approved cancer drugs provide substantial clinical value such as improvements in overall survival (OS) and quality of life (QoL) as compared to current standards of care, these expectations are often too high.[6] Moreover, although the EMA prefers OS as efficacy endpoint for SMA cancer drugs,[7] conclusive evidence on OS (and QoL) is often lacking when new cancer drugs and their indication(s) are approved. For example, Davis *et al.* reported for a cohort of 68 EMA-approved cancer indications that OS and QoL benefits had initially been demonstrated for 24 (35%) and seven (10%) of them. A median 5.4 years after approval, OS and QoL benefits were demonstrated for another three (4%) and five (7%) indications, respectively. For 33 (49%) of the indications, no OS or QoL benefits had been demonstrated, including for all ten that had been approved through the CMA expedited pathway.[8] Similar figures have been reported for the US.[9, 10]

The combination of i) infrequent demonstration of OS and QoL benefits upon approval and ii) regulatory acceptance of higher levels of uncertainty raises the question whether cancer drugs approved via expedited pathways live up to their initial promise of providing substantial value in clinical practice. An important validated instrument that may help to address these questions is the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS).[11] Such an instrument enables the assessment of clinical benefit taking into account clinical endpoints of efficacy, but also surrogate endpoints such as progression-free survival

(PFS) and overall response rate (ORR), as well as toxicity profiles. Davis *et al.* applied the ESMO-MCBS v1.0 to 23 EMA-approved solid cancer indications for which OS benefits had been demonstrated and showed that these were of substantial clinical benefit in only 11 (48%) cases due to too small effects on OS in the other cases.[8] However, the authors did not assess the clinical benefit of indications without OS benefits, did not specifically focus on expedited pathways, and were not able to evaluate single arm trials – which has only recently become possible with the updated ESMO-MCBS v1.1.[11]

We aimed to compare the availability of evidence and demonstrated clinical benefit of CMA versus SMA cancer indications in Europe, taking into account the contribution of post-approval confirmatory trials.

Methods

Study design and cohort selection

We performed a retrospective cohort study consisting of three groups of cancer indications. First, we identified all cancer drugs initially approved through the EMA's CMA pathway and converted to SMA until 31 December 2020, indicating that sufficient confirmatory evidence had been provided to fulfil so-called 'specific obligations'. For these drugs, we included all initial indications ('converted CMA indications'). Second, to benchmark their evidence and clinical benefit characteristics against SMA cancer indications, we identified an equal number of SMA cancer drugs. To allow a fair comparison that takes into account that the ability to conduct controlled clinical trials may differ between specific cancer types and their rarity, that toxicity may depend on whether drugs are targeted or not, and that evidence requirements and the availability of alternative drugs may change over time, we identified SMA drugs that were as similar as possible to the converted CMA drugs with respect to: i) pharmacotherapeutic group, based on the first five characters of the ATC code (Index 2020, www.whocc.no); ii) cancer type they were initially approved for; iii) initial approval date, and iv) whether the EMA had granted orphan status at their initial approval. We were kindly supported therein by a clinical assessor of the Dutch Medicines Evaluation Board (see acknowledgements). This approach is similar to previous research.[12] For these drugs, we also included all initial indications ('SMA indications'). Third, we identified all CMA cancer drugs that remained unconverted on 31 December 2020 and included their indications ('unconverted CMA indications') as a separate group to perform sensitivity analyses (see below). We excluded generics and biosimilars. Since we did not include patients or volunteers, ethics approval was not required.

Extraction of trial data

For all SMA and CMA indications, we identified the trials that formed the main evidence base for their initial approval ('pivotal trials'), as per the European Public Assessment Reports (EPARs) at www.ema.europa.eu. We extracted trial design characteristics and evidence concerning efficacy endpoints, QoL, and toxicity. For converted CMA indications, we also identified post-approval confirmatory trials imposed by the EMA as specific obligations. Since their characteristics and provided evidence are generally not available in EPARs, we extracted these from the EMA's confidential assessment reports that were accessed through a Memorandum of Understanding with the Dutch Medicines Evaluation Board. To ensure assessment of evidence availability and demonstrated clinical benefit for the initially approved indication, we only included post-approval confirmatory trials that delivered evidence on clinical and surrogate endpoints of survival, ORR, QoL and/or toxicity and had been performed in the approved or a highly related treatment setting, e.g. combination rather than monotherapy.

Scoring of trial data using the ESMO-MCBS

For each trial, we applied the ESMO-MCBS v1.1 to assess the demonstrated clinical benefit. The ESMO-MCBS offers multiple forms to differentiate between trial designs, endpoints and magnitudes of effects. It allows a higher score for randomized controlled trials (RCT) and clinical endpoints as compared to single arm trials and surrogate endpoints, ranging from 5 to 1 (non-curative settings) or A to C (curative settings). Scores 4, 5, A, and B indicate substantial clinical benefit. We validated our assessments of clinical benefit against those published by the ESMO at www.esmo.org/guidelines/esmo-mcbs for solid cancer indications, and against a recent publication by the European Hematology Association (EHA) for hematological cancer indications.[13]

Data analysis

We used descriptive statistics to compare the availability of evidence at the initial approval of SMA and CMA indications with respect to e.g. pivotal trial design, endpoints, and number of patients studied. Furthermore, for converted CMA indications, we compared the availability of evidence at conversion to SMA, i.e. the evidence derived from post-approval confirmatory trials, to that at initial approval. Finally, we compared the availability of evidence at conversion for CMA indications to that at initial approval for SMA indications, i.e. the moments that the EMA considers that comprehensive evidence is available.

We considered one clinical benefit score at initial approval for each SMA and CMA indication, taking the highest in case of multiple pivotal trials. Similarly, for converted CMA indications, we considered the highest score available after conversion to SMA. To allow numerical comparisons between groups, we used clinical benefit score 5 for one indication that was categorized as 'A', since both reflect the highest clinical benefit score. We then compared the scores available after conversion of CMA indications to i) those at initial approval of CMA indications and ii) those at initial approval of SMA indications. First, we tested for differences in overall scores using the Mann-Whitney U test. Second, we compared the chance that substantial clinical benefit (score ≥4) was demonstrated by calculating risk ratios (RR) and 95% confidence intervals (CI). Additionally, we visualized the contribution of post-approval confirmatory trials to the clinical benefit of converted CMA indications through a Sankey diagram.

The analyses described above only consider clinical benefit scores for the converted CMA cancer indications, which may introduce bias by skewing the findings towards the successful CMA indications. To address this, we performed sensitivity analyses that consider the potential impact of unconverted CMA cancer indications, using two scenarios. In scenario 1, we added clinical benefit scores for three types of unconverted CMA indications for which CMA conversion could have been reasonably expected in a counterfactual situation: i) indications that had been unconverted longer than the median time to conversion of the converted CMA indications; ii) indications that were ultimately found to lack efficacy, leading to revocation of the CMA; and iii) indications for which no specific obligations had been required. We added their last known clinical benefit score, i.e. a zero for those that lacked efficacy and the clinical benefit score at initial approval for the other indications. In scenario 2, we added clinical benefit scores for all unconverted CMA indications, i.e. also for those that had been unconverted shorter than the median time to conversion of the converted CMA indications.

Results

Description of the cohort

In 2006-2020, 30 CMA cancer drugs had been approved. Of these, 15 had been converted to SMA (50%). Of the 15 converted CMA drugs, one had been approved with two indications: sunitinib (Sutent) for renal cell cancer and gastrointestinal stromal cancer. Subsequently, we identified similar SMA drugs for 14 converted CMA drugs; all except pixantrone (Pixuvri) which was therefore excluded. Of the SMA

drugs, also one drug had been approved for two indications: idelalisib (Zydelig) for chronic lymphocytic leukemia (CLL) and follicular lymphoma. Only neratinib (Nerlynx) was approved for use in a curative setting: adjuvant treatment of early-stage hormone receptor positive HER2-overexpressed breast cancer. An overview of the included SMA and converted CMA drugs and indications is provided in Tables S1 and S2. In addition, an overview of the 15 unconverted CMA drugs and their 17 indications (including two for brentuximab vedotin [Adcetris]: Hodgkin lymphoma and systemic anaplastic large cell lymphoma; and two for entrectinib [Rozlytrek]: non-small cell lung cancer [NSCLC] and a tumor agnostic indication) is provided in Table S3. The main characteristics of all 15 SMA and 32 CMA indications are presented in Table 1.

Table 1 Characteristics of included SMA and CMA cancer indications

	SMA indications *n*=15		**Converted[a] CMA indications** *n*=15		**Unconverted[a] CMA indications** *n*=17	
Pharmacotherapeutic group						
Monoclonal antibodies (ATC code L01XC)	5	33%	5	33%	6	35%
Protein kinase inhibitors (ATC code L01XE)	8	53%	7	47%	8	47%
Other antineoplastic agents (ATC code L01XX)	2	13%	3	20%	3	18%
Year of approval						
2004-2008	2	13%	4	27%	0	0%
2009-2013	3	20%	4	27%	4	24%
2014-2018	10	67%	7	47%	4	24%
2019-2020	0	0%	0	0%	9	53%
Indication at initial approval						
Solid tumors	10	67%	11	73%	10	59%
- Breast cancer	*1*	*7%*	*1*	*7%*	*0*	*0%*
- Basal cell cancer	*1*	*7%*	*1*	*7%*	*0*	*0%*
- Colorectal cancer	*1*	*7%*	*1*	*7%*	*0*	*0%*
- Cutaneous squamous cell cancer	*0*	*0%*	*0*	*0%*	*1*	*6%*
- Epithelial ovarian/fallopian tube/peritoneal cancer	*0*	*0%*	*0*	*0%*	*1*	*6%*
- Gastrointestinal stromal cancer	*0*	*0%*	*1*	*7%*	*1*	*6%*
- Melanoma	*1*	*7%*	*0*	*0%*	*0*	*0%*
- Merkel cell cancer	*0*	*0%*	*1*	*7%*	*0*	*0%*

Table 1 *Continued*

	SMA indications *n*=15		**Converted[a] CMA indications** *n*=15		**Unconverted[a] CMA indications** *n*=17	
- Non-small cell lung cancer	*4*	*27%*	*4*	*27%*	*2*	*12%*
- Renal cell cancer	*2*	*13%*	*2*	*13%*	*0*	*0%*
- Soft tissue sarcoma	*0*	*0%*	*0*	*0%*	*1*	*6%*
- Thyroid cancer	*0*	*0%*	*0*	*0%*	*2*	*12%*
- Tissue agnostic	*0*	*0%*	*0*	*0%*	*2*	*12%*
Hematological tumors	5	33%	4	27%	7	41%
- Leukemia	*0*	*0%*	*0*	*0%*	*1*	*6%*
- Lymphoma	*4*	*27%*	*3*	*20%*	*4*	*24%*
- Multiple myeloma	*1*	*7%*	*1*	*7%*	*2*	*12%*
Curative setting	1	7%	0	0%	0	0%
Monotherapy	10	67%	14	93%	14	82%
First-line/line-agnostic treatment	3	20%	4	27%	6	35%
Orphan designation at initial approval	4	27%	6	40%	11	65%
US FDA approval						
Accelerated approval	4	27%	11	73%	11	65%
Standard approval	10	67%	4	27%	6	35%
Not approved	1	7%	0	0%	0	0%
Time (median months, IQR)						
To conversion (*n*=15)	NA		32	17-48	NA	
Unconverted (*n*=16)	NA		NA		19	7-73
To revocation (*n*=1)	NA		NA		32	NA
Amended indication after conversion to SMA	NA		3	20%	NA	

ATC code, Anatomical Therapeutic Chemical code; CMA, conditional marketing authorization; IQR, interquartile range; NA, not applicable; SMA, standard marketing authorization; US FDA, United States Food and Drug Administration
[a] (Un)converted per 31 December 2020

Table 2 Characteristics of pivotal trials at initial approval and post-approval confirmatory trials at conversion, per indication

	SMA indications (initial approval) *n*=15		**Converted[a] CMA indications** (initial approval) *n*=15		**Converted[a] CMA indications** (conversion) *n*=14		**Unconverted[a] CMA indications** (initial approval) *n*=17	
Number of trials								
Median, range	1	1-3	1	1-2	1	1-3	1	1-1
Availability of at least a:								
Phase III trial	11	73%	4	27%	11	79%	3	18%
Controlled trial	11	73%	4	27%	11	79%	5	29%
Trial with OS as primary endpoint	4	27%	0	0%	2	14%	0	0%
Trial with PFS/TTP or DFS as primary endpoint	7	47%	4	27%	9	64%	4	24%
Trial with ORR as primary endpoint	4	27%	11	73%	3[b]	21%	13[c]	76%
Trial in which OS data were collected	15	100%	15	100%	14	100%	17	100%
Trial in which QoL data were collected	14	93%	7	47%	13	93%	10	59%
Total number of patients included in trials								
Median, IQR	356	278-1109	196	116-356	414	320-1053	97	74-139

CMA, conditional marketing authorization; DFS, disease-free survival; IQR, interquartile range; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SMA, standard marketing authorization; TTP, time to progression

[a] (Un)converted per 31 December 2020

[b] One formally defined as ORR with a duration of at least 6 months, i.e. durable response rate

[c] Two formally defined as major cytogenetic response rate and complete response rate, respectively

Availability of evidence and clinical benefit at initial approval (SMA and converted CMA indications)

For SMA and converted CMA indications, we identified 19 and 18 pivotal trials, respectively, i.e. one pivotal trial for 12 indications in each group (80%) and two or more for the other indications. Their characteristics are presented in Table 2. A detailed overview on trial level is provided in Table S4.

While in all pivotal trials OS data were collected, four SMA indications (27%) and no converted CMA indications were supported by a pivotal trial with OS as (co-)primary endpoint. For two of these SMA indications (13%), acute lymphatic leukemia (ALL) of inotuzumab ozogamicin (Besponsa) and renal cell cancer of sorafenib (Nexavar), a statistically significant increase in OS was demonstrated. For the other two SMA indications, NSCLC of gefitinib (Iressa) and melanoma of pembrolizumab (Keytruda), two pivotal trials had OS as primary endpoint. For gefitinib, these failed to show a difference in OS and demonstrated non-inferiority to treatment with docetaxel, respectively. For pembrolizumab, these had planned interim analyses of the co-primary endpoint PFS that mainly supported approval while OS data were not yet mature. When also considering OS as secondary endpoint, for two further SMA indications (13%) a statistically significant increase in OS was demonstrated. For the remaining nine SMA and all 15 converted CMA indications, the main evidence of efficacy was based on the primary endpoints DFS (one SMA, 7%), PFS or TTP (four SMA, 27%; four CMA, 27%), and ORR (four SMA, 27%; 11 CMA, 73%). Additionally, for 14 SMA indications (93%) and seven converted CMA indications (47%), QoL data were collected, which demonstrated a statistically significant increase for three (20%) and one (7%), respectively. Lastly, for one SMA indication (7%) – NSCLC of gefitinib –, there was evidence of significantly reduced grade 3 or 4 toxicities. These evidence aspects and the resulting demonstrated clinical benefit are presented in Table 3.

Availability of evidence and clinical benefit after conversion to SMA (converted CMA indications)

No specific obligations had been required by the EMA for the gastrointestinal stromal cancer indication of sunitinib since sufficient evidence was considered already available.[14] For the remaining 14 converted CMA indications, we identified 36 specific obligations. Of these, we excluded 18 specific obligations – mostly trials in non-approved treatment settings, of which 15 had been required for the metastatic colorectal carcinoma (CRC) indication of panitumumab (Vectibix). The remaining 18 specific obligations (Table S1) comprised 19 post-approval confirmatory trials (at

least one for each of the 14 converted CMA indications with specific obligations) that we included in our analyses.

For these 14 converted CMA indications, the characteristics of post-approval confirmatory trials are presented in Table 2 and Table S4. In 11 cases (79%), the evidence initially provided at their approval was supplemented post-approval by a controlled phase III confirmatory trial, of which nine had been ongoing at time of initial approval. For two indications (14%), OS was the primary endpoint, i.e. CRC of panitumumab and ALL of blinatumomab (Blincyto). These trials demonstrated non-inferiority to treatment with cetuximab and superiority to standard of care chemotherapy, respectively. For the remaining 12 converted CMA indications (86%), OS was a secondary endpoint, but no differences were demonstrated. Rather, the main evidence of efficacy was based on the primary endpoints PFS or TTP (nine indications, 64%), or ORR (three indications, 21%). For these latter three indications, Merkel cell cancer of avelumab (Bavencio), CLL of venetoclax (Venclyxto) and basal cell cancer of vismodegib (Erivedge), all pivotal and post-approval confirmatory trials were single arm phase II trials. Additionally, for 13 converted CMA indications (93%), QoL data were collected in their post-approval confirmatory trial, which demonstrated a statistically significant increase for five (36%). Also, for three converted CMA indications (21%), there was evidence of significantly reduced grade 3 or 4 toxicities. In total, the post-approval confirmatory trials included more than twice as many patients as included in the pivotal trials for converted CMA indications: median 414 versus 196 patients.

For all but one converted CMA indication, the clinical benefit demonstrated by post-approval confirmatory trials was equal to or higher than that demonstrated by the pivotal trials (Figure 1). The only exception was the CRC indication of panitumumab for which the ASPECCT trial demonstrated non-inferiority in the absence of QoL or toxicity benefits and therefore a lack of clinical benefit as compared to treatment with cetuximab.[15] We thus retained the score for panitumumab at initial approval since this was the highest. At conversion to SMA, the demonstrated clinical benefit (Table 3) was higher than at initial CMA approval (p=0.0074). Moreover, the chance to be associated with substantial clinical benefit increased from 7% to 47%; RR 7.0 (95% CI 1.0-50). After completion of the post-approval confirmatory trials for CMA indications and their subsequent conversion to SMA, their median clinical benefit scores were similar to those of SMA indications at initial approval (p=0.31). Similarly, we identified no difference in their chance to be associated with substantial clinical benefit, although it was numerically higher for converted CMA indications than for SMA indications: 47% versus 33%; RR 1.4 (95% CI 0.57-3.4; Table 4).

Table 3 Clinical benefit qualifications and underlying evidence aspects

Clinical benefit (score)	Trial design	Endpoint scored	Preliminary score[a]	Increased toxicity	Reduced toxicity[b]	Improved QoL	SMA indications (initial approval) *n*=15	Converted[c] CMA indications (initial approval) *n*=15	Converted[c] CMA indications (conversion[d]) *n*=15	Unconverted[c] CMA indications (initial approval) *n*=17
Substantial							**5 (33%)**	**1 (7%)**	**7 (47%)**	**1 (6%)**
5/A	controlled	OS	4/4		+1	+1			1	
	controlled	DFS	A				1			
4	controlled	OS	4/4				1			1
	controlled	PFS/TTP	3/3			+1	2		4	
	controlled	PFS/TTP	3/3		+1				1	
	controlled, non-inferiority	OS	4/4		x[e]	x[e]	1			
	controlled, non-inferiority	PFS/TTP	4/4		x[e]				1	
	single arm	ORR	3/3			+1		1		
Moderate							**6 (40%)**	**8 (53%)**	**7 (47%)**	**12 (71%)**
3	controlled	OS	3/4				1			
	controlled	PFS/TTP	3/3				3	3	4	2
	single arm	ORR	3/3				2	5	3	10
Low							**4 (27%)**	**6 (40%)**	**1 (7%)**	**4 (24%)**
2	controlled	OS	2/4				1			
	controlled	PFS	3/3	-1						1
	controlled	CRR	2/2							1
	single arm	ORR	3/3	-1						2
	single arm	ORR	2/3				1	5		

Table 3 *Continued*

Clinical benefit (score)	Trial design	Endpoint scored	Preliminary score[a]	Increased toxicity	Reduced toxicity[b]	Improved QoL	SMA indications (initial approval) *n*=15	Converted[c] CMA indications (initial approval) *n*=15	Converted[c] CMA indications (conversion[d]) *n*=15	Unconverted[c] CMA indications (initial approval) *n*=17
1	controlled	PFS/TTP	1/4					1	1	
	controlled	OS	1/4				1			
	single arm	ORR	1/3				1			
Distribution of clinical benefit scores (median [IQR])							3.0 (2.5-4.0)	3.0 (2.0-3.0)	3.0 (3.0-4.0)	3.0 (3.0-3.0)

CMA, conditional marketing authorization; CRR, complete response rate; DFS, disease-free survival; IQR, interquartile range; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SMA, standard marketing authorization; TTP, time to progression

[a] The ESMO-MCBS preliminary clinical benefit score that is reflected by the available evidence on the scored endpoint. This score may be adjusted in case of increased toxicity, reduced toxicity and/or improved QoL.

[b] Grade 3/4, impacting daily well-being

[c] (Un)converted per 31 December 2020

[d] Including the gastrointestinal stromal cancer indication of sunitinib

[e] Preliminary score includes improved QoL and/or reduced toxicity: this indicates the clinical benefit in the context of the non-inferior efficacy outcome.

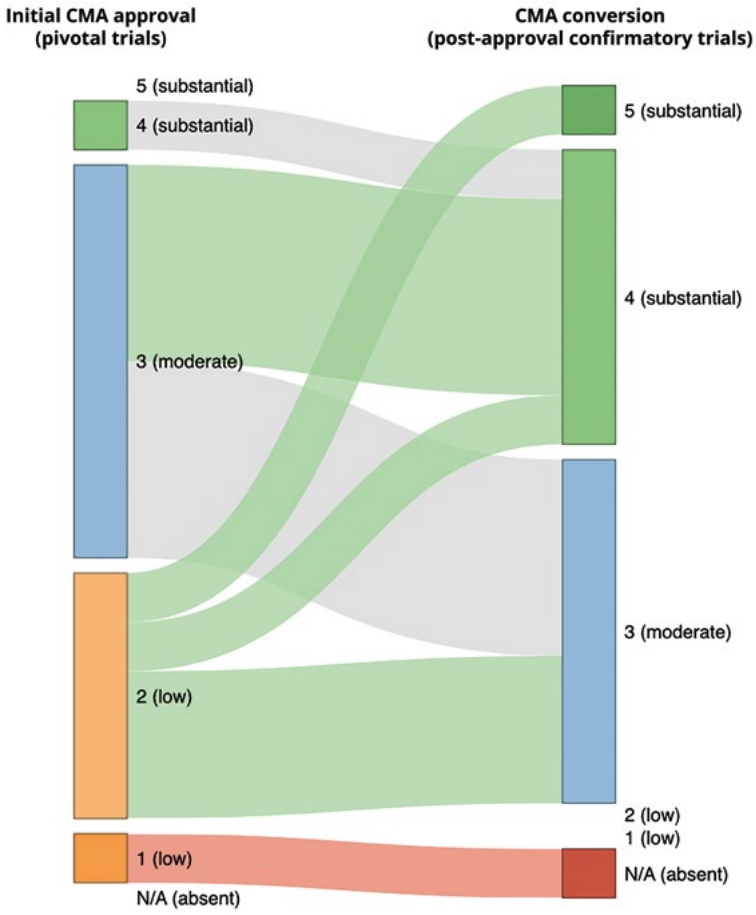

Figure 1 Contribution of post-approval confirmatory trials to the demonstrated clinical benefit of converted CMA cancer indications, reflected by change in ESMO-MCBS score

Colors of the connections between the time points indicate whether clinical benefit increased (green), remained the same (grey), or decreased (red). ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale

Sensitivity analyses: inclusion of unconverted CMA indications

The characteristics of the pivotal trials that supported the initial approval of unconverted and converted CMA indications were similar, with the exception that fewer patients were included in the pivotal trials of unconverted CMA indications (Table 2 and Table S4). This was also reflected by differences in orphan designations (Table 1). In addition, the clinical benefit scores of the two groups of CMA indications were also similar at initial approval: 3.0 (IQR 3.0-3.0) versus 3.0 (IQR 2.0-3.0) for

unconverted and converted CMA indications, respectively. Six versus seven percent of indications were associated with substantial clinical benefit (Table 3).

After initial approval, one unconverted CMA indication was found to lack efficacy and subsequently revoked by the European Commission: the soft tissue sarcoma indication of olaratumab (Lartruvo).[16, 17] In addition, for one indication, no specific obligations had been required – the NSCLC indication of entrectinib – and six indications remained unconverted longer than the median time to conversion of the converted CMA indications (32 months) – those of bosutinib (Bosulif; 93 months), brentuximab vedotin (n=2; 98 months), cabozantinib (Cometriq; 81 months), ixazomib (Ninlaro; 49 months) and vandetanib (Caprelsa; 106 months). When including these eight indications in the analyses, the median clinical benefit scores of CMA indications remained similar to those of SMA indications, but the point estimate of the association with substantial clinical benefit decreased (RR 0.91, 95% CI 0.35-2.3; Table 4, scenario 1). When including all 17 unconverted CMA indications in the analyses, the point estimate decreased further (RR 0.66, 95% CI 0.25-1.7; Table 4, scenario 2).

Table 4 Sensitivity analyses including unconverted CMA cancer indications

	Median clinical benefit score (IQR)	**p-value**	**Substantial clinical benefit (N)**	**Risk ratio (95% CI)**
SMA indications	3.0 (2.5-4.0)	Ref.	5/15 (33%)	Ref.
Original analysis Converted CMA indications	3.0 (3.0-4.0)	0.31	7/15 (47%)	1.4 (0.57-3.4)
Scenario 1 (+ 8 unconverted CMA indications)	3.0 (3.0-4.0)	0.79	7/23 (30%)	0.91 (0.35-2.3)
Scenario 2 (+ 17 unconverted CMA indications)	3.0 (3.0-3.0)	0.87	7/32 (22%)	0.66 (0.25-1.7)

CI, confidence interval; IQR, interquartile range

Discussion

We aimed to compare the availability of evidence and clinical benefit for CMA versus SMA cancer indications in Europe, taking into account the contribution of post-approval confirmatory trials. Our results indicate that after conversion of CMA cancer indications to SMA, the availability of evidence and the demonstrated clinical benefit is similar to that at initial approval of SMA cancer indications. This was mainly due to the CMA post-approval confirmatory trials, that increased the available evidence and improved the demonstrated clinical benefit as compared to the CMA pivotal trials. The results of sensitivity analyses that included unconverted CMA cancer indications supported these observations.

CMA approval was often supported by single arm trials with ORR as primary endpoint. Consistent with the EMA's CMA guideline,[5] this is indeed less 'comprehensive' evidence than the controlled trials with OS or a surrogate survival endpoint that mostly supported SMA approval. Similarly, around 80% of cancer indications granted AA by the FDA are supported by single arm trials and ORR data.[18] However, it should be noted that for our cohort of indications the types of EMA and FDA approval did not perfectly match.

For most converted CMA indications a post-approval confirmatory trial with similar characteristics was conducted. This suggests that 'comprehensive evidence' is similarly defined for approval of SMA indications and conversion of CMA indications. Nonetheless, still only few cancer indications were supported by statistically significant increases in OS and QoL, as reported before for both Europe[8, 19] and the US.[9, 10, 19] These are important findings that highlight that regulators' definitions of comprehensive evidence are not necessarily in line with physicians',[6] nor patients'[20] perceptions of clinically relevant evidence.

After conversion of CMA indications, there was no difference in demonstrated clinical benefit as compared to SMA indications, although the chance to provide substantial clinical benefit was numerically higher (47% versus 33%). In the sensitivity analyses that included unconverted CMA indications, this increase disappeared (30% versus 33% in scenario 1 that also included all CMA indications for which conversion could be expected and 22% versus 33% in scenario 2 that also included all unconverted CMA indications). Scenario 2 was the most conservative in assuming that none of the 17 unconverted CMA indications would ultimately demonstrate a clinical benefit higher than at their initial approval. This seems unlikely given that nine of the 15

converted CMA indications did demonstrate a higher clinical benefit. Scenario 1 – for which an unchanged clinical benefit compared to approval was only assumed for seven indications, including the six indications that remained unconverted longer than 32 months – provides a more likely estimate. Both scenarios considered that the soft tissue sarcoma indication of olaratumab was not associated with any clinical benefit (see also below).

Our findings demonstrate that the context of unmet medical need that is addressed by CMA indications appeared not necessarily associated with a high clinical benefit. Reasons may be that the concept unmet medical need is not necessarily defined taking clinical benefit into account,[21] or treatment effects proved smaller than expected. The latter occurred very recently when avelumab was converted to SMA although durable response rate, ORR and PFS decreased substantially as compared to initial approval.[22] This was deemed acceptable since no other approved drug treatments existed. Therefore, in contexts of unmet medical need, it seems that the existence of a positive treatment effect is ultimately considered more important than its actual size.

Our observation that substantial clinical benefit is demonstrated for one-third to half of the CMA cancer indications raises the question whether expedited pathways are of added value: is the glass half full or half empty? On the one hand, expedited pathways likely shortened pre-approval clinical development and thereby time to approval,[18, 23] probably due to reliance on uncontrolled pivotal trials with ORR as primary endpoint.[18, 24] Estimates of the degree of shortening range from around two years in Europe[23] to three and a half years in the US,[18] often leading to approvals in the US first.[25] On the other hand, post-approval evidence generation has been considered insufficient, in both Europe and the US, because of confirmatory trials that are uncontrolled and/or include surrogate endpoints,[4, 9, 10, 26] leaving patients exposed to uncertainties and risks. In addition, cancer indications approved through FDA's AA pathway have been suggested to be at increased risk for post-approval safety-related label changes.[27] However, studies investigating the EMA's CMA pathway did not report similar findings,[23] potentially because oncology dossiers are submitted later to the EMA than the FDA to include additional or more mature evidence.[28]

To adequately address uncertainties and identify risks while allowing timely approval of new cancer indications, comprehensive evidence should come available shortly after approval, preferably from RCTs.[24, 29] To prevent that feasibility issues lead to significantly delayed, downgraded or terminated RCTs, a suggested best-practice is that they should be initiated pre-approval and recruitment should be

well underway.[3, 4, 9, 30] Notably, EMA and FDA expedited approvals for olaratumab for treatment of soft tissue sarcoma were recently withdrawn because the post-approval ANNOUNCE trial could not confirm benefits suggested by the pivotal phase II trial.[16, 17] Since recruitment for this RCT was almost completed at initial approval, it could unambiguously inform further regulatory decision-making relatively shortly after. The olaratumab case concerned the first ever withdrawal of a CMA for such reason and few other withdrawals of AAs for cancer indications are known.[24] However, we recognize that with increasing approvals of drugs based on early phase evidence, unambiguous results from RCTs might not always be available. In these cases, it is imperative that when addressing uncertainties, regulators explicitly draw on available knowledge concerning benefit-risk of e.g. comparable drugs – in the same drug class or with a comparable mechanism – or in comparable patient populations. Moreover, performing an RCT may not always be feasible, especially in the context of (ultra)orphan disease.[31] Perhaps here, the principles underlying the ESMO-MCBS for single arm trials should be followed, restricting approval to situations where effect estimates are large enough to suggest at least a moderate clinical benefit.

Our study has several strengths. It was the first to comprehensively assess the availability of evidence for a cohort of cancer indications that had received expedited versus non-expedited approval and that were broadly similar, allowing control for disease characteristics that may affect evidence generation. Also, it was the first to apply ESMO-MCBS v1.1 to dynamically assess the clinical benefit of a cohort of cancer indications, including those approved on the basis of single-arm trials, and both at initial approval and after completion of post-approval confirmatory trials for expedited approvals. This approach may be beneficial for future studies that address other questions regarding evidence generation for cancer drugs. Finally, since we based our assessments of clinical benefit on trial results available in regulatory documents – including the EMA's confidential assessment reports –, we were able to determine the impact of regulatory decision-making on clinical benefit. Notably, although different data cut-offs and reporting standards between regulatory and scientific data sources may have influenced the availability of trial results that we based our analyses of clinical benefit on, the validation of our assessments of clinical benefit against the scores published by ESMO and EHA showed that 33 of the 35 available scores corresponded (94%). Reasons for divergent scores were our use of: i) data from predefined analyses[32] rather than retrospective biomarker subgroup analyses published years after initial approval[33] (trial 20020408 for the CRC indication of panitumumab), and ii) EPAR data with an early data cut-off[34] rather

than main trial results that included long-term follow-up data[35] (ELOQUENT-2 trial for the multiple myeloma indication of elotuzumab [Empliciti]).

Our study also has limitations. First, we had to make assumptions about the ultimately demonstrated clinical benefit of yet unconverted CMA cancer indications. However, the results of the sensitivity analysis based on these assumptions supported our main findings. Second, we applied the ESMO-MCBS to solid and hematological cancer indications. However, although the ESMO-MCBS has not yet been validated for hematological cancer indications, a recent feasibility study indicated that it was widely applicable to the vast majority of evaluated hematological trials and corresponded with the opinion of clinical experts.[13] Third, we selected the SMA indications based on their similarity to the converted CMA indications. We recognize that it is – by definition – impossible to obtain two perfectly alike groups. For example, we included a Merkel cell cancer CMA indication and a melanoma SMA indication. However, these were the most similar indications when also taking into account characteristics such as orphan designation, pharmacotherapeutic group and moment of approval in the ever-evolving regulatory and medical landscapes. Fourth, we studied a small cohort of cancer indications of which the majority concerned NSCLC and hematological cancers. While we included all CMA cancer indications that have been approved to date and formal statistical significance testing is thus not necessary when studying their clinical benefit, our findings may not be generalizable to future CMA cancer indications – especially when these comprise different cancer types.

In conclusion, we found that after conversion of CMA cancer indications to SMA, both the availability of evidence and the demonstrated clinical benefit are similar to that at initial approval of SMA cancer indications. This suggests that the definition of the regulatory concept 'comprehensive evidence' is similar for cancer indications that received standard and expedited approval. To ensure swift availability of comprehensive evidence, we stress that expedited approvals should preferably be granted only if well-designed confirmatory RCTs are ongoing.

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Supplementary material

Table S1 CMA drugs that were converted per 31 December 2020, their initially approved indications and specific obligations for post-approval confirmatory trials

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
alectinib (Alecensa)	Alecensa as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. Specific obligation: *In order to further confirm the efficacy and safety of alectinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study ALEX comparing alectinib versus crizotinib in treatment naïve patients with ALK-positive NSCLC.*
avelumab (Bavencio)	Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC). Specific obligation: *In order to confirm the efficacy for chemotherapy-naïve treated patients, the MAH should submit the final results of study EMR 100070-003 - Part B.*
blinatumomab (Blincyto)	Blincyto is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). Specific obligation: *Post-authorisation efficacy study (PAES): Study 00103311 (TOWER): A Study of BITE antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia (ALL).*
ceritinib (Zykadia)	Zykadia is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. Specific obligations: *1. In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase III efficacy study A2303 comparing ceritinib to chemotherapy.* *2. In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase II single-arm efficacy study A2201.*

Table S1 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
crizotinib (Xalkori)	Xalkori is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). Specific obligations: *1. The MAH should submit the CSR of study A8081007, expected in Q1 2013. The CSR should also include a detailed analysis of outcome on post-progression treatments in Study 1007 as well as efficacy and baseline data according to race (Caucasian/Asian) by treatment groups.* Subsequentially amended to: *The MAH is requested to update OS status of study A8081007 and provide the final data within 9 months after the required 238 OS events have been reached. The CSR should also include a detailed safety analysis.* *2. The MAH should submit updated safety (SAEs and deaths) and efficacy (PFS, OS) data for both studies 1001 and 1005. The MAH should compare and explain potential differences in OS for crizotinib in the 3 studies (1001, 1005 and 1007).*
daratumumab (Darzalex)	Darzalex as monotherapy is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. Specific obligations: *1. In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of DARZALEX, the MAH should submit the results of study MMY3003, a phase III randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.* *2. In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of DARZALEX, the MAH should submit the results of study MMY3004, a phase III randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.*
lapatinib (Tyverb)	Tyverb, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting (see section 5.1). Specific obligation: *To perform and submit an updated analysis of survival data for study EGF100151. A data cut-off date of August 2008 will be applied, with the results of the analysis to be submitted by December 2008.*

Table S1 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
ofatumumab (Arzerra)[i]	Arzerra is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab. Specific obligation: *To conduct an open label, multicenter study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine refractory chronic lymphocytic leukaemia (CLL). The final protocol will be submitted for CHMP agreement within 3 months of conditional marketing authorisation date. The study report is to be submitted by December 2014, but the timing will be confirmed at the time of submission of the final protocol, when feasibility will be complete.*
osimertinib (Tagrisso)	Tagrisso is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC). Specific obligation: *In order to further confirm the efficacy and safety of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC, the applicant should submit the clinical study report of the phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy.*
panitumumab (Vectibix)	Vectibix is indicated as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Specific obligation: *To complete a confirmatory trial examining panitumumab monotherapy in licensed indication. In particular to* *- Provide a study protocol outline for this study by February 2009* *- Based on Rapporteur feedback on the outline to provide a final protocol to CHMP in April 2009 to allow agreement of the final protocol with CHMP* *- Commit to start the study as soon as is possible* *- Agree a timeline for provision of data from the study once the design has been agreed* *Subsequentially amended to: - In particular to provide the clinical study report of the primary data analysis from the 20080763 study*

[i] The marketing authorization for Arzerra was withdrawn by the company during this study. See https://www.ema.europa.eu/en/documents/public-statement/public-statement-arzerra-withdrawal-marketing-authorisation-european-union_en.pdf.

Table S1 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
pazopanib (Votrient)	Votrient is indicated for the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease. Specific obligations: *1. Submit the study report for VEG108844 (a study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/or metastatic renal cell carcinoma) by February 2012.* *2. Submit a pooled analysis of data from study VEG108844 and VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma - a sub study of VEG108844). The studies should be appropriately powered to demonstrate non-inferiority with a margin of 1.22. A discussion on the applicability of the efficacy data from VEG113078 to the European population should be provided by June 2012.*
sunitinib 1 (Sutent)	Sutent is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. Efficacy is based on time to tumour progression and an increase in survival in GIST. (see section 5.1). *No specific obligations*
sunitinib 2 (Sutent)	Sutent is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy. Efficacy is based on objective response rates for MRCC. (see section 5.1). Specific obligation: *The Marketing Authorisation Holder commits to provide results of an ongoing study in cytokine-naive patients with metastatic renal cell carcinoma by September 2006.*
venetoclax (Venclyxto)	Venclyxto monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor. Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor. Specific obligation: *In order to further confirm the efficacy and safety of venetoclax, the MAH should submit the clinical study report of study M14-032 investigating venetoclax in patients with chronic lymphocytic leukaemia relapsed after or refractory to treatment with B-cell receptor signalling pathway inhibitors.*

Table S1 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
vismodegib (Erivedge)	Erivedge is indicated for the treatment of adult patients with: • symptomatic metastatic basal cell carcinoma • locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy (see section 5.1). Specific obligation: *The applicant should provide a safety update of the pooled safety population, a final SHH4476g (pivotal study) and an interims analysis of study MO25616 of 500 patients with a potential one year follow up.* Subsequentially amended to: *The applicant should provide further data on safety and data on efficacy in patients with symptomatic metastatic BCC from the final analysis of MO25616.*

CMA, conditional marketing authorization

Table S2 Included SMA drugs and their initially approved indication

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
afatinib (Giotrif)	Giotrif as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s) (see section 5.1).
brigatinib (Alunbrig)	Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.
cetuximab (Erbitux)	Erbitux in combination with irinotecan is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.
elotuzumab (Empliciti)	Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy (see sections 4.2 and 5.1).
everolimus (Afinitor)	Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.
gefitinib (Iressa)	Iressa is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (see section 5.1).

Table S2 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
idelalisib 1 (Zydelig)	Zydelig is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.
idelalisib 2 (Zydelig)	Zydelig is indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.
inotuzumab ozogamicin (Besponsa)	Besponsa is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).
neratinib (Nerlynx)	Nerlynx is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy.
nintedanib (Vargatef)	Vargatef is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.
obinutuzumab (Gazyvaro)	Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy (see section 5.1).
pembrolizumab (Keytruda)	Keytruda as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
sonidegib (Odomzo)	Odomzo is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.
sorafenib (Nexavar)	Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

SMA, standard marketing authorization

Table S3 CMA drugs that were unconverted per 31 December 2020, their initially approved indications and specific obligations for post-approval confirmatory trials

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
autologous anti-CD19-transduced CD3+ cells (Tecartus)	Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor. Specific obligations: *1. In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.* *2. In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2.*
avapritinib (Ayvakyt)	Ayvakyt is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation. Specific obligations: *1. In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of study BLU-285-1303 (efficacy data of the PDGFRA D842V-mutant population and safety data from the overall safety population), an ongoing open-label, randomized, Phase 3 study of avapritinib vs regorafenib in patients with locally advanced unresectable or metastatic GIST.* *2. In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of study BLU-285-1101, an ongoing single-arm, open-label multiple-cohort Phase 1 study in patients with GIST and other relapsed and refractory solid tumours.* *3. In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of an observational safety and efficacy study in patients with unresectable or metastatic PDGFRA D842V- mutant GIST.*

Table S3 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
belantamab mafodotin (Blenrep)	Blenrep is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. Specific obligations: *1. In order to confirm the efficacy and safety of Blenrep in relapsed/ refractory multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-2 (205678) study investigating the efficacy of belantamab mafodotin in patients with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody.* *2. In order to confirm the efficacy and safety of Blenrep in multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-3 (207495) study comparing the efficacy of belantamab mafodotin vs. pomalidomide plus low dose dexamethasone (pom/dex) in patients with relapsed/refractory multiple myeloma.*
bosutinib (Bosulif)	Bosulif is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. Specific obligation: *To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.*

Table S3 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
brentuximab vedotin 1 (Adcetris)	Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): 1. following autologous stem cell transplant (ASCT) or 2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. Specific obligations: *1. Further Overall Survival follow up of the patients included in study SG035-0003 and in study SG035-004 should be provided, including sub-analysis of patients ≥ 100 kg. The data should be presented in the context of historical controls.* *2. A Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500) should be performed including a sufficient number of sALCL patients (i.e. at least n=50, Study MA25101).* *3. To perform a single-arm studying r/r HL population not eligible for ASCT investigating response rate, PFS, OS, proportion of patients proceeding to transplant and safety (n=approx 60 pts) based on a CHMP agreed protocol.*
brentuximab vedotin 2 (Adcetris)	Adcetris is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL). Specific obligations: *1. See above* *2. See above* *3. To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP agreed protocol (Study C25006).*
cabozantinib (Cometriq)	Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma. For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1). Specific obligation: *A dose-comparison study (XL-184-401) (140 mg vs 60 mg) in 112 patients with hereditary or sporadic medullary thyroid cancer.*[ii]

[ii] Extensive description available at https://ec.europa.eu/health/documents/community-register/2014/20140321127850/anx_127850_en.pdf.

Table S3 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
cemiplimab (Libtayo)	Libtayo as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation. Specific obligations: *1. In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should provide interim data of a single-arm trial in the same population [study 1540 group 6]. The MAH should investigate biomarkers in order to confirm that PD-L1 expression is not predictive of efficacy. The study should be conducted according to an agreed protocol.* *2. In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should submit the final study report for Groups 1-3 in the phase 2 pivotal study 1540.*
entrectinib 1 (Rozlytrek)	Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, • who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and • who have not received a prior NTRK inhibitor • who have no satisfactory treatment options (see sections 4.4 and 5.1). Specific obligations: *1. In order to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of NTRK fusion-positive patients from the ongoing studies STARTRK-2, STARTRK-NG and any additional clinical trial conducted according to an agreed protocol. The MAH should submit the results of an interim safety and efficacy analysis of the NTRK efficacy-evaluable adult and paediatric patients including adolescents that are available as per integrated statistical analysis plan.* *2. In order to further investigate the impact of the presence/absence of other molecular alteration on the efficacy of entrectinib, the MAH should submit the results from tumour genomic profiling by plasma and/or tissue when possible at baseline and progression together with clinical outcomes association per tumour histology for the patients from the updated pooled analysis.*
entrectinib 2 (Rozlytrek)	Rozlytrek as monotherapy is indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors. *No specific obligations*

Table S3 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
ixazomib (Ninlaro)	Ninlaro in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Specific obligations: *1. C16010 China Continuation Study: In order to further investigate the efficacy the MAH should conduct a phase 3, randomized, double-blind, multicenter study comparing ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide in patients with relapsed and/or refractory multiple myeloma and provide the final report containing the final OS analysis results.* *2. C16014: In order to further investigate the efficacy the MAH should conduct a phase 3, randomized, double-blind, multicenter study comparing ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma not eligible for stem cell transplantation (SCT) and provide the final report for primary endpoint PFS.* *3. C16019: In order to further investigate the efficacy the MAH should conduct a phase 3, randomized, placebo-controlled, double-blind study ixazomib in maintenance therapy in patients with multiple myeloma following SCT and provide the final report for primary endpoint PFS.* *4. NSMM-5001: The MAH should conduct a global, prospective, non-interventional, observational study in multiple myeloma patients and provide a report of descriptive data on 1000 patients including 200 RRMM patients treated with ixazomib.*
larotrectinib (Vitrakvi)	VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, • who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and • who have no satisfactory treatment options (see sections 4.4 and 5.1). Specific obligations: *1. In order to further confirm the histology-independent efficacy of larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE).* *2. In order to further investigate the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, the MAH should submit the final report of study LOXO-TRK-15003 (SCOUT) including 5 year follow up data.*

Table S3 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
	3. In order to further confirm the appropriate dose recommended in paediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT).
lorlatinib (Lorviqua)	Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after: • alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or • crizotinib and at least one other ALK TKI. Specific obligations: *1. In order to further confirm the efficacy and safety of lorlatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study CROWN (1006) comparing lorlatinib versus crizotinib for the first-line treatment of advanced ALK-positive NSCLC.* *2. In order to further confirm the efficacy of lorlatinib in patients who progressed after alectinib or ceritinib as the first ALK TKI therapy, the MAH should conduct a prospective single arm study investigating patients in that same setting.*
olaratumab (Lartruvo)[iii]	Lartruvo is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin (see section 5.1). Specific obligations: *1. In order to further confirm the efficacy and safety of olaratumab in the treatment of patients with advanced soft tissue sarcoma, the MAH should submit the clinical study report of the phase III study JGDJ comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic STS (including exploratory biomarker data).* *2. In addition, the MAH will submit the second interim safety analysis of the phase III study JGDJ.*
polatuzumab vedotin (Polivy)	Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

[iii] The marketing authorization for Lartruvo was revoked by the European Commission. See https://www.ema.europa.eu/en/documents/referral/lartruvo-article-20-referral-chmp-assessment-report_en.pdf .

Table S3 *Continued*

Active substance (brand name)	Indication and specific obligations for post-approval confirmatory trials
	Specific obligations: *1. In order to further confirm the safety and efficacy of polatuzumab vedotin in combination with BR the MAH will provide the primary CSR for study GO29365 including the primary analysis of Arm H (n=64) as well as a pooled analysis of Arm G (n=42) and Arm H (n=64).* *2. In order to provide further evidence of efficacy and safety of polatuzumab vedotin in DLBCL, the MAH will provide Study GO39942, a randomized, double-blind, placebo controlled trial that evaluates polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma.*
rucaparib (Rubraca)	Rubraca is indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy. Specific obligation: *In order to further confirm the safety and efficacy of rucaparib in the treatment of platinum sensitive, relapsed or progressive, BRCA mutated (germline and/ or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, the MAH should submit the results of study CO-338-043 (ARIEL4), a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer.*
vandetanib (Caprelsa)	Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1). Specific obligation: *An open label trial based on a CHMP approved protocol, comparing RET negative and RET positive patients with sporadic medullary thyroid cancer treated with vandetanib. The study will include approximately 60 % of patients who receive vandetanib within the EU.*[iv]

CMA, conditional marketing authorization

[iv] Extensive description available at https://ec.europa.eu/health/documents/community-register/2012/20120217116029/anx_116029_en.pdf.

Table S4 Characteristics of pivotal trials at initial approval and post-approval confirmatory trials at conversion

	SMA pivotal trials (initial approval) *n*=19		**Converted[a] CMA pivotal trials** (initial approval) *n*=18		**Converted[a] CMA post-approval confirmatory trials** (conversion) *n*=19		**Unconverted[a] CMA pivotal trials** (initial approval) *n*=21[b]	
Drug regimen under study								
Monotherapy	12	63%	17	94%	16	84%	18	86%
Combination therapy	7	37%	1	6%	3	16%	3	14%
Trial phase								
I	0	0%	1	6%	0	0%	4	19%
I/II	0	0%	4	22%	1	5%	6	29%
II	6	32%	9	50%	6	32%	8	38%
III	13	68%	4	22%	12	63%	3	14%
Trial design								
Placebo-controlled	6	32%	2	11%	0	0%	3	14%
Active-controlled	9	47%	1	6%	12	63%	0	0%
Add-on	0	0%	0	0%	0	0%	2	10%
Add-on to best supportive care	0	0%	1	6%	0	0%	0	0%
Uncontrolled	4	21%	14	78%	7	37%	16	76%
Study hypothesis								
Superiority	13	68%	4	22%	10	53%	5	24%
Non-inferiority	2	11%	0	0%	2	11%	0	0%
Not applicable (no control arm)	4	21%	14	78%	7	37%	16	76%
Primary endpoint								
OS	6[c,d]	32%	0	0%	2	11%	0	0%
PFS/TTP/DFS	11[c,e]	58%	4	22%	10	53%	5[e]	24%
ORR	5[e]	26%	14	78%	5	26%	14[e,f]	67%
Other endpoint	1[d]	5%	0	0%	2	11%	3	14%
OS data collection								
Primary objective	6	32%	0	0%	2	11%	0	0%
Secondary objective	13	68%	18	100%	17	90%	14	67%
Tertiary/exploratory objective	0	0%	0	0%	0	0%	5	24%

Table S4 *Continued*

	SMA pivotal trials (initial approval) *n*=19		**Converted[a] CMA pivotal trials** (initial approval) *n*=18		**Converted[a] CMA post-approval confirmatory trials** (conversion) *n*=19		**Unconverted[a] CMA pivotal trials** (initial approval) *n*=21[b]	
No OS data collected	0	0%	0	0%	0	0%	2	10%
QoL data collection								
Secondary objective	13	68%	4	22%	14	74%	6	29%
Tertiary/exploratory objective	4	21%	4	22%	1	5%	4	19%
No QoL data collected	2	11%	10	56%	4	21%	11	52%
Number of patients included								
Median, IQR	410	278-1060	146	106-237	405	147-660	97	74-139[b]
If post-approval confirmatory trial:								
Ongoing trial at initial approval								
Pivotal trial at initial approval	N/A		N/A		3	16%	N/A	
Supportive trial at initial approval	N/A		N/A		4	21%	N/A	
Other ongoing trial	N/A		N/A		10	53%	N/A	
Newly initiated trial	N/A		N/A		2	11%	N/A	
Time to completion (months)								
Median, IQR	N/A		N/A		23	17-35	N/A	
Supported amended indication								
Yes	N/A		N/A		5	26%	N/A	
No	N/A		N/A		14	74%	N/A	

CMA, conditional marketing authorization; DFS, disease-free survival; IQR, interquartile range; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SMA, standard marketing authorization; TTP, time to progression

[a] (Un)converted per 31 December 2020

[b] For four CMA indications, the results of multiple pivotal trials had been pooled. The number of patients includes the sample size of these pooled analyses, while the other characteristics are described separately for each trial.

[c] Two SMA pivotal trials had OS and PFS as co-primary endpoints

[d] One SMA pivotal trial had OS and hematological remission as co-primary endpoints

[e] One SMA and one CMA pivotal trial had PFS and ORR as co-primary endpoints

[f] One CMA pivotal trial had major cytogenetic response rate as primary endpoint, and another had complete response rate as primary endpoint

Chapter 4

General discussion

Beter worden
Is niet alleen maar
vrij van kwalen zijn

Het is de weg vooruit zien
Door wat we weten te vertalen
Zodat we breder kunnen dragen
Een plan voor meer dan slechts begrip

Wie de weg van morgen
wil begaan
Kan niet alleen zichzelf verheffen
Er ligt nog zo veel voor ons open
Met ieders oog
daarop gericht

– Stucwerk Dichtkunst

The contemporary medicine regulatory system of the European Union (EU) has slowly evolved to its current size and complexity. It is built on the premise that public health can best be protected and promoted when a marketing authorisation (MA) should be obtained before a medicine can be marketed. The granting of such MA should be based on evidence of sufficient quality, safety and efficacy of a medicine that is assessed integratively during benefit-risk assessment. However, the resulting knowledge about benefits, risks and the balance between them is incomplete and always subject to uncertainty. In addition, the use of medicines in clinical practice is ever-evolving due to for example extensions of indications, restrictions following safety issues, off-label use and variation in uptake in national healthcare systems. This recently led to recognition of the need for continued learning and regulatory decision-making about the benefit-risk balance of any medicine in the post-authorisation phase, to strengthen the initial evidence. In addition, flexibility in the timing of evidence generation was introduced. In therapeutic areas with an unmet medical need, it was considered justified to require less comprehensive evidence for initial MA provided that it is supplemented post-authorisation. These two developments were discussed in the general introduction of this thesis (Chapter 1) as the latest developments in the evolution of the European regulatory system. Together, they gave rise to the generation of evidence throughout the medicine lifecycle and led to various new regulatory instruments and procedures to achieve this, including the risk management plan (RMP), the combined assessment of periodic safety update reports (PSUR) for similar medicines, the conditional marketing authorisation (CMA) pathway, specific obligations for post-authorisation studies and other evidence, and one-year validity of MA with the potential for annual renewal.

Drug regulatory science is a scientific field that among others evaluates the regulatory system and its specificities, especially evidence generation and subsequent decision-making. In this field, the two recent regulatory developments discussed above are important to evaluate in terms of how the generated evidence affects decision-making, both by regulators and downstream decision-makers. Such evaluations can provide learnings for how to deal with the difficult trade-off between (more) evidence generation and (earlier) access. More specifically, three important bodies of drug regulatory science literature evaluate aspects of this evidence generation process during the medicine lifecycle: i) early access pathways such as CMA and their timing of evidence generation, predominantly concerning benefits; ii) post-authorisation regulatory actions, especially those that respond to safety-related evidence, and factors associated with them; and iii) the impact of evidence generation on downstream decision-makers. However, substantial knowledge gaps remain while new gaps emerge as a consequence of regulatory innovation. These knowledge gaps

include whether and how required post-authorisation studies are fulfilled, whether and how post-authorisation learning about risks takes place in relation to learning about benefits, and how evidence aspects for regulatory decision-making such as uncertainties and less comprehensive evidence affect downstream decision-makers. In this thesis, we aimed to address these knowledge gaps. Therefore, the objective of this thesis was to provide insights into evidence generation on benefits and risks throughout the medicine lifecycle, and how it affects decision-making by regulatory and downstream decision-makers in the EU.

The current chapter discusses how the findings of the research performed in this thesis contributed to the above thesis objective, considers implications for drug regulatory science, discusses future perspectives, provides suggestions for future research as well as policy recommendations, and wraps up with a general conclusion.

Evidence generation on benefits for regulatory decision-making

In Chapter 2.1 we started from a perspective predominantly focused on evidence generation on benefits and the role of post-authorisation studies. Therefore, we used the CMA pathway and its specific obligations for post-authorisation studies as case study. We performed a longitudinal evaluation of these specific obligations, including changes made to them, timing of data submission and factors associated with change. Such evaluation can provide insights in regulatory learning about the evidence generation process.

Our results show that of 69 specific obligations for 26 medicines granted CMA between 2006 and 2016, 39% were changed at least once during follow-up and 55% were delayed. These findings highlight the complexity of defining and following up on (regulatory) requirements for evidence generation through post-authorisation studies. Relevantly, the findings can be interpreted from two perspectives. The first perspective acknowledges the complexity and the need to continuously adapt to evolving knowledge. Regulators must define initial requirements for post-authorisation studies based on the available evidence at time of authorisation. While such requirements may apply to any newly authorised medicine,[1, 2] defining them is probably most difficult in the case of CMA, when the evidence is typically less comprehensive. Thereafter, regulators use annual renewals to keep track of the progress of the studies as well as any changes in available evidence – whether from post-authorisation studies or other sources. This allows regulators to steer and adjust the requirements and deadlines for post-authorisation studies to ensure effective and optimal evidence generation and resolve outstanding uncertainties. Alternatively, the

second perspective considers that initial requirements for post-authorisation studies should ensure to provide the required evidence without any further amendments. Otherwise, patients are exposed to potentially ineffective and/or unsafe medicines for a prolonged time period. A recent review that assessed the worldwide performance of post-authorisation studies concluded that studies are often not completed or do not resolve uncertainties.[3]

The findings in Chapter 2.1 paint a nuanced picture of the regulatory learning about the evidence generation process. Four specific obligations underwent substantial changes including study design downgrades from randomised controlled trial to observational study. Such changes should be avoided when they cause uncertainties to remain unaddressed. However, it is not unlikely that other evidence than that requested by regulators as specific obligation might also help to address uncertainties. Unfortunately, such information is not publicly available. All other changes that we observed were less substantial. Also, while almost a quarter of the specific obligations were delayed more than half a year after the initial due date, all but two of these delays appeared to be agreed by the European Medicines Agency (EMA). We consider that the annual renewal process that is in place for the CMA[4, 5] provides regulators with the opportunity to adapt their requirements for post-authorisation studies and that it is used often. Regulators from the United States (US) Food and Drug Administration (FDA) acknowledged the need to adapt post-authorisation studies to scientific and clinical progress.[6] However, the lack of transparency on the EU annual renewal process hampers any conclusion about whether adaptations could have been avoided and whether they affect the extent to which uncertainties are addressed. Moreover, a similar annual renewal process may also be of value for other post-authorisation efficacy and/or safety studies (PAES/PASS), for which interim results are not generally required.[7] A previous study showed that interim results were available for almost half of the post-authorisation studies requested by EMA.[8] However, since this study was performed before the current pharmacovigilance legislation came into force,[9-11] it may not be fully representative of the current situation and requires replication using more recent data.

In addition, we identified medicine-, procedure- and obligation-related factors that were associated with changes to specific obligations. This may help regulators to understand and assess when changes to specific obligations after CMA are less or more likely to take place. The results of these analyses suggested that i) early discussion about and planning of evidence generation and ii) a low level of uncertainty to be addressed may result in fewer changes. Regarding the first point, a regulatory platform that facilitates early discussion and planning has since been put in place: the

PRIority MEdicines (PRIME) scheme, which allows early pre-authorisation regulatory support through e.g., scientific advice and early discussions with the so-called 'Rapporteur' or specific EMA committees. This is intended to facilitate the generation of robust evidence on benefits and risks through prospective discussions about design and planning of pre- and post-authorisation studies.[12] In addition, the guidance for the use of existing regulatory tools such as accelerated assessment and CMA has been updated to emphasise the importance of early discussions and planning and to better describe eligibility criteria, which may in turn allow better preparation for requesting access to these tools.[13] Regarding our second finding, a low(er) level of uncertainty to be addressed by post-authorisation evidence generation may be ensured by granting authorisation later in the medicine lifecycle. Whether the level of uncertainty and the timing of authorisation have changed for conditionally authorised medicines may be a relevant subject for further studies, especially in the light of the recent and heavily discussed authorisation of aducanumab for Alzheimer's disease by the FDA.[14, 15] A European decision about aducanumab is not expected before late 2021, roughly a year after its evaluation started.[16] Overall, while decisions about uncertainty in evidence will remain to be taken on a case-by-case basis, our findings in Chapter 2.1 indicate that early discussion about and prospective planning of post-authorisation evidence generation provide important means to address uncertainty at initial CMA.

Evidence generation on benefits and risks for regulatory decision-making

In Chapter 2.2 we switched to a broader perspective on evidence generation on risks and benefits. As discussed in the general introduction (Chapter 1.1), evidence that comes newly available during the post-authorisation phase may have an impact on the benefit-risk balance of a medicine and thus require regulatory actions. Such actions may include label updates or letters to inform healthcare providers – in the EU called Summary of Product Characteristics (SmPC) updates and Direct Healthcare Professional Communications (DHPC), respectively. Alternatively, an MA may be suspended or completely withdrawn. Studies have frequently evaluated the occurrence of a specific group of regulatory actions, so-called safety-related regulatory actions (SRRA) such as safety-related SmPC updates, DHPCs or withdrawals.[17-23] These generally respond to newly available evidence with a negative impact on risks. In Chapter 2.2, we showed that it is important to realise that SRRAs alone do not paint the complete picture of newly available evidence in the post-authorisation phase, nor do other actions that respond to evidence with a negative impact on benefits or risks.

During more than ten years of post-authorisation follow-up of 40 innovative medicines authorised in 2009 and 2010, 24% of European regulatory actions responded to evidence with a positive impact on benefits or risks. These mainly consisted of new indications. Moreover, 54% of SmPC updates occurred simultaneously with one or more other SmPC updates. These included instances where evidence that supported new or broadened indications or other medicine development-related actions also resulted in SRRAs. This deliberate generation of post-authorisation evidence on benefits thus had an important role in the generation of evidence on and further characterisation of risks. To our knowledge, similar observations have been reported only once. A Japanese study showed an almost twofold increase in Japanese SRRAs when the indication was expanded.[24] However, this phenomenon is not unexpected, and may for example occur when few patients have yet been exposed to a medicine.[25] Moreover, regulatory guidelines have highlighted that evidence supporting different indications, pharmaceutical forms or dosing regimens may also be associated with differences in safety profiles.[26, 27]

Previous studies that evaluated the occurrence of SRRAs often also assessed potential associations between medicinal, clinical development or regulatory characteristics and their occurrence.[21, 28, 29] In Chapter 2.2, we did not formally assess associations but identified three potentially important lifecycle characteristics that seem to play a role in the occurrence of European benefit- and risk-related regulatory actions, and thus benefit- and risk-related evidence generation. First, a low level of post-authorisation patient exposure to medicines seemed to play a role in lifecycles with low overall evidence generation. This reflects the well-known epidemiological concept that a sufficient sample size is needed to identify an outcome.[30, 31] Also, it is in line with a recent study that showed a linear association between patient exposure and reporting of adverse events (AE).[32] Reasons for a low patient exposure may for instance be that a medicine is indicated for an orphan disease or as last-line treatment, or not reimbursed or recommended in clinical practice guidelines. Second, a higher level of innovativeness of medicines seemed to stimulate simultaneous evidence generation about benefits and risks. This is in line with findings by previous research, which showed that i) clinical trial activities are highest once a new medicine is exclusively authorised and decrease thereafter, when generic versions come available,[33, 34] and ii) 92.5% of extensions of indications occur within this exclusivity period.[34, 35] Such indication would typically be considered an innovation. This benefit-related evidence that supports extensions of indications may also result in the concurrent evidence generation about risks as explained above. Furthermore, a direct relationship between innovation and risk-related evidence is also probable: previous studies showed that medicines that were first-in-class were associated

with increased risks for SRRAs,[24, 36, 37] likely because of the limited knowledge of the safety profile at the time of MA. Third, the level of innovativeness seemed to stimulate more risk-related evidence generation when there was a high need for regulatory learning, as is the case for conditionally authorised medicines. This likely follows from the inherent lack of comprehensive evidence at time of authorisation.[5] However, our suggestion that these medicines may be associated with increased evidence generation about risks and consequentially regulatory actions is not supported by previous studies.[38, 39] This may simply be a consequence of differences in outcome definitions since these studies only focused on the most impactful SRRAs, or a lack of power. We recognise that these studies were performed when few medicines had yet been granted CMA. Therefore, a similar analysis for an updated cohort of CMA medicines may be warranted.

In Chapter 2.3, we further evaluated the role of European regulatory processes in the occurrence of regulatory actions for the 2009-2010 cohort of innovative medicines. The results indicate that the level of complexity of the EMA's assessment process – which comprised a composite of procedural characteristics – was associated with time-varying effects on evidence generation about benefits and risks during the medicine lifecycle. While a high level of complexity seemed associated with a two-fold increased risk of evidence with a negative impact on benefits and risks until 39 months post-authorisation, thereafter it seemed associated with a decreased risk. A similar association was observed for evidence with a positive impact on benefits and risks, but with an initially even higher, six-fold increased risk.

These observations could have different explanations. First, the initially increased and later deceased risk could be the consequence of initial regulatory requirements for enhanced evidence generation in response to the observed high level of complexity. These requirements could include PAES, PASS or (other) pharmacovigilance activities that led to early characterisation of a large part of the safety profile. Alternatively, the high level of complexity could be associated with an inherently increased risk of SRRAs and other issues that necessitated actions that severely impacted post-authorisation patient exposure such as restrictions of the indication[40, 41] or changes in clinical decision-making.[42] As a consequence, the lower patient exposure may have limited the ability to collect further risk-related evidence.[32] Unfortunately, the publicly available regulatory data used for this study could not provide sufficient information to clarify whether and to what extent these perspectives played a role. Such evaluation would require internal regulatory data, as discussed below.

Chapter 2.2 and 2.3 highlight that it is imperative to consider both benefits and risks of medicines as well as relations between them when planning or evaluating evidence generation for regulatory decision-making during the lifecycle. Regulators may use these findings to stimulate simultaneous evidence generation about benefits and risks through for example PAES or PASS, or when scientific advice for further medicine development is requested. The lifecycle characteristics could form criteria to define the need for such simultaneous evidence generation.

Future research should further explore these relations between evidence generated about benefits versus risks, including the potentially driving role of regulatory instruments such as the RMP or specific obligations, and of further development strategies of companies. First, the RMP may list studies that address questions about the occurrence or characteristics of safety concerns.[43] Relevantly, such studies may include clinical studies that support further medicine development in closely related areas such as broadened indications. Second, specific obligations for medicines that were granted CMA or authorisation under exceptional circumstances (AEC) could also result in simultaneous generation of evidence on benefits and risks. These specific obligations often concern post-authorisation studies that may address both benefit- and risk-related evidence requirements and are important to address the lack of comprehensive evidence.[5, 44] Lastly, in addition to regulator-requested studies, company-initiated studies that are primarily performed to generate benefit-related evidence for new indications may provide a third driver. Importantly, in-depth evaluations of relations between evidence generated about benefits versus risks would require access to internal regulatory data.

Impact on downstream decision-makers

Over the medicine lifecycle, health technology assessment (HTA) agencies and healthcare professionals also play an important role as decision-makers. Before patients have access to innovative medicines, MA must often be followed by positive decisions on reimbursement by HTA agencies – especially in Europe. Thereafter, patient access obviously requires the actual prescribing by physicians, in which clinical guidelines play an important role.[45] These decision-makers 'downstream' of the regulatory process are initially largely dependent on the evidence that is generated for regulatory decision-making. However, their roles and therefore their evidence requirements and preferences might differ, which may limit the usefulness of 'regulatory evidence' for downstream decision-makers. Consequently, the lack of required and preferred evidence may lead to negative decisions concerning reimbursement or treatment choice, which affect patient access.[45] In Chapter 3,

we evaluated whether evidence generated for regulatory decision-making affects downstream decision-makers, specifically HTA agencies (Chapters 3.1 and 3.2) and physicians (Chapter 3.3). For both decision-makers, we considered evidence that was used to support regulatory decision-making on initial (C)MA and on post-authorisation conversion of CMA to standard MA (SMA).

First, in Chapter 3.1 we evaluated whether uncertainties in clinical evidence that supported initial MA affected HTA relative effectiveness assessment (REA) outcomes and overall reimbursement recommendations. These uncertainties concerned trial methods, clinical outcomes and/or clinical relevance, which were combined to form a low (none of the above), medium (one aspect) or high (two or more aspects) level of uncertainty. A high level of uncertainty was associated with increased risks for both negative REAs and negative overall reimbursement recommendations as compared to a low level of uncertainty. These results suggest that regulators accepted a higher level of uncertainties in clinical evidence than HTA agencies – perhaps because they await additional post-authorisation evidence. Moreover, REA outcomes seemed to be affected especially by uncertainties concerning trial methods, which is not unexpected given the known differences in clinical evidence requirements and preferences between regulatory and HTA agencies with respect to, e.g., comparators, endpoints and trial duration.[46, 47] Furthermore, while REA outcomes were relatively consistent between most HTA agencies, we observed relatively large differences in overall reimbursement recommendations. Here, a high level of uncertainty in clinical evidence seemed to play a smaller role in the decision-making, probably explained by the fact that HTA agencies may also take aspects that are not relevant to regulatory decision-making into account such as cost-effectiveness and pricing.[48-50] A recent study that showed that medicines granted CMA or AEC were substantially more likely than medicines granted SMA to be associated with commercial arrangements confirms that this is an important means to deal with uncertainties.[51] Similarly, HTA agencies may also restrict the indication to be reimbursed to mitigate uncertainties in the supporting clinical evidence,[52, 53] or consider the presence of an unmet medical need[54] to render them acceptable.

Second, in Chapter 3.2 we evaluated whether post-authorisation clinical evidence required by regulators affected HTA decision-making. Again, we used the CMA pathway and the generation of evidence through specific obligations as a case study. Given that less comprehensive evidence is initially accepted to support CMA, it may be expected that the post-authorisation studies required to provide comprehensive evidence for regulatory decision-making are also of relevance for HTA decision-making. However, the results painted a mixed picture. For 16 of the 81 initial REAs that

we identified (20%), clinical evidence from post-authorisation studies was available. The evidence was subsequently included in 14 REAs (88%). The limited availability of these studies for the initial REA is not unexpected, given that initial HTA decision-making often takes place relatively shortly after initial MA.[49] In Chapter 2.1, we show that it generally takes longer for new clinical evidence to come available. In addition, for ten of the only 13 reassessments that we identified (77%), clinical evidence from post-authorisation studies was available. The evidence was subsequently included in all ten REAs (100%) and changed the outcome of four, two more positive and two more negative. The lack of reassessments – fewer than one for every six initial REAs – seems in line with a recent study. This study showed that conversion of CMA to SMA – when comprehensive evidence is considered available by regulatory agencies – did not trigger HTA reassessments in England.[51] On the one hand, not performing a reassessment may be a missed opportunity, considering that we found that REAs were affected relatively often by the outcome of specific obligations. On the other hand, the new clinical evidence is not necessarily relevant to HTA decision-making, as illustrated by four reassessment reports that noted that major concerns flagged in the initial REA could still not be resolved. This was also highlighted by two other studies that reported that HTA agencies issued their own evidence requirements in addition to those of regulatory agencies, comprising among others data on clinical or patient-relevant endpoints, other comparators and generalisability to clinical practice.[51, 55]

Both chapters highlight the need for discussions between regulatory and HTA agencies about their requirements for and assessment of clinical evidence, and about the timing of their processes. Previous research showed that regulatory and HTA agencies agree on most pre-authorisation clinical evidence requirements during parallel scientific advice,[56] but not often on the choice of comparator.[56, 57] Thus, early involvement of both decision-makers in the medicine development process seems an important strategy, especially to minimise divergences between benefit-risk assessment and REA outcomes due to technical evidentiary preferences. However, the generalisability of parallel scientific advice to HTA in general was limited because of the often few national HTA agencies that joined.[56] To address this, the Parallel Consultation procedure was initiated in 2017, in which the EMA and the European Network for Health Technology Assessment (EUnetHTA) – a collaborative network of national and regional HTA agencies – cooperated to provide advice concerning pre-authorisation evidence generation.[58] In addition to these dialogues early in the medicine lifecycle, this collaboration also led to enhanced and timely sharing of regulatory decisions and documents, optimisation of the contents of these documents for HTA decision-making, increased understanding of each other's definitions, assessments and assessment outcomes, among others.[58] These developments may

prove important means to reduce the presence of uncertainties in clinical evidence and their impact on HTA decision-making that we identified in Chapter 3.1, which should be evaluated by future studies.

Relevantly, the EMA-EUnetHTA collaboration also extended the Parallel Consultation procedure to provide advice concerning post-authorisation evidence generation,[58] which representatives from regulatory agencies, HTA agencies and pharmaceutical industry reflected upon in the scientific literature.[59] The authors conclude that such advice facilitates a lifecycle approach towards evidence generation that may help to address remaining uncertainties and improve patient access. In addition, HTA agencies noted that newly generated post-authorisation evidence should be assessed during a reassessment.[59] This combination of joint advice to optimise evidence generation and timely assessment of this evidence to ensure that uncertainties are addressed may resolve some of the issues that we identified in Chapter 3.2. Perhaps, the HTA reassessments may even provide incentives to perform post-authorisation evidence generation in a timely manner, which could address some of the issues that we identified in Chapter 2.1. In addition, careful planning and coordination of the generation and assessment of post-authorisation evidence may also support HTA developments such as outcome-based managed entry agreements.[60-63]

To better coordinate the multi-decision-maker process of evidence generation throughout the medicine lifecycle, it may be worthwhile to establish a medicine-specific joint evidence generation plan. Such a plan could roughly mimic the structure of the RMP, starting with the identification of key uncertainties in the evidence – specified and prioritised per decision-maker. This could then be followed by a detailed strategy to address these uncertainties, including for example specifications of study designs, population characteristics, comparators, endpoints and duration of follow-up. In case of high levels of uncertainty, simultaneous (re)assessments of the available evidence could incentivize timely completion of evidence generation requirements, as discussed above. Notably, the plan should not be used to strive for complete alignment in evidence preferences and requirements between decision-makers – which is impossible – but rather as a platform to facilitate discussion about preferences and priorities, mutual understanding, and the recording of agreements. It could then also provide a basis for joint discussions about definitions and/or quantification of unmet medical need. Obviously, these collaborations would require significant capacity from all decision-makers involved, so it seems useful to prioritise medicines with the highest level of uncertainty. For medicines with a lower but substantial level of uncertainty, perhaps a more high-level evidence generation plan on the disease-level

could still be helpful while saving resources. Lastly, such initiatives should be informed and evaluated by drug regulatory science studies.

Last, in Chapter 3.3 we evaluated how pre- and post-authorisation evidence generation may be perceived by physicians in terms of demonstrated clinical benefit. To that end, we performed a case study for a cohort of oncology medicines and their indications granted CMA and compared these to oncology medicines and indications granted SMA with respect to available evidence and demonstrated clinical benefit. Clinical benefit was assessed through the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS).[64] The results of our study indicate that specific obligations for post-authorisation evidence generation are instrumental in increasing both the available evidence and the clinical benefit that it demonstrates. These were ultimately similar for CMA and SMA oncology indications, when regulators agreed to convert CMAs into SMAs. However, overall, only few oncology indications were supported by evidence of increased overall survival (OS) or quality of life (QoL). Furthermore, for fewer than half of the CMA and SMA indications a substantial clinical benefit could ultimately be demonstrated, and for only one CMA indication at initial authorisation. This is likely against expectations that physicians and their patients have of newly authorised medicines and perhaps especially of 'medicines that address an unmet medical need',[65-68] which is a poorly defined concept among decision-makers.[54, 69] Future studies should evaluate whether common aspects of unmet medical need, such as disease severity and availability and shortcomings of alternative treatments, are similarly quantified and weighed among decision-makers, including physicians.

Importantly, our finding that for few indications a substantial clinical benefit could be demonstrated is relevant information that could influence decision-making by physicians. However, at the time of our study, MCBS scores were readily available for very few CMA pivotal trials.[70] Considering our findings in Chapter 2.1 that post-authorisation studies for conditionally authorised medicines are often delayed, this suggests that physicians remain unaware of the clinical benefit of conditionally authorised medicines for years. Perhaps the best way forward is that outlined repeatedly in the EMA's strategy for regulatory science: increased involvement of physicians and other healthcare professionals in regulatory processes, supported by training activities to increase their understanding of evidence generation in the regulatory process.[71, 72]

Implications for drug regulatory science

This thesis comprises several typical drug regulatory science studies that evaluated aspects of evidence generation for regulatory decision-making and impact on downstream decision-makers. To do so from a lifecycle perspective, we drew on multidisciplinary expertise in medicine regulation and regulatory, pharmaceutical and innovation sciences. This expertise allowed thorough understanding of the regulatory system and its broader context that was essential to: synthesise specific medicine-, procedure- and obligation-related characteristics into regulatory lifecycle approaches that may help prevent change to required post-authorisation studies (Chapter 2.1); integratively study post-authorisation evidence generation on benefits and risks (Chapters 2.2 and 2.3); and bridge the perspectives of regulatory and downstream decision-makers on evidence generation (Chapters 3.1, 3.2 and 3.3). More in general, the understanding of the regulatory system supported the study of processes of evidence generation throughout the lifecycle rather than observations at a fixed time-point (Chapters 2.1, 2.3, 3.2 and 3.3). Also, it aided in identifying relevant medicine-, procedure- and obligation-/study-related factors associated with aspects of evidence generation (Chapters 2.1, 2.3 and 3.1), and the narrative contextualisation of the results of all studies from a research and policy perspective. An overview of policy recommendations is provided below.

To adequately perform the above-mentioned research activities, we applied a number of clinical and epidemiological research methodologies to our drug regulatory science studies. First, we frequently used a longitudinal study design, following cohorts of medicines, indications or studies over time (Chapters 2.1, 2.3, 3.2 and 3.3). In addition, we applied long follow-up windows in all studies, which allowed extensive data collection and subsequent in-depth analyses. Second, we used robust epidemiological methods that ranged from relatively straightforward (Chapters 2.1, 3.1 and 3.3) to complex (Chapter 2.3) measures of association, supported by time-dependent analyses (Chapter 2.3) and restricted analyses to limit variation and ascertain assumptions (Chapters 3.1). Third, we meticulously characterised the data, which helped to contextualise observed associations (Chapters 2.1, 2.3, 3.1 and 3.3) or describe relations (Chapters 2.2 and 3.2).

Limitations

Of course, there are also limitations to the studies in this thesis that may be addressed by future research. First, the cohorts of medicines, indications or studies that we investigated were generally small. For some studies, this was inherent to regulatory cohort characteristics such as the CMA pathway (Chapters 2.1, 3.2 and 3.3), which

was used so far to authorise a relatively small number of medicines. In these cases, we evaluated all available medicines, indications or studies and our statistical analyses should be interpreted as being for a total population, not a sample. For other studies, the small cohorts were a consequence of the extensive and meticulous data extraction with longer periods of follow-up than is usually the case in regulatory science research (Chapters 2.2, 2.3 and 3.1). This limited the feasibility to perform studies with larger cohorts. In these cases, statistical analyses should be interpreted with more caution, which is one reason why we supported these with time-dependent or restricted analyses and narratively contextualised them (see above). In any case, all studies should be replicated when larger cohorts are available. Such studies may profit from data science methods, for example to perform cohort selection and data collection steps more efficiently. Second, several cohorts included medicines that were authorised more than ten years ago (Chapters 2.2, 2.3 and 3.1). This was important to allow the long follow-up and longitudinal analyses described above. However, while many medicinal characteristics are similar to those of currently authorised medicines, the direct applicability of these findings to the present-day regulatory system may decrease over time due to continuous innovation in medicine development and the regulatory system.

Policy recommendations

Regulatory recommendations

Facilitate post-authorisation evidence generation by:

- Ensuring early dialogue about and prospective planning of CMA, along with timely consideration of relevant and feasible requirements for post-authorisation evidence generation;
- Paying specific attention to formulation and follow-up of requirements for post-authorisation evidence generation that address a high level of uncertainty;
- Carefully considering the moment of MA and the impact of any uncertainties in available evidence, bearing in mind that additional evidence may come available later than expected;
- Requiring, where possible, the post-authorisation finalisation of ongoing studies rather than initiation of new studies to limit delayed, downgraded or terminated evidence requirements.

Stimulate simultaneous evidence generation about benefits and risks through, for example, required post-authorisation efficacy studies or scientific advice for post-authorisation medicine development.

Use the PSUR submission frequency criteria also for other regulatory tools that allow evidence generation. For example, to define the frequency of electronic Reaction Monitoring Reports or the need to simultaneously characterise risks in post-authorisation efficacy studies.

Increase transparency of the post-authorisation evidence generation process and enable evaluation of its impact by drug regulatory science studies by publishing and communicating the following:

- Changes in requirements for post-authorisation evidence generation and reasons for them;
- CMA annual renewal and conversion assessment reports;
- Details of evidence that led to regulatory actions in European Public Assessment Reports, including, where applicable, data source, study design, and whether it resulted from a PASS, PAES, other regulatory-required activity, or company-initiated activity.

Enhance understanding of regulatory decision-making by other decision-makers through:

- Better communicating regulatory evidence standards and assessment methods;
- Explaining potential discrepancies with their expectations of evidence standards, for example those underlying the ESMO-MCBS.

Downstream decision-maker recommendations

HTA agencies: apply a systematic approach to reassessments, aligned with the timing of evidence availability.

Clinical practice: ensure evaluation of medicines authorised on less comprehensive evidence – such as conditionally authorised medicines – through guidelines or clinical benefit scores like the ESMO-MCBS to increase understanding of their evidence base.

Multi-decision-maker recommendations

Establish a joint medicine-specific evidence generation plan to guide and provide an overview of (decision-maker-specific) outcomes of at least the following:

- Multi-decision-maker discussions about definitions and perhaps quantification of unmet medical need, and how unmet medical need may impact requirements for evidence generation.

- Multi-decision-maker advice to medicine developers about evidence generation for innovative medicines, starting at early development phases and continuing throughout the medicine lifecycle to ultimately improve patient access.
- Coordination of the timing of assessment of pre- and post-authorisation evidence to stimulate timely finalisation of requirements for post-authorisation evidence generation.

Future perspectives

As noted several times earlier, the context and specifics of evidence generation for regulatory decision-making are continuously evolving. Below, we describe three important developments in the regulatory system that will affect evidence generation and may draw from the learnings in this thesis. First, significant innovations in medicine development are ongoing, among which most prominently the diverse group of advanced therapy medicinal products (ATMP) that includes cell therapies, gene therapies, tissue-engineered medicines and combinations of these. ATMPs are a disruptive group of highly personalised medicines that have required and will require further rethinking of the evidence needed to support sound decision-making – by regulators but also by other downstream decision-makers. For example, research has shown that ATMPs more often have deficiencies in their pre-authorisation clinical evidence than biologicals. These deficiencies included non-randomised, unblinded trials, low numbers of patients included in trials, and modest effect sizes or secondary analyses to support efficacy. Moreover, to address these deficiencies and to provide evidence on long-term safety and efficacy, ATMPs more often require further post-authorisation evidence generation.[73] As discussed above (Chapters 2.1, 3.1, 3.2, 3.3), such deficiencies in pre-authorisation evidence may affect regulatory decision-making as well as downstream decision-making. Furthermore, while HTA agencies agree on the need for post-authorisation evidence, they seem sceptical about the studies requested by regulators.[74] These challenges call for early multi-decision-maker discussions about and planning of pre- and post-authorisation evidence generation, as emphasised in Chapters 3.1 and 3.2.

Second, several developments in types of evidence to inform decision-making are ongoing. For example, the use of so-called 'real-world evidence' (RWE) from observational studies will most likely increase in the near future,[71, 75-78] not the least by the EMA's initiative to establish the Data Analysis and Real World Interrogation Network (DARWIN EU).[79] Other promising types of evidence include that obtained through digital health technologies that allow the conduct of remote trials[80, 81] or smarter reporting of AEs.[82] These developments in types of evidence could benefit

from several learnings that this thesis provides, such as the potential to simultaneously generate evidence about benefits and risks (Chapters 2.2 and 2.3) and situations in which that may be especially helpful (Chapter 2.2). Furthermore, multi-decision-maker coordination of the use of these types of evidence is required to enable it to be valuable for all decision-makers in the medicine lifecycle (Chapters 3.1 and 3.2). This should also include the patient itself, since these types of evidence may facilitate his or her perspective to be better reflected in the assessment process.[71, 83] Importantly, given the potential biases associated with (especially benefit-related) RWE, which has been around for decades as 'evidence from observational data sources', other experts such as pharmacoepidemiologists should also be involved to ensure that the basic principles of pharmacoepidemiology are followed.[84-86] Additionally, evidence on benefits generated in investigator-initiated rather than company-initiated or regulatory-required studies may also start to play role in the future.[87] Such evidence could concern for example new indications for 'old' medicines[88] or different dose schemes.[89] The use of such evidence could severely impact the current process of evidence generation about benefits and risks during the lifecycle. For example, the generation of evidence on risks could be lagging behind, while our findings in Chapters 2.2 and 2.3 suggest that it could be an excellent opportunity to generate this evidence. Also, investigator-initiated evidence could hamper additional evidence generation because there is no company responsible for performing it. Again, early discussions about and planning of evidence generation (Chapters 2.1, 3.1 and 3.2) are then highly needed to ensure that it informs regulatory and downstream decision-making.

Third, developments in regulatory assessment of evidence are expected, such as real-time monitoring of effectiveness and safety based on RWE.[82] Also, the current COVID-19 pandemic has resulted in a new type of continuous assessment of available data prior to authorisation: rolling review.[90] Although its use is currently restricted to emerging health threats, it may be extended in the future when more experience is gained, for example to further shorten accelerated assessment of medicines that address an unmet medical need. These developments underscore that the lifecycle approach to evidence generation continues to be work in progress, as illustrated in the general introduction (Chapter 1). The implementation of real-time monitoring and assessment will typically require multi-decision-maker coordination to ensure availability and quality of evidence and facilitate timely assessment and decision-making about benefits and risks, as discussed in Chapters 3.1 and 3.2. The drug regulatory science field can help to inform and shape these developments by performing evaluations of the real-time monitoring and assessment tools as well as of the preferences of and interactions between decision-makers.

Importantly, several improved collaborations between decision-makers in the medicine lifecycle can soon be expected, which will facilitate the above-mentioned developments and support their implementation. Recently, the European Parliament and the Council agreed on the European HTA regulation,[91] which will change the currently voluntary EUnetHTA to a permanent means for HTA agencies to cooperate – amongst themselves and with the EMA. Among others, this regulation will obligate HTA agencies to perform and use joint REAs for their decision-making, unless justified.[92] This will also increase the impact of the EMA-HTA collaboration on evidence generation.[71] Moreover, many other forms of collaborations between regulatory and HTA agencies that impact evidence generation are ongoing.[46, 62] Furthermore, increased collaboration with and training of academia, as well as training of regulators by academics will enable the translation of academic expertise in robust evidence for regulatory decision-making: by using the academic expertise and capacity to generate important evidence and by contextualising that evidence with knowledge of the regulatory system to ensure that it informs regulatory decision-making.[71, 72] In addition, international collaboration among regulators[93] may ensure regulatory alignment on evidence generation,[94] while increased collaboration with patients and health-care professionals may enhance the 'clinical' impact of regulatory decision-making.[82]

Naturally, the above-mentioned developments should be evaluated in drug regulatory science studies, in replications of earlier studies or completely new studies. Such studies should include those that evaluate the impact of regulatory measures on public health[95, 96] and thereby help to differentiate between effective and non-effective regulation of medicines. Altogether, the evidentiary developments, the increased collaborations between decision-makers and the impact evaluation by drug regulatory science studies aim to move towards more patient-centred regulation of innovative medicines.[45, 71, 97, 98] Importantly, the European pharmaceutical legislation will be revised in the coming years.[99] This revision may incorporate and support several of the above-mentioned advances, thereby drawing on the expertise and knowledge generated in the drug regulatory science field.

Conclusion

This thesis has generated knowledge about evidence generation for innovative medicines in the EU. It shows that it is important to comprehensively consider multiple facets of evidence generation: from the simultaneous generation of evidence concerning benefits and risks to the process of continued evidence generation throughout the medicine lifecycle, and how this affects decision-making by regulators,

HTA agencies and physicians. In doing so, it not only provides a perspective on evidence generation, but also on drug regulatory science as a scientific field, including its role in evaluating the broad public health system and the methods that may be employed to perform this evaluation. With continuous regulatory innovations and advances in science and technology, the need for drug regulatory science to monitor and evaluate the regulatory system will remain high in the future. Apart from evaluating past and ongoing developments in evidence generation, the thesis therefore also offers a basis to evaluate and contextualise those future developments.

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Chapter 5

Summaries

Summary

Introduction

In the European Union (EU), the medicine regulatory system aims to protect and promote public health by assessment of quality, safety and efficacy data before a marketing authorisation (MA) can be obtained and a medicine can be marketed. This so-called benefit-risk assessment is always based on partially incomplete knowledge and thus subject to uncertainty. Also, the context of use of medicines in clinical practice is ever-changing. Therefore, regulatory pathways and instruments have been put into place to allow for continuous evidence generation and subsequent decision-making about the benefit-risk balance of a medicine after it is authorised. Specifically for medicines that address an unmet medical need, enhanced flexibility in the timing of evidence generation on benefits and risks was made possible. Chapter 1.1 and 1.2 describe these regulatory pathways and instruments as the latest developments in the evolving European regulatory system, including for example the risk management plan (RMP), the conditional marketing authorisation (CMA) pathway, specific obligations for post-authorisation studies, and MAs that require to be renewed annually. Together, these developments contribute to a regulatory 'lifecycle approach' to continuous evidence generation and decision-making.

Chapter 1.1 also highlights the need to evaluate such developments and their impact on evidence generation and subsequent decision-making. Drug regulatory science is a scientific field that among others performs such evaluations, which may inform discussions about the trade-of between (more) evidence generation and (earlier) access. Some important bodies of literature in this field that evaluate the evidence generation process comprise evaluation of the functioning of early access pathways – such as the CMA pathway – and their timing of evidence generation, post-authorisation regulatory actions and factors associated with them, and the impact of evidence generation on downstream decision-makers. However, relevant knowledge gaps in this literature remain and arise from new regulatory and technological innovations. Therefore, the objective of this thesis was to provide insights into evidence generation on benefits and risks throughout the medicine lifecycle, and how it affects decision-making by regulatory and downstream decision-makers in the EU.

Evidence generation for regulatory decision-making

In Chapter 2, we studied evidence generation for European regulatory decision-making. In Chapter 2.1, we studied the specific obligations that are imposed for CMA medicines to address remaining uncertainties and provide comprehensive evidence on benefits and risks. We characterised whether, when and how they were changed after authorisation and determined when required data were submitted. We identified 69 specific obligations for 26 medicines that were granted CMA between 2006 and 2016. Thereof, 27 specific obligations were changed (39%). In total, we identified 39 changes, of which four substantially changed an obligation. Furthermore, for 26 of the 47 obligations that were considered fulfilled (55%), data were submitted too late. In addition, we identified 11 medicine-related, procedure-related and obligation-related factors that were associated with change, including the use of the CMA pathway as a rescue option. These results seem to indicate a continuous search by regulators to reduce uncertainties. However, data that are submitted too late may cause patients being exposed to unknown risks for a longer period of time, particularly when the level of uncertainty is high.

In Chapter 2.2, we built on previous studies that assessed mainly post-authorisation safety-related regulatory actions that reflect a negative impact on medicine risks. We performed an in-depth characterisation of medicine lifecycles and identified all relevant post-authorisation regulatory actions that occurred during ten years of follow-up. These included safety-related regulatory actions that reflected a negative impact on medicine risks, but also those that reflected a positive impact, as well as benefit-related regulatory actions. In addition, we assessed relations between them. Such a broader evaluation of regulatory actions better reflects the typical concurrent assessment of benefits and risks in regulatory practice. For a cohort of 40 innovative medicines that were authorised in 2009 and 2010, we identified 14 direct healthcare professional communications (DHPC) and 361 updates to the Summary of Product Characteristics (SmPC). Of the SmPC updates, 85 (24%) reflected a positive impact, mostly concerning new or broadened indications. In addition, 276 (76%) reflected a negative impact, mostly new adverse drug reactions. Many updates (54%) occurred simultaneously with other updates, also if these reflected a different impact. The simultaneous learning about benefits (indications) and risks (adverse drug reactions) suggests an important role for further development of medicines in risk characterisation. Furthermore, we found that levels of patient exposure, innovativeness, needs for regulatory learning and unexpected risks may contribute to specific patterns of regulatory actions.

We further evaluated these post-authorisation regulatory actions in Chapter 2.3. Here we studied whether a composite measure of pre-authorisation aspects that reflect complexity of European Medicines Agency's (EMA) assessment process was associated with the occurrence of the regulatory actions. These complexity aspects included a prolonged assessment procedure, MA decisions that were not taken by consensus but by majority vote, re-examination procedures that occurred after initially negative MA decisions, and concerns about the methodological robustness of clinical studies. We fitted recurrent time-to-event models based on likelihood and estimated adjusted intensity rate ratios (aIRR) and 95% confidence intervals (CI) to compare levels of complexity. We adjusted the analyses for the number of patients that had been exposed to each medicine prior to authorisation, to control for potential differences in knowledge of medicines at time of authorisation. Of the 40 medicines, we assessed the level of complexity of the assessment process as low for 11 and high for 29 medicines. As compared to a low level of complexity, a high level appeared to be associated with an increased risk for post-authorisation regulatory actions that reflected a positive impact on benefits and risks: aIRR 0.69 (95% CI 0.35-1.33). On the contrary, complexity appeared not to be associated with regulatory actions that reflected a negative impact: aIRR 1.01 (95% CI 0.56-1.80). However, likelihood-based model fitting suggested two different patterns of associations up to and beyond 39 months after authorisation. High complexity was associated with an increased risk of both types of regulatory actions up to 39 months after authorisation: aIRRs 6.12 (95% CI 0.93-40.47) and 3.51 (95% CI 1.01-12.16). In the period beyond 39 months, high complexity was associated with a decreased risk: aIRRs 0.47 (95% CI 0.22-0.99) and 0.54 (95% 0.31-0.93). This earlier occurrence of regulatory actions may indicate that medicines for which the assessment process was highly complex were monitored more actively during early lifecycle stages.

Impact on downstream decision-makers

In Chapter 3, we studied the impact of evidence for regulatory decision-making on downstream decision-makers, whose decisions also affect patient access to medicines. Chapter 3.1 and 3.2 focused on the role of health technology assessment (HTA) agencies, which provide recommendations or decisions on reimbursement of medicines. Whereas in Chapter 3.1 we studied the impact of evidence generation for initial regulatory decision-making for a new medicine on initial HTA decision-making, in Chapter 3.2 we studied the impact of evidence generation for post-authorisation regulatory decision-making on HTA decision-making. First, in Chapter 3.1, we evaluated the impact of three regulatory uncertainty aspects: uncertainty identified by the EMA regarding the methodology of pivotal clinical

studies, uncertainty regarding the clinical outcome demonstrated by these studies, and uncertainty regarding the clinical relevance of these outcomes. We studied whether a higher level of these combined uncertainty aspects was associated with negative relative effectiveness assessments (REA) and negative overall reimbursement recommendations by the Dutch, English, French and Scottish HTA agencies. For a cohort of 36 innovative medicines (excluding vaccines) that were authorised in 2009 and 2010, we identified 121 reimbursement recommendations that had been issued by the HTA agencies between September 2009 and July 2018. As compared to low uncertainty (no uncertainty aspects), high uncertainty (two or more uncertainty aspects) was associated with an increased risk for negative REAs and negative overall reimbursement recommendations: risk ratios (RR) 1.9 (95% CI 0.9-3.9) and 1.6 (95% CI 0.7-3.5), respectively, which was supported by further sensitivity analyses. We identified a lack of agreement between 33 (27%) REA outcomes and overall reimbursement recommendation outcomes. These were mostly restricted recommendations that followed on negative REAs in case of low or medium uncertainty. To reduce uncertainty and ultimately facilitate efficient patient access, regulators, HTA agencies and other stakeholders should discuss how uncertainties should be weighed and addressed early in the medicine lifecycle of innovative treatments.

Second, in Chapter 3.2, we focused on the CMA pathway again because of its typical specific obligations for post-authorisation studies. We investigated whether evidence resulting from these studies was used by the Dutch, English, French and collaborative European HTA agencies within REAs, and whether and how this affected HTA assessments. For all 36 CMA medicines that had been authorised up to December 2018, we identified 98 post-authorisation studies, 81 initial REAs and 13 reassessments of REAs. Study results were available for 16 initial REAs (20%) and 10 reassessments of REAs (77%) and included in 14 initial REAs (77%) and all reassessments of REAs (100%). Of the reassessments, five differed in outcome from the initial REA. In four instances, these differences were directly related to the study results, leading to two more positive outcomes and two more negative outcomes. Relevantly, in many reassessment reports a lack of usefulness of post-authorisation studies to resolve initial REA concerns was noted. Although post-authorisation study results can thus be relevant to HTA decision-making, their potential is limited by a lack of alignment and coordination between regulators and HTA agencies in the availability of these results and the performance of reassessments.

Lastly, in Chapter 3.3, we focused on the clinical decision-maker perspective, specifically regarding cancer medicines. Cancer medicines are often authorised

without evidence on important clinical endpoints such as overall survival (OS) and quality of life (QoL), and often through the CMA pathway. We compared the availability of evidence and demonstrated clinical benefit for CMA cancer indications with similar standard MA (SMA) cancer indications, thereby taking into account the contribution of post-authorisation studies for CMA indications. We identified 15 CMA cancer indications that were converted to SMA between 2006 and 2020 and identified 15 similar SMA cancer indications. The authorisation of 11 SMA (73%) and four CMA indications (27%) was supported by controlled studies. Improved OS was demonstrated for four SMA indications (27%). Improved QoL was demonstrated for three SMA (20%) and one CMA indication (7%). Of the subsequent CMA post-authorisation confirmatory studies, 11 were controlled (79%), one demonstrated improved OS (7%) and five improved QoL (36%). We then assessed the demonstrated clinical benefit through the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS). After conversion, CMA indications had similar clinical benefit scores compared to SMA indications: median score 3.0 (interquartile range 3.0-4.0) versus 3.0 (2.5-4.0; p=0.31). Furthermore, the chance to be associated with substantial clinical benefit (scores 4 or 5) was also similar: 7/15 (47%) versus 5/15 (33%), RR 1.4 (95% CI 0.57-3.4). To account for the clinical benefit of unconverted CMA indications, we performed sensitivity analyses that confirmed the main results. Given that regulators require 'comprehensive evidence' at time of conversion of CMA medicines versus at time of authorisation of SMA medicines, our findings suggest that its definition is similar for cancer indications that received conditional and standard authorisation.

Implications

In Chapter 4, we have placed the findings of the research presented in this thesis in a broader perspective. First, we discussed the value of post-authorisation evidence generation for CMA medicines. We concluded that early discussion about and prospective planning of post-authorisation evidence generation provide important means to address uncertainty at initial CMA. Second, we discussed the relative importance of studying both risk-related and benefit-related post-authorisation regulatory actions as well as the learnings of our studies on regulatory actions for regulatory decision-making. We concluded that it is imperative to consider this broader perspective including potential relations between benefits and risks of medicines when evaluating or planning evidence generation for regulatory decision-making in the medicine lifecycle. Regulators may for example use these findings to stimulate simultaneous evidence generation about benefits and risks through post-authorisation studies, or when scientific advice for further medicine development

is requested. Third, we discussed the role of evidence generated for regulatory decision-making on downstream decision-makers, specifically HTA agencies and physicians. We concluded that there is a need for discussions between regulatory and HTA agencies about their requirements for and assessment of clinical evidence, and about the timing of their processes. To coordinate this multi-decision-maker process of evidence generation throughout the medicine lifecycle, we suggest that a medicine-specific joint evidence generation plan could be established that mimics the structure of the RMP. In addition, we concluded that specific obligations for post-authorisation studies are instrumental in increasing both the available evidence and the demonstrated clinical benefit of CMA (cancer) medicines, but that the clinical benefit offered by these medicines may be less substantial than physicians and patients expect. To increase their understanding of and input in the regulatory evidence generation process, physicians and other healthcare professionals should be more frequently involved in regulatory processes, supported by training activities. Fourth, we discussed several aspects that enabled and strengthened the typical drug regulatory science studies that were performed for this thesis, including the multidisciplinary expertise of the research team and the integration of clinical and epidemiological research methodologies. These observations may support and strengthen future studies in this field. Fifth, we provided extensive policy recommendations for regulatory, HTA and clinical practice decision-makers in line with the conclusions drawn above. Last, we described three important developments in the regulatory system that will affect future evidence generation and may draw from the learnings in this thesis: significant innovations in medicine development such as advanced therapy medicinal products, developments in types of evidence such as 'real-world' evidence, and developments in the regulatory assessment of evidence such as real-time monitoring of effectiveness and safety. In conclusion, this thesis shows that it is important to comprehensively consider multiple facets of evidence generation on benefits and risks of medicines and offers a basis to evaluate and contextualise future developments.

Samenvatting

Introductie

In de Europese Unie (EU) heeft het systeem van geneesmiddelregulering tot doel de volksgezondheid te beschermen en te bevorderen. Dit gebeurt door de kwaliteit, veiligheid en werkzaamheid van een geneesmiddel te beoordelen voordat een vergunning voor het in de handel brengen wordt afgegeven en het geneesmiddel op de markt kan worden gebracht. Deze zogenaamde baten-risicobeoordeling is altijd gebaseerd op deels onvolledige kennis en dus onderhevig aan onzekerheid. Bovendien verandert de context van het gebruik van het geneesmiddel in de klinische praktijk voortdurend. Om deze onzekerheid te verminderen zijn er speciale procedures en instrumenten ontwikkeld die het continu genereren van bewijsmateriaal stimuleren. Daarmee kan de baten-risicoverhouding van een geneesmiddel regelmatig beoordeeld worden, ook nadat een handelsvergunning is verleend. Daarnaast is specifiek voor geneesmiddelen die voorzien in een onvervulde medische behoefte een grotere flexibiliteit in de timing van het genereren van bewijs over baten en risico's mogelijk gemaakt. Hoofdstuk 1.1 en 1.2 beschrijven deze procedures en instrumenten als recente ontwikkelingen in de evolutie van het Europese systeem van geneesmiddelregulering. Een aantal voorbeelden hiervan zijn het risicomanagementplan (RMP), de voorwaardelijke handelsvergunning (*conditional marketing authorisation* of CMA), verplichtingen tot het uitvoeren van studies na toelating (*specific obligations*) en handelsvergunningen die jaarlijks moeten worden verlengd. Samen dragen deze ontwikkelingen bij aan een 'levenscyclusbenadering' in geneesmiddelregulering, waarbij continu bewijs gegenereerd wordt en vervolgens besluitvorming kan plaatsvinden.

Hoofdstuk 1.1 benadrukt daarnaast de noodzaak om dergelijke ontwikkelingen en hun impact op het genereren van bewijs en de daaropvolgende besluitvorming te evalueren. *Drug regulatory science* is een wetenschappelijke discipline die onder andere dergelijke evaluaties uitvoert. De uitkomsten hiervan kunnen discussies voeden over de afweging tussen het genereren van (meer) bewijsmateriaal enerzijds en (eerdere) toegang tot geneesmiddelen anderzijds. Belangrijke wetenschappelijke literatuur waarin het genereren van bewijsmateriaal over baten en risico's van geneesmiddelen geëvalueerd wordt, behandelt onder andere de evaluatie van vroege toegangsroutes zoals de CMA-route en de daarbij horende timing van het genereren van bewijsmateriaal, maatregelen die na de initiële goedkeuring genomen worden en daarmee samenhangende factoren en de impact van het genereren van bewijs

op verdere besluitvorming door andere partijen in de geneesmiddelenketen. In deze literatuur resteren echter kennislacunes en bovendien ontstaan er nieuwe lacunes als gevolg van innovatie in regelgeving en technologie. Het doel van dit proefschrift was daarom inzicht te verschaffen in het genereren van bewijs over baten en risico's gedurende de levenscyclus van geneesmiddelen en hoe dit besluiten van regulatoire autoriteiten en andere partijen in de Europese geneesmiddelenketen beïnvloedt.

Het genereren van bewijs voor besluitvorming door regulatoire autoriteiten

In hoofdstuk 2 hebben we het genereren van bewijs voor besluitvorming door de Europese regulatoire autoriteiten bestudeerd. In hoofdstuk 2.1 hebben we de specific obligations bestudeerd die worden opgelegd om resterende onzekerheden over CMA-geneesmiddelen te verminderen en zogenaamde *comprehensive evidence* over baten en risico's te leveren. We hebben gekarakteriseerd of, wanneer en hoe specific obligations werden gewijzigd na goedkeuring en bepaald wanneer de vereiste gegevens werden ingediend. We identificeerden 69 specific obligations voor 26 tussen 2006 en 2016 goedgekeurde CMA-geneesmiddelen. Daarvan werden 27 specific obligations gewijzigd (39%). In totaal identificeerden we 39 wijzigingen, waarvan er vier substantieel waren. Voor 26 van de 47 specific obligations die als afgerond werden beschouwd, werden gegevens te laat ingediend (55%). Daarnaast identificeerden we 11 geneesmiddel-, procedure- en obligation-gerelateerde factoren die verband hielden met wijzigingen, waaronder het gebruik van de CMA-route als goedkeuring via de standaardroute het niet lijkt te halen. Deze resultaten lijken te wijzen op een continue zoektocht van regulatoire autoriteiten naar mogelijkheden om onzekerheden te verminderen gedurende de levenscyclus van geneesmiddelen. Echter, vertraging in het aanleveren van gegevens kan ervoor zorgen dat patiënten langer worden blootgesteld aan onbekende risico's, zeker als er veel onzekerheid is.

In hoofdstuk 2.2 borduurden we voort op eerdere studies die voornamelijk veiligheidsgerelateerde maatregelen bestudeerden die genomen werden na goedkeuring. We voerden een uitgebreide karakterisering uit van de levenscycli van een cohort van geneesmiddelen en identificeerden alle relevante maatregelen die gedurende een periode van tien jaar na goedkeuring genomen werden. Deze maatregelen omvatten veiligheidsgerelateerde maatregelen die een negatief of positief effect op geneesmiddelrisico's weerspiegelden en ook baten-gerelateerde maatregelen. Daarnaast hebben we de relaties tussen deze maatregelen in kaart gebracht. Een dergelijke brede evaluatie van maatregelen komt beter overeen met de samenhang tussen baten en risico's in geneesmiddelregulering. Voor een cohort van 40 innovatieve geneesmiddelen die in 2009 en 2010 werden goedgekeurd,

identificeerden we 14 *direct healthcare professional communications* (DHPC) en 361 updates van de samenvatting van de productkenmerken (SmPC). Van de SmPC-updates weerspiegelden 85 (24%) een positieve impact, voornamelijk met betrekking tot nieuwe of bredere indicaties. Daarnaast weerspiegelden 276 (76%) een negatief effect, voornamelijk nieuwe bijwerkingen. Veel updates (54%) vonden gelijktijdig plaats met andere updates, ook als deze een ander effect weerspiegelden. Dit gelijktijdig leren over baten (indicaties) en risico's (bijwerkingen) suggereert een belangrijke rol voor verdere geneesmiddelontwikkeling in risicokarakterisering. Verder vonden we dat niveaus van patiëntblootstelling, innovativiteit, behoefte aan aanvullend bewijsmateriaal en onverwachte risico's kunnen bijdragen aan specifieke patronen van maatregelen.

We evalueerden deze na goedkeuring genomen maatregelen verder in hoofdstuk 2.3. Hierin onderzochten we of een samengestelde maat van aspecten die complexiteit van de beoordelingsprocedure van het Europees Geneesmiddelenbureau (EMA) weerspiegelen, verband hield met het optreden van de maatregelen. Deze complexiteitsaspecten omvatten: een langdurige beoordelingsprocedure, besluiten over handelsvergunningen die niet bij consensus maar bij meerderheid van stemmen werden genomen, herzieningen van aanvankelijk negatieve besluiten over handelsvergunningen en geuite zorgen over de methodologische robuustheid van klinische studies. We gebruikten *recurrent time-to-event*-modellen en schatten intensiteitsratio's (aIRR) en 95%-betrouwbaarheidsintervallen (BI) om niveaus van complexiteit te vergelijken. Om te corrigeren voor mogelijke verschillen in kennis over geneesmiddelen op het moment van toelating, hebben we het aantal patiënten dat voorafgaand aan toelating aan een geneesmiddel was blootgesteld meegenomen in de analyse. Van de 40 geneesmiddelen beoordeelden we de complexiteit van de beoordelingsprocedure als laag voor 11 en hoog voor 29 geneesmiddelen. Vergeleken met een laag niveau van complexiteit bleek een hoog niveau geassocieerd te zijn met een verhoogd risico op maatregelen die een positief effect op baten en risico's weerspiegelden: aIRR 0,69 (95% BI 0,35-1,33). Daarentegen bleek complexiteit niet geassocieerd te zijn met maatregelen die een negatieve impact weerspiegelden: aIRR 1,01 (95% BI 0,56-1,80). Echter, op *likelihood* gebaseerde analysemodellen suggereerden twee verschillende associatiepatronen tot en na 39 maanden na goedkeuring. Hoge complexiteit was geassocieerd met een verhoogd risico op beide typen maatregelen tot 39 maanden na goedkeuring: aIRR's 6,12 (95% BI 0,93-40,47) en 3,51 (95% BI 1,01-12,16). In de periode na 39 maanden was hoge complexiteit geassocieerd met een verminderd risico: aIRR's 0,47 (95% BI 0,22-0,99) en 0,54 (95% 0,31-0,93). Dit eerdere voorkomen van maatregelen voor geneesmiddelen met een

complexe beoordelingsprocedure kan erop wijzen dat deze geneesmiddelen actiever gemonitord werden tijdens de vroege stadia van de levenscyclus.

Impact op verdere besluitvorming

In hoofdstuk 3 hebben we de impact van bewijs voor besluitvorming door regulatoire autoriteiten op verdere besluitvorming bestudeerd, aangezien deze mede de toegang van patiënten tot geneesmiddelen beïnvloedt. Hoofdstuk 3.1 en 3.2 waren gericht op de rol van instanties die gezondheidstechnologiebeoordelingen (*health technology assessments* of HTA) uitvoeren. Zij doen aanbevelingen of beslissen over de vergoeding van geneesmiddelen. We bestudeerden de impact van het genereren van bewijs vóór (hoofdstuk 3.1) en ná (hoofdstuk 3.2) het verlenen van een handelsvergunning op HTA-besluitvorming. Eerst evalueerden we in hoofdstuk 3.1 de impact van drie onzekerheidsaspecten in geneesmiddelregulering: door de EMA geïdentificeerde onzekerheid met betrekking tot de methodologie van klinische studies, onzekerheid met betrekking tot de resultaten uit deze studies en onzekerheid met betrekking tot de klinische relevantie van deze resultaten. We onderzochten of een hoger niveau van deze gecombineerde onzekerheidsaspecten geassocieerd was met negatieve relatieve effectiviteitsbeoordelingen (*relative effectiveness assessments* of REA) en negatieve vergoedingsaanbevelingen door de Engelse, Franse, Nederlandse en Schotse HTA-instanties. Voor een cohort van 36 innovatieve geneesmiddelen (exclusief vaccins) die in 2009 en 2010 waren goedgekeurd, identificeerden we 121 vergoedingsaanbevelingen die tussen september 2009 en juli 2018 door de HTA-instanties waren gedaan. In vergelijking met lage onzekerheid (geen onzekerheidsaspecten) was hoge onzekerheid (twee of meer onzekerheidsaspecten) geassocieerd met een verhoogd risico op negatieve REA's en negatieve vergoedingsaanbevelingen. De bijbehorende risicoratio's (RR) waren respectievelijk 1,9 (95% BI 0,9-3,9) en 1,6 (95% BI 0,7-3,5). Deze resultaten werden ondersteund door sensitiviteitsanalyses. We identificeerden bovendien een gebrek aan overeenstemming tussen 33 (27%) REA-uitkomsten en vergoedingsaanbevelingen. Dit waren veelal aanbevelingen tot een beperkte vergoeding die volgden op negatieve REA's, in een context van lage of gemiddelde onzekerheid. Om de onzekerheid te verminderen en uiteindelijk patiënttoegang te bevorderen, moeten regulatoire autoriteiten, HTA-instanties en andere belanghebbenden bespreken hoe onzekerheden vroeg in de levenscyclus van innovatieve geneesmiddelen moeten worden gewogen en geadresseerd.

Daarna richtten we ons in hoofdstuk 3.2 opnieuw op de CMA-route vanwege de typische specific obligations, de verplichtingen om studies uit te voeren na

goedkeuring. We onderzochten of bewijs dat uit deze studies voortkwam, werd gebruikt door de Engelse, Franse, Nederlandse en samenwerkende Europese HTA-agentschappen in hun REA's, en of en hoe dit van invloed was op HTA-beoordelingen. Voor de 36 CMA-geneesmiddelen die tot december 2018 waren goedgekeurd identificeerden we 98 na goedkeuring uitgevoerde studies, 81 initiële REA's en 13 herbeoordelingen van REA's. Resultaten van deze studies waren beschikbaar voor 16 initiële REA's (20%) en 10 herbeoordelingen van REA's (77%) en opgenomen in 14 initiële REA's (77%) en alle herbeoordelingen van REA's (100%). Van de herbeoordelingen verschilden er 5 in uitkomst van de initiële REA. In 4 gevallen waren deze verschillen direct gerelateerd aan de studieresultaten, wat leidde tot 2 positievere beoordelingen en 2 negatievere beoordelingen. Relevant is dat in veel herbeoordelingsrapporten werd benadrukt dat de studies niet in staat bleken om in eerdere REA's opgemerkte beperkingen weg te nemen. Hoewel resultaten van na goedkeuring uitgevoerde studies dus relevant kunnen zijn voor HTA-besluitvorming, wordt hun potentieel beperkt door een gebrek aan afstemming en coördinatie tussen regulatoire autoriteiten en HTA-instanties, voornamelijk ten aanzien van de beschikbaarheid van deze resultaten en het uitvoeren van herbeoordelingen.

Ten slotte hebben we ons in hoofdstuk 3.3 gericht op het perspectief van de clinicus, in het bijzonder voor geneesmiddelen tegen kanker. Geneesmiddelen tegen kanker zijn vaak goedgekeurd zonder bewijs over effectiviteit op belangrijke klinische eindpunten, zoals algehele overleving (*overall survival* of OS) en kwaliteit van leven (*quality of life* of QoL). Bovendien worden ze vaak goedgekeurd via de CMA-route. We vergeleken de beschikbaarheid van bewijs en bewezen klinische waarde voor CMA-kankerindicaties met vergelijkbare standaard goedgekeurde (*standard marketing authorisation* of SMA) kankerindicaties, waarbij we rekening hielden met de bijdrage van na goedkeuring uitgevoerde studies voor CMA-indicaties. We identificeerden 15 CMA-kankerindicaties die tussen 2006 en 2020 waren omgezet naar SMA en identificeerden 15 vergelijkbare SMA-kankerindicaties. De goedkeuring van 11 SMA- (73%) en vier CMA-indicaties (27%) werd ondersteund door gecontroleerde studies. Verbeterde OS werd aangetoond voor vier SMA-indicaties (27%). Verbeterde QoL werd aangetoond voor drie SMA- (20%) en één CMA-indicatie (7%). Van de na goedkeuring uitgevoerde studies voor CMA-indicaties waren er 11 gecontroleerd (79%), toonde één verbeterde OS aan (7%) en toonden vijf verbeterde QoL aan (36%). Vervolgens hebben we de bewezen klinische waarde beoordeeld door middel van de European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS). Na conversie tot SMA waren CMA-indicaties geassocieerd met vergelijkbare klinische waardescores als SMA-indicaties: mediane score 3,0 (interkwartielafstand 3,0-4,0) versus 3,0 (2,5-4,0; p=0,31). Bovendien was de kans om geassocieerd te

zijn met substantiële klinisch waarde (scores 4 of 5) ook vergelijkbaar: 7/15 (47%) versus 5/15 (33%), RR 1,4 (95% BI 0,57-3,4). Om rekening te houden met de klinische waarde van niet-geconverteerde CMA-indicaties hebben we sensitiviteitsanalyses uitgevoerd, die de resultaten bevestigden. Aangezien regulatoire autoriteiten voor CMA-geneesmiddelen 'comprehensive evidence' vereisen op het moment van conversie en voor SMA-geneesmiddelen op het moment van goedkeuring, suggereren onze bevindingen dat de definitie daarvan vergelijkbaar is voor kankerindicaties die voorwaardelijk en standaard goedgekeurd zijn.

Implicaties

In hoofdstuk 4 hebben we de bevindingen van het onderzoek in dit proefschrift in een breder perspectief geplaatst. Eerst bespraken we de waarde van het genereren van bewijs na goedkeuring van CMA-geneesmiddelen. We concludeerden dat een vroege discussie over en prospectieve planning van het genereren van bewijs na goedkeuring belangrijke middelen zijn om onzekerheid bij de initiële CMA-goedkeuring te verminderen. Ten tweede bespraken we het relatieve belang van het bestuderen van zowel risico- als baten-gerelateerde maatregelen na goedkeuring, evenals de lessen van onze studies over dergelijke maatregelen voor geneesmiddelregulering. We concludeerden dat het noodzakelijk is om dit bredere perspectief in acht te nemen bij het evalueren of plannen van het genereren van bewijs voor geneesmiddelregulering tijdens de levenscyclus van geneesmiddelen, inclusief mogelijke relaties tussen baten en risico's van geneesmiddelen. Regulatoire autoriteiten kunnen deze bevindingen bijvoorbeeld gebruiken om gelijktijdige bewijsvergaring over baten en risico's te stimuleren door middel van na goedkeuring uitgevoerde studies, of wanneer wetenschappelijk advies voor verdere ontwikkeling van geneesmiddelen wordt gevraagd. Ten derde bespraken we de rol van bewijs voor geneesmiddelregulering op verdere besluitvorming, specifiek door HTA-instanties en clinici. We concludeerden dat er behoefte is aan discussies tussen regulatoire autoriteiten en HTA-instanties over hun vereisten voor en beoordeling van klinisch bewijs en over de timing van hun processen. Om dit proces van overleg en afstemming tussen diverse betrokken instanties tijdens de levenscyclus van een geneesmiddel te coördineren, stellen we voor een gezamenlijk geneesmiddelspecifiek bewijsontwikkelplan in te stellen dat een vergelijkbare structuur heeft als het RMP. Daarnaast concludeerden we dat specific obligations, de verplichtingen voor na goedkeuring uitgevoerde studies, van groot belang zijn om zowel het beschikbare bewijs als de bewezen klinische waarde van CMA-geneesmiddelen (tegen kanker) te vergroten. Echter, we constateerden ook dat de klinische waarde van deze geneesmiddelen mogelijk minder groot is dan artsen en patiënten verwachten. Om hun begrip van en inbreng in het proces van het

genereren van bewijsmateriaal voor geneesmiddelregulering te vergroten, moeten artsen en andere zorgverleners vaker betrokken worden bij dit proces, waar mogelijk ondersteund door opleidingsactiviteiten. Ten vierde bespraken we verschillende aspecten die de typische *drug regulatory science* studies die voor dit proefschrift werden uitgevoerd mogelijk maakten en versterkten, waaronder de multidisciplinaire expertise van het onderzoeksteam en de integratie van klinische en epidemiologische onderzoeksmethodes. Deze observaties kunnen toekomstige studies op dit gebied ondersteunen en versterken. Ten vijfde hebben we uitgebreide beleidsaanbevelingen gedaan voor besluitvormers op het gebied van geneesmiddelregulering, HTA en de klinische praktijk, in overeenstemming met de hierboven getrokken conclusies. Als laatste beschreven we drie belangrijke ontwikkelingen in de geneesmiddelregulering die van invloed zullen zijn op het genereren van bewijsmateriaal in de toekomst en waarvoor lessen getrokken kunnen worden uit dit proefschrift: belangrijke innovaties in de ontwikkeling van geneesmiddelen, zoals zogenoemde *advanced therapy medicinal products*; ontwikkelingen in typen bewijs, zoals 'real-world' bewijs; en ontwikkelingen in de beoordeling van bewijs, zoals *real-time monitoring* van effectiviteit en veiligheid. Concluderend laat dit proefschrift zien dat het belangrijk is om meerdere facetten van het genereren van bewijs over baten en risico's van geneesmiddelen in overweging te nemen en biedt het een basis om toekomstige ontwikkelingen te evalueren en te contextualiseren.

Chapter 6

Appendices

List of publications

Related to this thesis

Lourens T Bloem, Aukje K Mantel-Teeuwisse, Hubert GM Leufkens, Marie L De Bruin, Olaf H Klungel, Jarno Hoekman. Postauthorization changes to specific obligations of conditionally authorized medicines in the European Union: a retrospective cohort study. *Clin Pharmacol Ther* 2019;105:426-435.

Lourens T Bloem[*], Rick A Vreman[*], Stijn van Oirschot, Jarno Hoekman, Menno E van der Elst, Hubert GM Leufkens, Olaf H Klungel, Wim G Goettsch, Aukje K Mantel-Teeuwisse. The role of regulator-imposed post-approval studies in health technology assessments for conditionally approved drugs. *Int J Health Policy Manag* 2020 Oct 27. Online ahead of print.

Lourens T Bloem[*], Rick A Vreman[*], Niels WL Peeters, Jarno Hoekman, Menno E van der Elst, Hubert GM Leufkens, Olaf H Klungel, Wim G Goettsch, Aukje K Mantel-Teeuwisse. Associations between uncertainties identified by the European Medicines Agency and national decision-making on reimbursement by HTA agencies. *Clin Transl Sci* 2021;14:1566-1577.

Lourens T Bloem, Mariana Karomi, Jarno Hoekman, Menno E van der Elst, Hubert GM Leufkens, Olaf H Klungel, Aukje K Mantel-Teeuwisse. Comprehensive evaluation of post-approval regulatory actions during the drug lifecycle – a focus on benefits and risks. *Expert Opin Drug Saf* 2021 Jul 15. Online ahead of print.

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Lourens T Bloem, Richard De Abreu Lourenço, Melvin Chin, Brett Ly, Marion Haas. Factors impacting treatment choice in the first-line treatment of colorectal cancer. *Oncol Ther* 2016;4:103-116.

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Chiel F Ebbelaar, Anne ML Jansen, **Lourens T Bloem**, Willeke AM Blokx. Genome-wide copy number variations as molecular diagnostic tool for cutaneous intermediate melanocytic lesions: a systematic review and individual patient data meta-analysis. *Virchows Arch* 2021 Apr 13. Online ahead of print.

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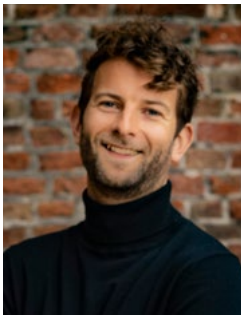

Lourens (Leeuwarden, 1989) obtained his PharmD in 2016 at Utrecht University, the Netherlands. As part of his studies, he undertook an 8-month research placement in Sydney, Australia, at the Centre for Health Economics Research and Evaluation of the University of Technology Sydney and in collaboration with the University of New South Wales. Thereafter, he enrolled in the Regulatory Science collaboration programme of the Utrecht Institute for Pharmaceutical Sciences (UIPS) and the Dutch Medicines Evaluation Board (MEB).

As a PhD candidate at UIPS' division of Pharmacoepidemiology and Clinical Pharmacology (2016-2021), Lourens strived to perform his studies at the interface of the division's three focus areas: policy, pharmacoepidemiological methods and clinical practice. In addition, he was chair of UIPS' first cohort of Fellows of the Future Medicines Graduate Programme (2016-2018), which was supported by the Netherlands Organisation for Scientific Research. Furthermore, he was enrolled in the MSc Epidemiology Postgraduate programme and the University Teaching Qualification programme.

Over the years, Lourens enjoyed teaching graduate and postgraduate courses in medicines' regulation, pharmacoepidemiology, oncology and psychopharmacology, as well as supervising student research projects. In 2017, he became a member of the International Society for Pharmacoepidemiology. He regularly presented his research at the society's annual conference and became a member of the society's Real World Evidence Task Force.

As a pharmacovigilance assessor at the MEB (2016-2020), Lourens was involved in the assessment of safety data and risk management plans for medicines authorised on the national and European level, particularly in the field of psychiatry, neurology and the musculo-skeletal system. He was also a member of the "Commissie Praktijk", a committee through which the MEB liaises with clinical practice.

After leaving the MEB, Lourens combined his PhD studies with a role as programme manager Drug Regulatory Science for the Utrecht Science Park, thereby drawing on his specific research experience and work experience as a regulator.

Next to his PhD studies and other work, Lourens is a sports, music and travel enthusiast.