Improving the EU system for the marketing authorisation of medicines

Learning from regulatory practice

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** The views expressed in this report are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the CBG-MEB.*

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AESGP	Association of the European Self-Medication Industry
ATC	Anatomical therapeutic chemical
BE	Bioequivalence
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMA	Conditional marketing authorisation
CMDh	Co-ordination group for Mutual Recognition and Decentralised procedures - human
CMS	Concerned Member State
CNS	Central nervous system
CRO	Contract research organization
DCP	Decentralised procedure
DHPC	Direct healthcare professional communication
EC	European Commission
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPAR	European public assessment report
EU	European Union
EVMPD	EudraVigilance Medicinal Product Dictionary
FDA	Food and Drug Administration
FTE	Full-time equivalent
GCP	Good clinical practice
GMP	Good manufacturing practice
GRevP	Good review practice
GSL	General sales list
GVP	Good pharmacovigilance practices
HIV	Human immunodeficiency virus
HTA	Health technology assessment
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IDMP	Identification of Medicinal Products
IQR	Interquartile range
IRC	Independent Review Committee
ISO	International Organization for Standardization
MA	Marketing authorisation
MAA	Marketing authorisation application
MAH	Market authorisation holder
MAPPs	Medicines Adaptive Pathways to Patients
MRP	Mutual recognition procedure
MS	Member State
NAS	New active substance
NCE	New chemical entity
NGO	Non-governmental organisation
OTC	Over-the-counter

PASS	Post-authorisation safety study
PBRER	Periodic benefit-risk evaluation report
PD	Pharmacodynamic
PDCO	Paediatric Committee
PhV	Pharmacovigilance
PIL	Patient information leaflet
PIP	Paediatric investigation plan
PK	Pharmacokinetic
PL	Package leaflet
POM	Pharmacy-only medicines
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance system master file
PSRPH	Potential serious risk to public health
PSUR	Periodic safety update report
QALY	Quality-adjusted life year
QPPV	Qualified person responsible for pharmacovigilance
RCT	Randomised controlled trial
R&D	Research and development
REMS	Risk Evaluation and Mitigation Strategies
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment)
RMP	Risk-management plan
RMS	Reference Member State
RR	Relative risk
SAG-O	Scientific Advisory Group on Oncology
SC	Steering Committee
SME	Small and medium-sized enterprise
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SPC	Supplementary protection certificate
TE	Therapeutic equivalence
UU	Utrecht University

PREFACE

The regulatory framework for medicines in the European Union (EU) is evolving constantly. The system changes in order to adapt to scientific developments; address medical needs; bring medicines to patients earlier (and with better evidence); and also to keep prescribing information up to date.

A number of pilots and experiments are underway to strengthen the link between marketing authorisation (MA) and health technology assessment (HTA), and to explore how evidence generated during development can better reflect 'real world' safety and effectiveness. The effects of system changes need to be studied in order to see if public health objectives are being met, and to assess whether or not society is getting 'value for money'. When such research is not undertaken, important opportunities for learning may not be captured.

Escher is the platform for regulatory innovation of TI Pharma, the independent research enabler based in the Netherlands. Its ambition is to help extract important learnings, capitalising on a strong track record of studying important regulatory issues and providing input for dialogue and discussion.

This report is built around a number of case studies, the selection of which was based on the experiences of a group of 'users' of the regulatory system: pharmaceutical companies. In the case studies we discuss a variety of topics in detail such as pharmacovigilance, paediatric investigation plans and the conditional marketing authorisation pathway. The intention is not, however, to provide a holistic overview of the regulatory system. Emphasis is placed on what can be done better, rather than on what is already good. This is a conscious choice: Escher holds the view that the European regulatory system is already effective in performing its key functions. At the same time we see an opportunity to build on solid foundations and to make progress within the current system.

Escher seeks to foster an environment for open dialogue and discussion. During the current project, which was financially supported by two umbrella organisations, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Association of the European Self-Medication Industry (AESGP), we were able to work with various stakeholders on the private and public side, using a variety of data sources and making the most of experiences within different organisations.

An ability to work independently in this environment is ensured by the Escher governance structure. The Escher Steering Committee (SC) is the highest decision-making body, supported by the Independent Review Committee (IRC) as an advisory board. This arrangement aims to provide an independent and transparent operating framework (see Annex 1 & 2). With a strong record in the field of regulatory science, Utrecht University (UU) in the Netherlands was Escher's academic research partner, conducting a number of analyses for this project. All text in the report is solely the responsibility of the authors mentioned.

We hope that the work presented in this report will form a basis for future policy discussions and research – and we are poised to take on new projects and challenges!

André W. Broekmans MD PhD
TI Pharma
Chair Escher Steering Committee

SUMMARY

Introduction, survey of companies' perspectives, and case study selection (Chapter 1 & 2)

The ongoing evolution of the EU regulatory system for medicines means that continuous reflection is needed on whether or not the system is achieving its aims in the best way possible. This report has two objectives:

- To provide a scientific analysis of topics in a number of key areas in the regulatory system;
- To reflect on how the regulatory system can be improved and benefit from further research.

After a short introduction in Chapter 1, the report continues with the description of a survey on the perspectives of pharmaceutical companies regarding the regulatory system (Chapter 2). This survey formed the basis for selecting a number of areas for further investigation through case studies (Chapter 3). Chapter 4 and 5 subsequently provide a broader reflection on two crosscutting themes, and the final Chapter (6) provides a general discussion and recommendations.

A survey among 47 EFPIA and AESGP companies (response rate 69.6%) identified 'areas in high need of improvement' within the regulatory system. The top 12 areas mentioned were paediatric medicines; variations; areas in the pharmacovigilance phase; costs/funding of the system; Article 46 paediatric studies; transparency and accountability; harmonisation; new regulatory pathways; conditional marketing authorisation; accelerated assessment; risk-management plans; and the mutual recognition procedure.

Additional general themes in the survey responses were the perception of an unnecessary regulatory burden (from a public health perspective) and the fear that this burden is increasing. Other problem areas mentioned were the balance between flexibility and (un)-certainty in the system; underutilisation of regulations; timelines; (lack of) harmonisation; the link between marketing authorisation and health technology assessment; and interactions between companies and authorities.

Within the top 12 areas, five topics were selected for case studies:

1. Experiences with the mutual recognition and decentralised procedures;
2. Use of the conditional marketing authorisation pathway for oncology medicines;
3. Timing of submission, development status, and outcomes of paediatric investigation plans;
4. Pharmaceutical industry resources required for compliance with European pharmacovigilance requirements;
5. The cost-effectiveness of post-authorisation safety studies for new active substances in Europe.

Case studies on high priority areas (Chapter 3)

1. Experiences with the mutual recognition and decentralised procedures (MRP/DCP)

This study quantified negative outcomes of the MRP/DCP procedure and identified determinants for those outcomes. Furthermore, the duration of the granting of a marketing authorisation (MA) at the national level of MRP/DCP procedures was investigated.

A total of 10,392 MRP/DCP procedures were finalized between January 2006 and December (2822 MRP and 7570 DCP). 377 (3.6%) procedures resulted in a CMDh referral procedure. Of these referrals, 70 (0.7%) had an overall negative outcome, and MRP procedures were 3.8 times more likely to result in a negative referral outcome than DCP procedures. 'Potential serious risk to public health' (PSRPH) objections were mostly related to the design and outcomes of the clinical studies in the dossier, whereas procedural discussions on authorised indications rarely led to negative opinions. A limited number of MRP/DCP procedures resulted in a negative outcome after a CMDh referral procedure, although other negative outcomes such as withdrawals in one or more Member States, occurred more frequently. Considerable differences between Member States were observed with respect to the time to national approval after a positively concluded MRP/DCP procedure. The underlying reasons for this require further study, however the results show room for improvement of the national phase.

2. Use of the conditional marketing authorisation (CMA) pathway for oncology medicines

This study investigated how the conditional marketing authorisation procedure was used by companies and regulators between 2006 and 2013 for oncology products. It analysed (1) how CMA compared with standard MA regarding evidence characteristics, procedural characteristics and timelines; and (2) how CMA was applied during individual MA procedures. A mix of quantitative and qualitative research methods was used.

The study found that compared with standard MA for oncology medicines, CMA is granted on the base of less comprehensive data, but assessment timelines for CMA were longer as compared with standard MA. A lack of sufficient incentives for companies to request CMA upfront is probably responsible for this. The study observed that for a substantial number of oncology products, regulators initially use standard evaluation criteria for data assessment, while CMA is only discussed after consensus is reached that standard MA cannot be granted. CMA is then perceived as a 'rescue' option by regulators and companies, rather than as a prospectively planned pathway to provide early access.

3. Timing of submission, development status, and outcomes of paediatric investigation plans (PIPs)

The aim of this case study was first to identify factors that contribute to the early availability of information on the use of medicines in children (i.e. the completion of at least one paediatric study as measured by Article 46 procedures); and second to provide insight into the number of downstream modifications and the number of PIPs for which the development plan was terminated following submission of the PIP.

Data for the cohort of all PIPs and waivers from 2007 until 2010 were collected from the EMA website, and a survey among pharmaceutical companies was performed to collect additional data regarding the status of the PIPs in the cohort. The results indicated that PIPs with downstream modifications were more likely to have completed at least one of the paediatric studies in the PIP (i.e. Article 46 outcomes), suggesting that agreed PIPs change more often once applicants initiate paediatric

studies. Furthermore, the study found that 21% of all agreed PIPs were subsequently abandoned because of discontinuation of the adult development program for the product. Further research needs to determine the exact level of redundancy, and discussions are required on acceptable levels for stakeholders. The results of this study indicate that there is room to increase the efficiency of the Paediatrics Regulation without negative consequences for public health and paediatric use. Policy options include differential requirements for new active substances (Article 7 products) versus products already marketed (Article 8 products); a staggered approach for PIP submissions; and adapting the level of detail in PIPs submitted early in development.

4. Pharmaceutical industry resources required for compliance with European pharmacovigilance requirements

This case study sought to measure the company resources needed for pharmacovigilance activities, and to assess the impact of the new pharmacovigilance legislation for marketing authorisation holders (MAHs) in the EU by means of a survey among all EFPIA and AESGP members.

19 pharmaceutical companies provided data, representing >50% of the entire European industry in terms of 2013 sales. The results (response rate 35%) indicated that one year after the legislation came into force, 95% of respondents experienced an increase in workload. Furthermore, the results showed both foreseen changes in pharmacovigilance activities, such as an increase in the number of risk-management plans (RMPs) submitted annually per company, and unforeseen changes in pharmacovigilance activities, such as an increase in the number of hours spent per periodic safety update report (PSUR) (now called a periodic benefit-risk evaluation report [PBRER]). Although companies may become more efficient in adapting to new requirements in the coming years, monitoring company activities and the impact on workload of the new legislation is warranted.

5. The cost-effectiveness of post-authorisation safety studies (PASSs) for new active substances in Europe

The aim of this case study was to assess the cost-effectiveness of PASSs that were requested at market entry for centrally approved new active substances (NASs) that received a positive opinion in 2007.

Two regulatory scenarios were compared for the cohort of 47 NASs that were approved in 2007. For 22 of these products, at least one PASS was requested at market entry. A hypothetical regulatory scenario was created that assumed that for all 47 products, only routine pharmacovigilance activities had been required, and none of the PASSs had been conducted. Subsequently, all safety-related changes to the summary of product characteristics (SmPC) were assessed for the cohort of products to identify whether or not a requested PASS resulted in an SmPC change. The costs of all PASSs were estimated using company data. Results indicated that after six years of follow-up, 52% of all requested PASSs resulted in a change to the product's SmPC, which represented 9.5% of all post-marketing safety-related label changes. Total costs of conducting the 31 PASSs were estimated to be in the range of €84 and €126 million, resulting in an incremental cost-effectiveness ratio of €6.5 million to €18.0 million per additional SmPC change. Although the majority of requested PASSs in 2007 resulted in a change to the product's label, PASSs that are specifically requested by regulatory authorities are not the main source of new safety information listed in the SmPC, but the costs of conducting these studies appear substantial. Ways to increase the efficiency of PASSs, as well as the societal value of pharmacovigilance activities, should be explored.

Dealing with regulatory uncertainty around marketing authorisation (Chapter 4)

Regulators need a certain amount of flexibility to deal with a wide variety of products, but this can lead to uncertainty about which standards and procedures will be applied to products in development. This 'regulatory uncertainty' may influence the behaviour of both companies and regulators in unintended ways.

Examples of sources of regulatory uncertainty are:

- The interpretation of key terms in the regulations, e.g. interpretation of the benefit-risk balance of products in CMA or 'potential serious risk to public health (PSRPH)' in MRP/DCP procedures;
- The absence of specific guidance, e.g. for CMA compared with standard MA;
- Timelines of procedures, e.g. the timelines of the national phase of MRP/DCP;
- The consequences of choosing between alternative strategies, e.g. choosing between the centralised procedure and MRP/DCP route, or the standard centralised procedure and the CMA.

To reduce regulatory uncertainty, better mutual understanding on how current regulation is applied is needed and two measures are key. First, constructive and timely dialogue between regulators and companies is needed to increase mutual understanding of the content and format of development plans and MAAs from early phases of development onwards. Second, further efforts to increase consistency in decision-making should be encouraged and embedded in broader efforts to monitor and evaluate regulatory instruments.

The evaluation of regulatory instruments (Chapter 5)

The regulatory system for medicines consists of a large number of individual regulatory instruments such as legislations, directives, guidelines and notes for guidance. In this chapter, a framework is proposed for evaluating such regulatory instruments. The framework distinguishes the need to assess input, process, output and outcome measures of regulatory instruments. It emphasises the need for systematic measurement of these outcomes, preferably both before the implementation of an instrument and also periodically after implementation. Furthermore, a high-quality evaluation of a regulatory instrument requires that the mechanism responsible for translating regulatory outputs into actual public health effects is clear.

Additional considerations for enabling the systematic performance of regulatory evaluations include the need for a joint stakeholder effort for supporting evaluations and discussing implications; the need to promote data sharing between stakeholders so that evaluations can be performed; reaching consensus on the methodology used for regulatory evaluations; the set-up of an independent platform or environment to conduct such analyses; the conduct of continuous monitoring and timed assessments of regulatory instrument; and a specific focus on the availability of data in the post-marketing space.

Although impact assessments are performed for major regulatory reforms before implementation, they are not always conducted in a systematic manner, nor are the policy consequences of subsequent evaluations always clear. Performing systematic evaluations, including regulatory cost-effectiveness analyses, could help the regulatory system to become more evidence-based, to be clearer about its policy objectives and to increase its efficiency in achieving these objectives.

Concluding remarks and recommendations (Chapter 6)

In conclusion, we highlight three main messages, that emerge from this report:

- Discrepancies between the initial objectives of legislation and the effects of regulatory

instruments in actual practice should be addressed: in several cases, it can be questioned whether or not *a priori* objectives (e.g. around public health) are being achieved and if regulatory instruments are providing 'value for money';

- Learning during implementation of legislation can make regulatory instruments more effective: we can increase the value of regulatory instruments via better or more detailed written guidance and by optimising the interactions between regulators and companies;
- Regulatory science studies can help to assess the real-world outcomes of the system and to identify opportunities for improvement: insight into the use and performance of the regulatory system is needed, through performing monitoring, analysis and evidence-based assessments.

1 INTRODUCTION

Jean Philippe de Jong, Pieter Stolk

1.1 Background

In 2010, an Ernst & Young evaluation, commissioned by DG Enterprise and Industry, confirmed the overall operational effectiveness of the EU regulatory system for the marketing authorisation of medicines in Europe. Moreover, external and internal stakeholders recognise the central agency of this system, the European Medicines Agency (EMA), as delivering 'complete, clear and highly valued opinions within regulatory tight deadlines' (Ernst & Young 2010). However, the EMA has also had to cope with an increasing workload and various parts of the regulatory system have seen considerable changes over the last decade: new regulatory pathways such as conditional approval and accelerated assessment have been developed; a more life-cycle based approach has been facilitated by intensifying post-approval evidence generation; and a closer collaboration between HTA bodies and regulators in early dialogue with applicants is being explored. Furthermore, a revision of the pharmacovigilance processes in the EU has provided a set of new tools and working practises following the introduction of new legislation in July 2012. More recently, additional reforms have been proposed under the heading of 'adaptive licensing' or 'Medicines Adaptive Pathways to Patients' (MAPPs). Such adaptive strategies propose an iterative approach to evidence generation and evaluation in order to facilitate earlier access to needed medicines. These abovementioned changes underscore the ambition of the EMA and its European network to learn and adapt to new challenges.

All these changes to different parts of the regulatory system are directed at finding a better way to balance its two main goals: on the one hand, to ensure timely patient access to medicines that address healthcare needs and; on the other hand, to ensure that medicines are marketed only when there is sufficient confidence about a positive benefit-risk balance. Therefore, these changes demand a continuous reflection on whether or not the regulatory system is achieving its intended aims. Questions that could be raised in this respect are numerous. For example, do we know what the added value is of recent changes? What can we learn from the introduction of these changes and how can we make sure that new ones are implemented in an effective manner? To be able to answer these kind of questions, more insight into the use and performance of the regulatory system is needed through performing monitoring, analysis and evidence-based assessments. Via this report, Escher wants to contribute to providing this insight.

1.2 Aim and focus of this project

The project described in this report had two objectives:

- To provide a scientific analysis of topics in a number of key areas in the regulatory system;
- To reflect on how the regulatory system can benefit from further research.

The report focuses on the EU regulatory system. In this context, the 'regulatory system' consists of the marketing authorisation procedures itself, and also related regulation on research and development and post-marketing activities. We take 'regulatory system' to include not only the legislative framework but also 'soft' regulation such as scientific guidelines and the application of requirements through procedures, work processes and communication between companies and regulators. The words 'regulations', 'legislative/regulatory framework', and 'legislation' are used to encompass both EU level legislation and guidance (Directives and Regulations and Guidelines) and national legislation.

1.3 Approach of the project and this report

For this project, we started with a survey on the perspectives of two groups of users of the regulatory system: pharmaceutical companies that were members of EFPIA and AESGP. We asked these companies what they perceived as areas in high need of improvement. The survey and its results are described in Chapter 2. On the basis of the results of the survey we selected several key areas for further investigation (Chapter 2.4). In Chapter 3, these areas form the basis for five case studies: the mutual recognition and decentralised procedures (MRP/DCP); the conditional marketing authorisation (CMA) pathway; paediatric investigation plans (PIPs); resources required for compliance with European pharmacovigilance (PhV) legislation; and the cost-effectiveness of post-authorisation safety studies (PASSs).

Chapter 4 provides a broader reflection on the crosscutting theme of regulatory uncertainty, while Chapter 5 reflects on how the effects of various parts of the regulatory system can be measured and how regulatory instruments can be evaluated. Both Chapters 4 and 5 build on insights from the survey and the case studies. Chapter 6 provides a general discussion of the various studies and analyses, recommendations for how to improve the current regulatory system and suggestions for further study.

Figure 1, below, gives a depiction of the structure of the report. The Annexes to this report give additional background information on the overall project and the results presented in individual chapters.

For the work described in this report, we made use of scientific publications, grey literature, interviews, data sets from companies and regulatory authorities and a broad stakeholder workshop (see Annex 3). A more detailed account of the methodology used in the project and additional analyses will be reported through future journal publications.

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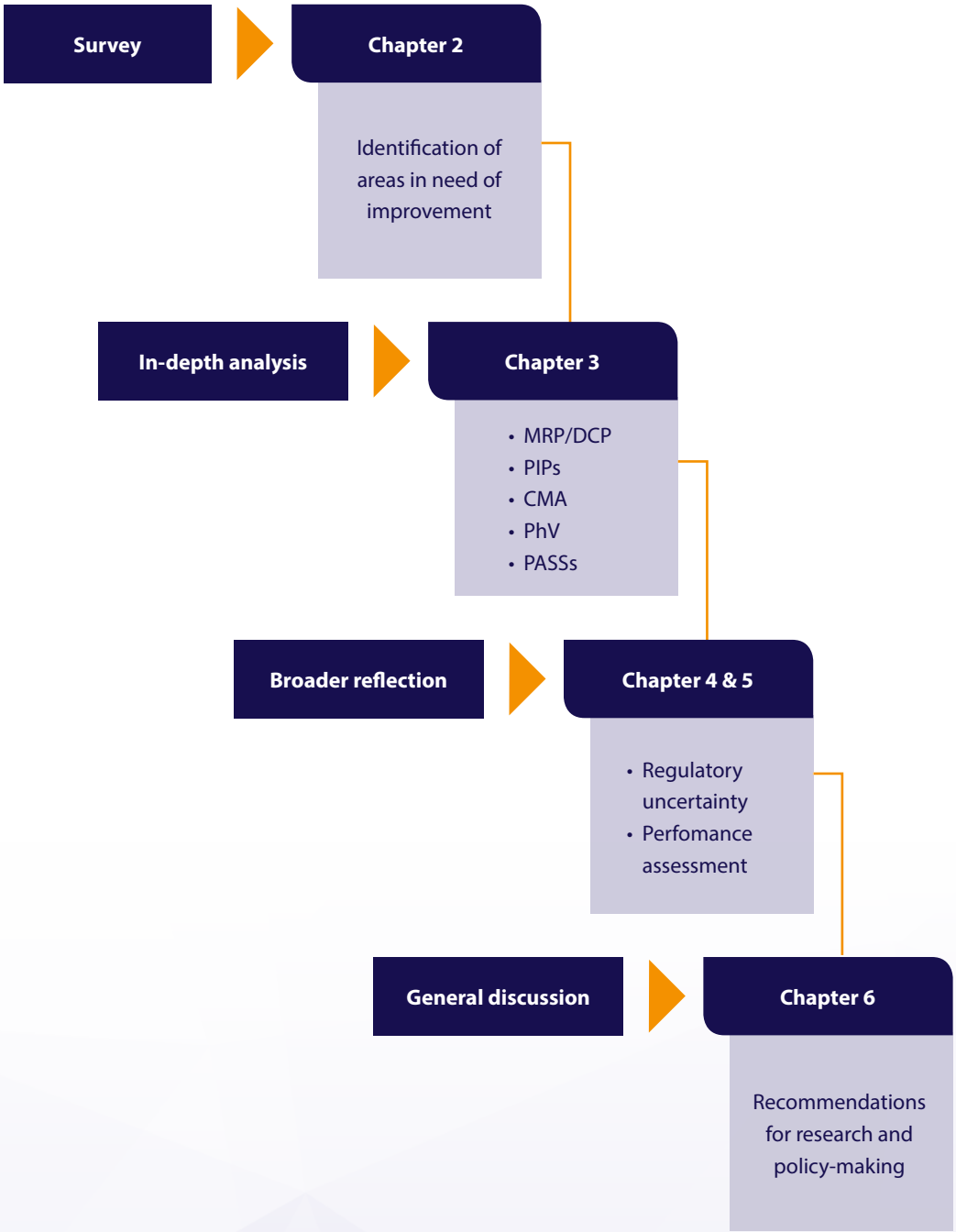
Ernst & Young. 2010. "Evaluation of the European Medicines Agency. Final report to the European Commission". Available from: http://ec.europa.eu/health/files/pharmacos/news/emea_final_report_vfrev2.pdf (last accessed 1 September 2014).

Figure 1: Project approach and structure of the report



2 AN OVERVIEW OF REGULATORY AREAS IN NEED OF IMPROVEMENT: A SURVEY OF COMPANIES' PERSPECTIVES

Jean Philippe de Jong, Pieter Stolk

2.1 Introduction

Over the years, many areas of the regulatory system for marketing authorisation have been highlighted as in need of improvement by various stakeholders. For example, the European Medicines Agency Road Map to 2015 highlights several strategic areas where progress is needed, such as the development of medicines in areas of unmet medical need and strengthening the evidence base in the post-authorisation phase (EMA 2010). To acquire an up to date overview of what pharmaceutical companies perceive as high priority areas and to help focus the analyses in this report, we conducted a broad survey of the regulatory landscape in two groups of users of the regulatory system: members of EFPIA and members of AESGP. We asked them what they considered to be areas in high need of improvement, to explain why they did so and to provide examples.

In this chapter we describe our approach (Chapter 2.2) and the results of this broad survey (Chapter 2.3). In Chapter 2.4, we reflect on the results. We also describe how the results of the survey informed the topic selection for five case studies, the results of which are reported in Chapter 3, with two broader reflections in Chapters 4 and Chapter 5.

2.2 Approach of survey

For the design of the survey we consulted the website of the EMA. We extracted the areas from the website's sitemap mentioned under the major subheading 'human regulatory' in order to compile a comprehensive list of regulatory areas (EMA 2014a). We combined detailed subheadings and skipped uninformative subheadings (e.g. ' guidance' or 'Q&A'). The resulting list covered 91 areas subdivided into seven categories: the pre-authorisation phase; the authorisation phase; the pharmacovigilance phase; other (non-pharmacovigilance) areas in the post-authorisation phase; types of products; disease areas; and other cross-cutting areas in the regulatory system (e.g. costs/funding, transparency, and harmonisation). See Annex 4 for the full survey. To ensure that no important areas were missed, we included open comment sections in which we asked for 'other areas' in need of improvement within each of the aforementioned seven categories.

The survey was sent to 56 contacts in 47 large pharmaceutical companies: 32 pharmaceutical companies were members of EFPIA, six of AESGP and nine of both EFPIA and AESGP. These latter nine companies received the survey twice, although through different divisions in the company. EFPIA represents the 33 European national pharmaceutical industry associations as well as 40 major companies. AESGP

represents 2000 companies operating in the consumer healthcare sector in Europe, who are affiliated with AESGP directly or indirectly through the national associations. The AESGP constituency includes multinational companies as well as European small and medium-sized enterprises (SMEs). Together, these two organisations represent a significant part of the global pharmaceutical industry that is active in Europe. The primary contact persons for the survey were the companies' representatives in the regulatory affairs organisations at either AESGP or EFPIA; in many companies, other people were also involved in filling out the survey. We used a web-based tool (Survey Monkey) to collect responses. The survey was sent out on 23 October 2013 and respondents were requested to respond within four weeks.

We asked respondents to grade each of the 91 areas on a four-point scale according to what they believed to be the need for improvement in that area, from '1: no need for improvement', to '4: high need for improvement'. Respondents could also leave questions blank. We calculated the number of respondents that graded each area and the mean score of their responses. We ranked the areas according to the mean score, resulting in a ranked list of prioritised areas.

In cases where a respondent graded an area with a '3' or '4' (a high need for improvement), we asked them to explain the perceived need for improvement by commenting in a few sentences. We performed a qualitative analysis on these comments in two steps.

In the first step, we summarised the comments made on each of the top 12 areas in our rank list of prioritised areas (Table 2). We included in our summary only comments that were made by at least two of the respondents. We interpreted comments as little as possible and mainly used direct quotations for writing the summaries (Annex 6).

In the second step, we searched for interconnecting themes amongst these 12 summaries. We coded the material using an iterative process, working through the material in several rounds using a list of emerging interconnecting themes. This list was altered and expanded in each round and we stopped when the list provided a comprehensive account of the material (i.e. saturation).

At the end of the survey we asked respondents to submit up to five detailed examples of situations in which they experienced that the system could be improved. We provided a list of questions to help respondents generate a comprehensive account of these issues (Annex 4). These examples were used as background material to provide context for the design of case studies and the analyses in Chapter 4 and Chapter 5.

2.3 Results of survey

Almost 70% of the companies that were invited to participate in the survey responded (Table 1). A list of respondents can be found in Annex 7. All companies were large, internationally operating pharmaceutical companies with a broad product portfolio.

Prioritised list of regulatory areas in need of improvement

Table 2 shows the top 12 of 91 regulatory areas, based on average scores, ranked according to the perceived need for improvement. The complete list can be found in Annex 5. There is considerable variation in how respondents graded areas: 'paediatric medicines' received the highest mean score (3.44 on a scale from 1 to 4), whereas the lowest scoring area is 'SME guidance' (1.29 on a scale from 1 to 4). Not every respondent graded each area on the need for improvement: the number of respondents that scored an area ranged from 39 (i.e. all respondents) for 'periodic safety update reports', to 4 for 'herbal medicinal products'.

Table 1: Survey response rate

	Number	Percentage
Response rate total	39/56	69.6%
Response rate EFPIA contacts	28/41	68.3%
Response rate AESGP contacts	11/15	73.3%

Comments on high priority areas

Respondents provided 1138 comments on the regulatory areas that they perceived to be in high need of improvement. Comments vary from a single keyword to several paragraphs. Summaries of the top 12 areas can be found in Annex 6.

Readers are encouraged to take a look at these summaries as they provide insight in how companies currently experience the regulatory system. A more in-depth analysis of the material also reveals themes that surface in many of these regulatory areas, i.e. there are interconnecting themes that link comments made in different areas. One recurrent theme in respondents' comments was that the system results, in some respects, in an unnecessary burden on companies, in light of a perceived limited contribution to public health. Moreover, respondents noted that this burden is increasing. The following areas, amongst others, were cited in this respect: paediatric regulation, variations, new regulatory pathways and the enhanced pharmacovigilance processes including risk-management plans. In many instances, respondents specified this general concern and highlighted two effects: costs for companies, and the effects on public health.

Table 2: Prioritised list of regulatory areas in need of improvement

Rank	Area
1	Paediatric medicines
2	Variations (e.g. type IA/IB/II/unforeseen (article 5) variations
3	Other areas in the pharmacovigilance phase †
4	Costs/funding of the system (including fees)
5	Article 46 paediatric study
6	Transparency and accountability (e.g. confidentiality, transparency measures, release of trial data, data exclusivity)
7	Harmonisation (e.g. between Member States, between EU and other regions)
8	New regulatory pathways (e.g. adaptive licensing)
9	Conditional marketing authorisation
10	Accelerated assessment
11	Risk-management plans
12	Mutual recognition procedure

† *'Other areas in the pharmacovigilance phase' is a residual category. See Annex 4 for the areas related to pharmacovigilance that were listed.*

- Costs for companies

  In several areas, respondents expressed concerns about the costs of regulation. Examples were the resource investments for paediatric investigation plans and the enhanced vigilance processes, including risk-management plans; the high costs for the mutual recognition/decentralised procedure in some countries; and the recent increase in fees for variations and pharmacovigilance, which are considered to be disproportionate by some respondents.

- Effects on public health

  Some respondents felt that the requirements of certain instruments have a limited impact on public health. For instance, respondents believed that the Paediatric Regulation is not bringing more medicines to children, and that some of the risk-management plan requirements have no effect on safety. Unfortunately, respondents did not further specify these assertions with concrete examples. There were also areas where respondents believed that benefits for public health are attainable but currently not accomplished to their full extent. For example, there was a feeling that the conditional marketing authorisation pathway and the accelerated assessment procedure are used suboptimally.

Besides highlighting the ways in which the regulatory system affects companies, respondents also reported a number of underlying problems. These problems can be related to the legislation itself or to the implementation of the legislation.

An example of the former is that respondents believed that the conditional marketing authorisation pathway excludes subsequent use for additional, new indications. Another example is that some respondents believed that proposed adaptive pathways would require changes to the legal framework, although other respondents contested this.

In most of the areas however, respondents believed that the legislation itself is acceptable, but implementation of the legislation could be improved. Respondents expressed concerns about rigid interpretation and stringent implementation of the legislative requirements in the areas of paediatrics, variations, risk-management plans and conditional marketing authorisation. As an example of the latter, respondents believed that the conditional marketing authorisation pathway is hindered by the fact that the criterion for a positive benefit-risk is interpreted too strictly, resulting in a requirement for too high a degree of certainty about the benefit-risk profile of a product. Furthermore, respondents believed that the application of some procedures is inadequate, for example the practical execution of accelerated assessment and the national phase of mutual recognition procedures.

Respondents also mentioned a number of general problem areas: the balance between flexibility and (un)certainty in the system; underutilisation of regulation; timelines; harmonisation; the link with HTA; and the interactions with authorities. These interconnecting themes are described below.

- Flexibility and (un)certainty

  A theme that emerged from respondents' comments is the need for a balance between flexibility and certainty in how legislation is implemented. In some areas, respondents stressed the need for a more flexible application of legislation and requirements. Examples of this include requirements for paediatric studies; the way variations can be grouped; the use of the conditional marketing authorisation pathway; and timelines in the accelerated assessment procedure. However, in other areas respondents desired less flexibility and more predictability on the

outcome, for instance by asking for more detailed guidance and more specific requirements. Areas where respondents would prefer more detailed guidance included the classification of variations, and risk-management plans. Furthermore, respondents thought that more specificity could be beneficial in the following areas: a better differentiation between fees for innovative products, well-established products and orphan products; and for when deciding when and how to disclose patient data.

- Underutilisation

  Furthermore, respondents believed that some regulatory instruments are being underused, both from the side of the regulatory authorities and from the side of companies. Examples of this are the conditional marketing authorisation pathway and the accelerated assessment procedure, which could both be used more often according to respondents' experiences.

- Timelines

  Timelines could be improved in several ways according to respondents. Assessment reports are, for instance, not always provided in due time by the authorities (for example in the MRP, the accelerated approval procedure, and with respect to risk-management plans and variations). In some cases respondents considered the requested timelines inappropriate, e.g. with respect to the early submission of paediatric investigation plans.

- Harmonisation

  Harmonisation is another theme that, according to respondents, underlies much of the regulatory complexity and burden. Respondents believed, for instance, that better alignment with the US is needed for paediatric investigation plans; the publication of clinical trial data; good manufacturing practice; and the introduction of 'adaptive' pathways. Respondents also believed that harmonisation could be improved between Member State agencies, for example with regard to the classification and timelines of variations; the timelines of the MRP/DCP; the legal status of medicines; and dossier requirements.

- Linkage with health technology assessment

  Another area where respondents believed improvements are needed is the linkage between marketing authorisation and HTA/reimbursement. For instance, respondents thought that a better alignment is needed between approval and market access procedures in order for the conditional marketing authorisation procedure to become a success, something that is thought to be even more important for future adaptive licensing developments.

- Interaction between companies and authorities

  A final theme is that respondents believed that the interaction with agencies could be improved. They mentioned the need for more open discussions regarding requests for conditional marketing authorisation; more support during accelerated assessment procedures; and a dialogue with payers early in development. Some respondents also believed that the European Commission consultation process could be strengthened in order to involve companies in a more constructive way.

Alongside comments submitted by respondents that specified the need for improvement in high priority areas, 23 respondents also submitted in total 60 detailed examples of situations in which they experienced that the system could be improved. A number of topics

were frequently mentioned in these examples: paediatrics regulation/PIPs; cost/funding of the system; variations; the mutual recognition procedure/decentralised procedure; and pharmacovigilance. Annex 8 contains the complete list of examples provided.

2.4 Reflection and topic selection for further study

A reflection now follows on the results of the survey, and how these results guided topic selection for further in-depth case studies described in Chapter 3.

Prioritised list of regulatory areas in need of improvement

Due to the approach chosen for the survey, the results focused mainly on potential negative aspects of the regulatory system. Therefore, survey results do not provide a balanced evaluation of the merits of the current system, but should rather be seen as a list of bottlenecks from the perspective of companies. In this context, the top 12 areas that were seen as needing improvement are listed in Table 2.

The relevance of this prioritised list is supported by the fact that all top 12 areas are also very much at the forefront in current discussions between companies and regulators. The merits of recent changes to the paediatrics regulation and the variations regulations are, for instance, under discussion between EFPIA and EMA (EMA 2011; EFPIA/EBE/EVM 2013; EFPIA 2014), and the topic of transparency has been extensively discussed between companies, regulatory authorities and public stakeholders, resulting in new EMA policies, to be published in October 2014. Also, the implications and practical implementation of new pharmacovigilance legislation, including risk-management plans, play an important role in discussions as first experiences with the new legislation are shared and evaluated. Furthermore, the topics of system cost (including fees) and the need for harmonised (application of) regulation have been part of discussions about the system for many years, both within the EU and between different regions. Finally, although the topics of conditional marketing authorisation and accelerated assessment are less visible in current debates as standalone topics, they are an important part of discussions about new 'adaptive' pathways and 'Medicine's Adaptive Pathways to Patients' (De Jong et al. 2013; Eichler et al. 2012; EMA 2014b).

The prioritised list of regulatory areas has several limitations. We have surveyed large pharmaceutical companies through EFPIA and AESGP and the results do therefore not include the perspectives of generic companies and smaller (biotech) companies. This is illustrated by the fact that SME guidance is the lowest scoring area in our survey. This low score is probably more related to the fact that we did not specifically target SMEs, than that there is no need for improvement in this area (Putzeist et al. 2011). Moreover, future studies should look at whether the views of healthcare providers, regulators and patients are in concordance with the views expressed by companies. Another point is that respondents could have focused on recently encountered problems, rather than on the most important problems from a systems perspective. For example, the areas that have recently been subject to change, such as paediatrics, variations and transparency, all score highly.

Comments on high priority areas

Respondents provided many comments in order to explain the need for improvement in specific regulatory areas. Our summaries of the comments related to the top 12 areas can be found in Annex 6. In order to appraise these summaries some considerations should be kept in mind.

The survey specifically asked respondents to comment on areas that were in need of improvement: they were not asked to provide a balanced view of areas, highlighting both positives and negatives. As a consequence, the summaries focus on bottlenecks, not on the many areas of the system that are seen as unproblematic and well-functioning. In addition, the summaries presented here express only the views of respondents, and we did not perform a factual check of their comments. Another consideration is that comments were made in the period 23 October, 2013 - 20 November, 2013, and some issues mentioned have undergone major changes since then, such as clinical data transparency on which a new policy is about to be finalised.

Furthermore, the nature of our qualitative analysis is that it cannot be ascertained to what extent the findings apply to how companies experience the system. For example, we cannot indicate what percentage of companies believes that the interaction between stakeholders is suboptimal. Quantitative methods could be used to further substantiate our findings. Finally, because of the broad nature of our approach, the survey did not capture information of sufficient detail, or breadth of coverage, to provide, on its own, adequate insight into the underlying problems or to guide future policy. More in-depth investigations are needed for this.

With the above considerations in mind, we are nevertheless confident that our findings provide a valuable overview of which areas in the regulatory system are in need of improvement according to large pharmaceutical companies. We believe that having insight into the perspectives of companies is highly relevant to other stakeholders, such as regulators and policy makers, even in areas where direct or immediate action may not possible or desirable. Understanding how companies experience the regulatory system can support mutual understanding and help guide further study of the regulatory system.

Topic selection for further study

The second goal of the survey was to help select a number of topics for further analysis in case studies (Chapter 3) and for broader reflection (Chapters 4 and 5). The selection of these topics focused on the top 12 areas as prioritised by respondents and on the comments made on those areas.

The research team made a number of proposals for detailed case studies to the project's Steering Committee. The research proposals were based on an analysis of comments made by respondents; on current gaps in the scientific literature; and on an assessment by the research team of the feasibility of performing a case study in this area. The proposals for case studies focused in on specific issues within the top 12 areas.

The Steering Committee selected proposals for case studies based on two criteria: (1) the feasibility of generating objective information on a topic in terms of required resources, acceptable timelines and accessibility of data; (2) the likelihood that new evidence would help to inform policy discussions. For example, this led to a decision not to further investigate the topics of variations and transparency within the current project. The rationale for not studying transparency was the upcoming new EMA policy on transparency, which would make a study of the current ('old') situation superfluous. And although the topic of variations is very important, and further analysis and evaluation is desirable, we did not conduct a scientific analysis at this time. The reason for this was that changes to regulation through Commission Regulation (EU) No 712/2012 came into force only in August 2013. This would make an assessment at a later date more appropriate. Moreover, the issues appeared to be more of an administrative nature, and appropriate data

sources (both for centralised and decentralised routes) may be lacking at the moment. Further scientific research on these topics should be undertaken when there is sufficient data and experience with the regulations and policies.

The following topics were selected for further investigation through case studies:

- Experiences with the mutual recognition and decentralised procedures;
- Use of the conditional marketing authorisation pathway for oncology medicines;
- Timing of submission, development status, and outcomes of paediatric investigation plans;
- Pharmaceutical industry resources required for compliance with European pharmacovigilance requirements;
- The cost-effectiveness of post-authorisation safety studies for new active substances in Europe.

These case studies link to several of the top 12 areas: the mutual recognition procedure; conditional marketing authorisation; Article 46 paediatric studies; paediatric medicines; costs/funding of the system; and pharmacovigilance. Together, the case studies provide a mix of more established regulatory pathways/instruments, such as the MRP/DCP and conditional marketing authorisation, and more recent additions to the system, such as PIPs and the revised and expanded (e.g. through PASSs) pharmacovigilance system. The approach and results of the in-depth studies are described in Chapter 3.

In order to select two themes for a broader reflection on the regulatory system in Chapters 4 and 5, we also looked at the survey results, together with the topics that were selected for case studies. Chapter 4 provides a reflection on one of the interconnecting themes that emerged from our analysis of respondents' comments: flexibility and (un)certainty. The analysis there focuses in particular on how stakeholders deal with uncertainties in the use of licensing pathways. In Chapter 5, the authors reflect on two other interlinked themes: the societal costs of regulation and the system's contributions to public health. They do so by focusing on how the performance of various parts of the regulatory system can be measured and on how instruments can be evaluated.

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3 CASE STUDIES ON HIGH PRIORITY AREAS

3.1 Introduction to the case studies

Introduction

This chapter presents five case studies that were conducted by Utrecht University. Study topic selection was based on the survey described in Chapter 2.

The five case studies are as follows:

- Experiences with the mutual recognition and decentralised procedures (Chapter 3.2);
- Use of the conditional marketing authorisation pathway for oncology medicines (Chapter 3.3);
- Timing of submission, development status, and outcomes of paediatric investigation plans (Chapter 3.4);
- Pharmaceutical industry resources required for compliance with European pharmacovigilance requirements (Chapter 3.5);
- The cost-effectiveness of post-authorisation safety studies for new active substances in Europe (Chapter 3.6).

The case studies use different methods, both quantitative and qualitative, selected for their suitability for answering specific research questions. In this report, these methods are presented in an abbreviated form to enhance readability, with full versions of the surveys and other relevant details in separate annexes.

Forthcoming publications in peer-reviewed journals will give a more in-depth exploration of the data.

Data were used from a variety of sources including companies, regulatory agencies and public databases. Furthermore, for several case studies we made use of interviews and expert discussion for study design and interpretation of results.

Our goal when conducting these case studies was not to stipulate policies, but rather to provide input and evidence for discussions along with directions for future research.

3.2 Experiences with the mutual recognition and decentralised procedures

Hans C Ebbers, Joris Langedijk, Marie L De Bruin

Background

A foundation of the EU is the principle of the single market, which allows free movement of goods, services, capital and people between Member States. Following the adoption of Directive 93/39/EEC and Regulation 2309/93, two European routes for authorising medicinal products were created (Council of European Communities 1993a; Council of European Communities 1993b). One is the centralised authorisation procedure, which results in a single marketing authorisation that is valid throughout the EU, and which is mandatory for marketing authorisation applications (MAAs) of most new active substances and all biologicals. The other is the mutual recognition procedure (MRP), through which Member States recognise a pre-existing marketing authorisation granted by another Member State; the Reference Member State (RMS). Since 1 January 1998, the MRP is mandatory for any product to be marketed in multiple Member States, when it is already marketed in the EU (Council of European Communities 1998).

Directive 2004/27/EC, introduced the decentralised procedure (DCP), which can be used to apply for a marketing authorisation in multiple Member States at once (EC 2006). The DCP is also based on recognition by national authorities of a first assessment performed by one RMS, but unlike the MRP there is no pre-existing marketing authorisation in any Member State. For both MRP and DCP procedures, a positive outcome will result in (harmonised) national marketing authorisations in the Member States included in the procedure, granted by the respective national competent authorities.

Despite the aim of a harmonised single market, there are still differences between Member States in the way regulations are applied. During the mutual recognition/decentralised procure (MRP/DCP), Member States can disagree with the assessment of the RMS only on the grounds of a 'potential serious risk to public health' (PSRPH). In these cases, the issue is referred to the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh), through a so-called Article 29(1) procedure. A PSRPH has been defined by the European Commission as a 'situation where there is a significant probability that a serious hazard resulting from a human medicinal product in the context of its proposed use will affect public health' (EC 2006). The CMDh works by finding consensus between the Member States. If it does not find consensus to approve or refuse the marketing authorisation application within 60 days, the case is referred to the Committee for Medicinal Products for Human Use (CHMP) for binding arbitration through an article 29(4) procedure.

The MRP/DCP is a widely used procedure and any differences between Member States may lead to delays in the authorisation of medicines. Differences between Member States are not limited to those occurring during the assessment procedure. Also, on the national level there may be considerable differences between Member States, which can lead to delays in implementing national marketing authorisations after a positively concluded MRP/DCP procedure. Limited data are currently available on the outcomes of MAAs via the MRP/DCP procedure.

Objectives

The primary objective of the study was to quantify negative outcomes of the MRP/DCP procedure and to identify determinants for these negative outcomes, including product characteristics, legal basis and nature of objections raised by Member States. The secondary objective was to gain insight in the duration of the granting of a MA at the national level following a positively concluded MRP/DCP procedure.

Methods

We performed a descriptive analysis to assess the frequency of negative outcomes of the MRP/DCP procedures during the period January 2006 to December 2013. Data were obtained from different sources. The total number of finalised MRP/DCP procedures and all data relating to article 29(1) procedures, including procedure type (i.e. DCP or MRP), legal basis and prescription status were obtained from statistics and reports available from the CMDh website and from public assessment reports (CMDh 2014). Additional data on individual products, including pharmaceutical form, legal status and Anatomical Therapeutic Chemical (ATC) classification were retrieved from the Mutual Recognition Product Index, which is maintained by the Heads of Medicines Agencies (Heads of Medicines Agencies 2014). Article 29(4) arbitration reports were obtained from the European Commission pharmaceuticals community register (EC 2014). Negative outcomes were defined as those procedures not resulting in a marketing authorisation, which could include refusals or withdrawals by the applicant. A scoring system was developed to categorise objections raised during the CMDh procedure; multiple issues were scored as combinations, unless the issues concerned the same category (see Annex 9). Two researchers (HE & JL) independently scored the objections. Consensus was used to resolve disagreement. Our analysis was limited to initial MAAs, renewal procedures and procedures concerning type II variations were excluded.

If a procedure results in a negative opinion of the RMS (in the DCP), or if the application (including national MA) is withdrawn before day 90 of the MRP or day 120 of the DCP procedure, this will not be discussed at the CMDh level and therefore these data are not included in the CMDh website. To supplement the data from publicly available sources, a survey was performed under AESGP and EFPIA members to estimate withdrawals during the early phase of the MRP/DCP procedure.

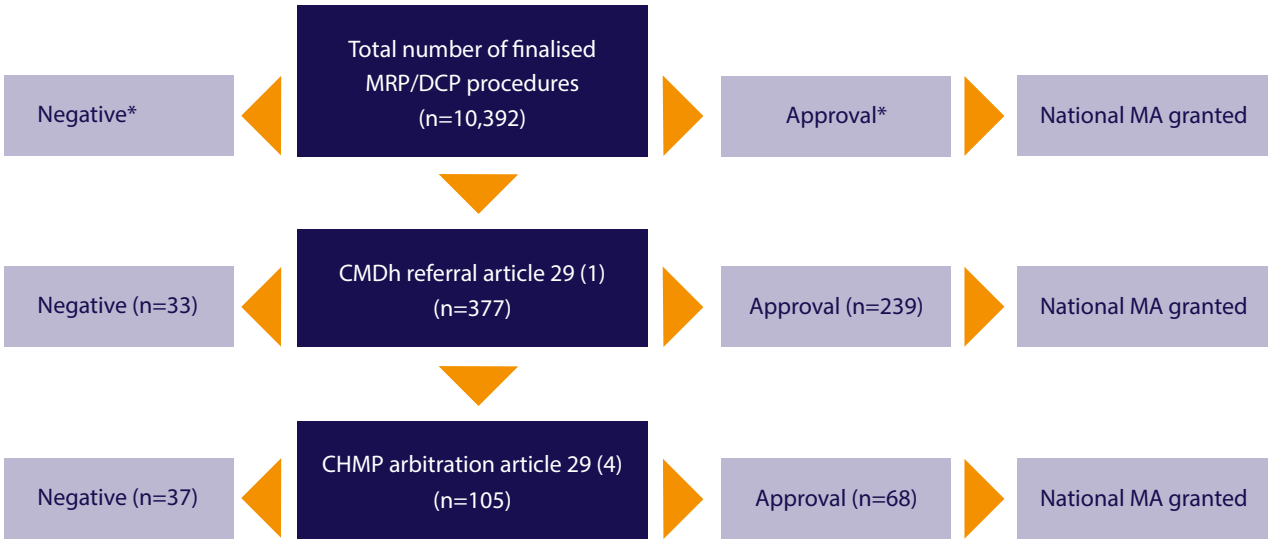
Data relating to the national implementation phase were also obtained from the survey. Respondents were asked to provide data on time taken from positive MRP/DCP opinions to the granting of a national marketing authorisation.

Results

Quantification of negative outcomes

A total of 10,392 MRP/DCP procedures were finalised during the study period (2822 MRP and 7570 DCP procedures): see Figure 1. The majority of the procedures concerned prescription-only products (9890, versus 502 non-prescription products). Generic applications accounted for 78% of the procedures and hybrid procedures for 10%. Full dossiers were provided for 6% of the applications, bibliographic applications accounted for 4% and the remaining 2% were other applications. During this period, 377 (3.6%) CMDh referral procedures were started. Of these, 70 (0.7%) had an overall negative outcome.

Figure 1: Flowchart of MRP/DCP procedures.



** These data are not publicly available.*

In total, 58 companies were invited to take part in the survey, and 16 (28%) responded. Of these, four companies provided two surveys from different departments within the same company, (e.g. consumer healthcare and innovative medicines), resulting in 20 completed surveys. These companies reported a total of 208 MRP/DCP procedures in the study period. Out of all MRP/DCP procedures, 156 (75%) resulted in a MA in all Member States involved in the procedure without a referral or withdrawal. Ten (4.8%) procedures were referred to the CMDh and 34 (16%) procedures were withdrawn in at least one or all Member States (Table 1).

The majority of the withdrawals occurred for reasons other than safety concerns. Five out of 17 (29%) respondents indicated that their company withdrew MAAs (and MAs) in response to safety concerns at least once. These five companies (three non-prescription, one innovative and one generic) reported on a total of seven procedures. Of these, three MAAs were withdrawn in all Member States, while four were withdrawn in one or more Member States (but not all). Three out of 14 respondents (21%) indicated that they decided not to market a product in one or more Member States because of restrictions imposed during the MRP/DCP procedure.

Assessment of determinants for negative outcomes of the MRP/DCP procedure

We analysed the CMDh referral data for determinants of a negative outcome. MRP procedures were 3.8 times more likely to result in a negative referral outcome during or after CMDh referral than DCP procedures (data not shown). No significant differences were observed for (non-) prescription status, authorisation legal basis, biologicals versus small molecules, pharmaceutical form, or anatomic therapeutic class main group. The majority of PSRPH raised to start a CMDh referral were based on clinical concerns (Table 2).

Table 1: Survey results on marketing authorisation applications using MRP/DCP

		Total	Outcome of procedure Positive	Outcome of procedure Negative	CMDh referral
Completed in all MS	combined	174 (84%)	156 (75%)	9 (4%)	9 (4%)
	MRP	86 (41%)	74 (36%)	7 (3%)	5 (2%)
	DCP	88 (42%)	82 (39%)	2 (1%)	4 (2%)
Withdrawn >1 MS †	combined	20 (10%)	19 (9%)	0	1 (<1%)
	MRP	5 (2%)	4 (2%)	0	1 (<1%)
	DCP	15 (7%)	15 (7%)	0	0
Withdrawn in all MS prior to CMDh referral	combined	14 (7%)	0	14 (7%)	0
	MRP*	3 (1%)	0	3 (1%)	0
	DCP	11 (5%)	0	11 (5%)	0
Total number of procedures		**208 (100%)**	**175 (84%)**	**23 (11%)**	**10 (5%)**

MS: Member State

† Outcome in remaining Member States

** Including MA in RMS*

Table 2: Association between categories of 'potential serious risk to public health' leading to CMDh referrals and negative outcomes of CMDh referrals finalised in the period 2006 to 2013.

Main category	Outcome Positive	Outcome Negative	RR (95% CI) for negative outcome
Clinical (equivalence concerns)	43	21	ref
Clinical (study design issues)	43	20	1.0 (0.6-1.6)
Clinical (benefit-risk concerns)	75	8	0.3 (0.1-0.6)
Quality	35	4	0.3 (0.1-0.8)
Regulatory/procedural	38	2	0.2 (0.0-0.6)
Combinations of multiple concerns	73	15	0.5 (0.3-0.9)
TOTAL	**307**	**70**	

RR: relative risk; CI: confidence interval

Referrals were mostly started for concerns regarding the design and outcomes of the clinical studies submitted in the dossier. Discussions around quality and manufacturing issues, or discussions on regulatory and/or procedural issues rarely led to negative outcomes in CMDh referrals.

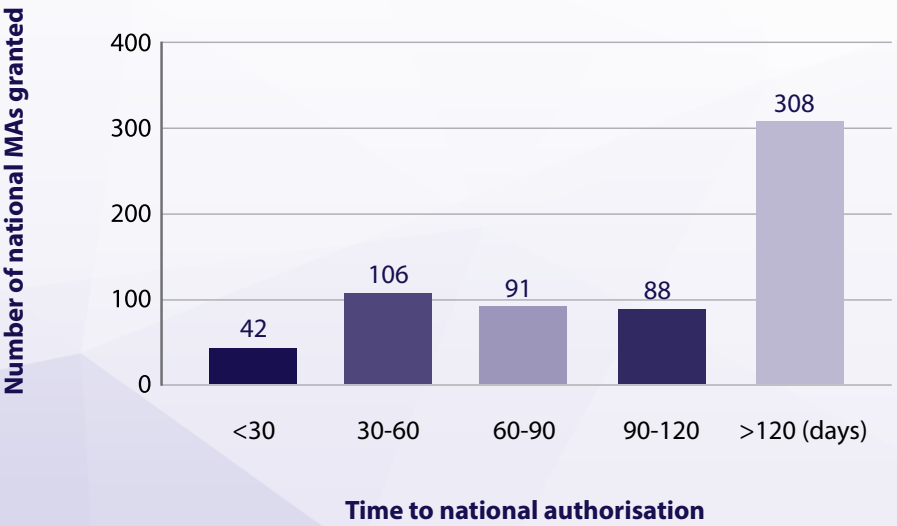
Time to national approval

Respondents to the survey provided information on 50 MRP/DCP procedures, including a total of 635 national implementations (a median of 12 Member States per procedure). In 42 out of 635 instances (6.6%), the national marketing authorisation was approved within the 30 days as mandated by Article 28(5) of Directive 2001/83/EC (Figure 2). There are considerable differences between Member States in time to national approval. Some Member States manage to approve products nationally within 30 days in about a third of the procedures; others fail to authorise 95% of the products within 120 days.

Discussion

Based on the publicly available data from CMDh, the MDP/DCP pathway seems to be quite efficient, with only a limited number of applications being referred to CMDh and the majority of these referrals resulting in positive decisions. However, these data did not include refusals at the RMS level and withdrawals that occur early in the procedure. Data from our survey suggest that 16% of all MAAs via the MRP/DCP are withdrawn in one or all Member States at some point during the procedure, with most withdrawals reportedly for reasons other than safety concerns. However, care must be taken to extrapolate our survey results to all users of these procedures, as the survey sample included only a few generic companies that account for the majority of the MRP/DCP procedures. The proportion of MRP/DCP procedures that resulted in a CMDh referral in the survey-subset (10/208 = 4.8%) is in the same range as observed in the total CMDh database (377/10392 = 3.6%), providing some

Figure 2: Time to national implementation after adoption of MRP/DCP procedures (subset of n=50 MRP/DCP procedures finalised between 2006 and 2013, corresponding to n=635 national licenses)



reassurance with respect to the representativeness of the survey sample.

PSRPH objections relating to the design and outcome of clinical studies were most likely to lead to a negative outcome, whereas discussion on quality or regulatory concerns rarely resulted in an overall negative outcome. This outcome is best explained by the fact that the MRP/DCP has become the pathway of choice for generic applications, accounting for 78% of all procedures. MRP procedures were more frequently associated with referrals than DCP procedures: a possible explanation is that the fact a national authorisation already exists may make RMS more reluctant to accept changes to the existing summary of product characteristics (SmPC). Also, given the fact that DCPs do not have pre-existing MAs, companies may withdraw an MAA more easily in response to objections raised during the assessment procedure, in order to resubmit with different claims, or in different member states. Finally, there is less time to resolve differences between Member States. The duration of the MRP is 90 days vs. 210 days of the DCP.

Non-prescription medicines were not associated with a higher frequency of negative outcomes. Nevertheless, it has also been recognised that the MRP/DCP is underutilised by the non-prescription sector, which is mainly explained by different approaches towards self-medication in the various member states. Decisions of legal status remain a national competence, resulting in considerable differences in authorised terms of use of these medicines throughout the EU (CMDh 2012). Companies may anticipate concerns during the procedure and opt not to submit in certain countries because they know they might raise concerns during the procedure, but run multiple procedures for the same product, sometimes in parallel.

Our study focused on negative overall outcomes. For some products, the authorised indications and/or patient populations were restricted at the end of the MRP/DCP procedure, which resulted in decisions not to market a product. Our survey did not systemically investigate the underlying reasons for the restrictions placed on the use of the product. Also, the current study did not take into account the assessment time of the MRP/DCP procedure.

The time to national authorisation after a European decision differs considerably between Member States. There may be various factors responsible for delays in the national phase, including discussions on packaging, brand names, quality of translations of the product information or merely workload at the national competent authority (AESGP/EFPIA/EGA 2014). Our study merely quantified the duration of the national authorisation phase from the time of a positive EU decision; it did not take into account clock stop times until the submission of the translated product information. Nevertheless, the reasons for delay observed during the national authorisation phase and the differences between competent authorities in various Member States with regard to the time to national approval should be further explored.

Conclusion

A limited number of MRP/DCP procedures resulted in a negative outcome after a CMDh referral procedure, although other negative outcomes such as withdrawals in one or more Member States prior to the start of a CMDh procedure occurred more frequently. PSRPH objections were mostly related to the design and outcomes of the clinical studies included in the dossier, whereas procedural discussions on authorised indications, rarely lead to negative opinions. MRP procedures are more likely to result in negative opinions than DCP procedures. There are considerable differences

between Member States regarding the implementation of European decisions at the national level. Even though the underlying reasons for this require further study, our results support the conclusion that there is room for improvement of the national phase.

Acknowledgements

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3.3 Use of the conditional marketing authorisation pathway for oncology medicines

Jarno Hoekman, Marie L De Bruin, Wouter PC Boon

Background

The conditional marketing authorisation (CMA) pathway was created in 2006 to accommodate wishes of patients for early access to medicines that fulfil an unmet medical need (EC 2006). CMA can be granted based on limited clinical data, but only on four conditions: that medicines show a positive benefit-risk balance; that they fulfil an unmet medical need; that the benefit to public health of immediate availability outweigh the risks; and that more data will be generated after marketing authorisation (MA). So far, CMA has been mostly used for the authorisation of oncology products (11 out of 20 medicines having received CMA up until 2013).

Little is known about the experiences of regulators and companies with the use of CMA. A formal evaluation of CMA use has not been conducted and although scientific research has provided insight in the association between CMA status and the detection of safety issues (Boon et al. 2010; Arnardottir et al. 2011), it has not yet focused on how CMA is applied during the MA procedure. For instance, requests for CMA can be made upfront by companies or CMA use may be proposed by regulators during the MA procedure, but it is unknown whether there is a common practice. Moreover, market authorisation holders (MAHs) have expressed concerns that the procedure has not been used to its full potential up to now (see Chapter 2). Therefore, it is of interest to study how the CMA pathway has been used by companies and regulators.

Objectives

The aim of this study was to investigate how the CMA procedure has been used by companies and regulators in the period 2006-2013, using oncology products as an example. We do so by analysing 1) how use of CMA for oncology medicines compares to use of standard MA for oncology medicines, and 2) how CMA was applied in individual MA procedures of oncology medicines.

Methods

We conducted a mixed quantitative-qualitative study covering medicines that were granted an initial MA for any oncology indication by the EMA in the period 2006-2013. In the quantitative part of the study we compared standard MA and CMA in terms of product and procedural characteristics. Data on these characteristics were extracted from European public assessment reports (EPARs) and Annual Reports of the EMA. We extracted and compared data on evidence characteristics of the pivotal trial (number of patients, primary endpoint and randomised controlled trial [RCT] design); number of patients in the safety database; assessment time (total, active and clock stop time, accelerated assessment); and procedural characteristics (scientific advice before MA procedure, advice of the Scientific Advisory Group on Oncology (SAG-O) during MA procedure, consensus vote on MA by CHMP, appeal procedure). Summary statistics of products receiving standard MA and CMA were compared using Wilcoxon rank-sum tests for continuous data and Fisher's exact tests for categorical variables.

The qualitative part of the study aimed to provide insight into how CMA was used in individual MA procedures. To do so, we conducted eight semi-structured interviews with six MAHs on the MA procedures of ten (out of 11) oncology medicines that were granted CMA

in the period 2006-2013. The interviews were conducted by two investigators after in-depth reading of the EPARs. Interview questions aimed to discern the perspective of companies on discussions about CMA (both internally and with regulators) and decisive moments and motives that led to the decision to grant a CMA. To gain a better general understanding of the creation and use of CMA, we also conducted three general interviews with (former) European Commission officials and regulators.

Results

Quantitative comparison of standard versus conditional MA

In the period 2006-2013, 46 oncology medicines were approved by EMA, of which 32 (70%) were granted a standard MA, 11 (24%) a CMA and three (6%) authorisation under exceptional circumstances (Figure 1). Table 1 compares characteristics of medicines that received a CMA and standard MA.

In terms of data availability there were clear differences between standard MAs and CMAs. Oncology medicines that received a CMA enrolled on average less than half the number of patients in the pivotal trial (265 vs. 662, P<0.001) and had a smaller safety population (453 vs. 981, P=0.006), compared with medicines receiving standard MA. In addition, while the pivotal trial supporting a standard MA was almost always a RCT (91%), the pivotal trial supporting a CMA was a RCT in less than half of the cases (45%, P=0.004). There were also differences in primary endpoints used in the pivotal trials (P<0.001), with CMA products being more often authorised on the base of response rate as a primary endpoint.

When looking at the duration of the procedures, assessment timelines for medicines receiving CMA were longer as compared with standard MA (P=0.005), which was due to a significantly longer clock-stop time rather than a longer active assessment time. Furthermore, accelerated assessment was never applied for products that received a CMA, as compared with six times for products that received a standard MA (P=0.312).

While we observed no clear differences between conditional and standard MA

Figure 1: Marketing authorisation of oncology medicines in the period 2006-2013

in whether or not scientific advice was taken before MA, medicines receiving CMA were more often referred to the SAG-O during the MA procedure than standard MA medicines (73% vs 28%, P=0.014). Furthermore, medicines receiving CMA were less often authorised with a consensus vote by CHMP (55% vs 88%, P=0.034).

CMA use in individual MA procedures

For 2 out of 11 oncology medicines that were granted CMA, companies requested CMA upfront as judged from the EPAR. For one product, the request for CMA was initially refused by CHMP due to a perceived lack of unmet medical need. This implied that regulators initially applied standard benefit-risk evaluation criteria for the assessment of 10 out of 11 dossiers that were eventually granted a CMA. There were two main reasons for companies not to request CMA upfront. First, for three products companies expected that the data were strong enough to justify standard MA. Second, three MAHs (with five authorised products) stated that they would always try to obtain standard MA. Reasons they mentioned for this strategy were perceived difficulties with reimbursement; regulatory burden of post-marketing obligations; and a perception that an upfront CMA request limits the possibility for obtaining an immediate standard MA.

Table 1: Product and procedural characteristics of oncology medicines receiving standard or conditional MA

	Standard MA (n=32)	Conditional MA (n=11)	P-value
Data			
Number of patients in pivotal study	662 (347)	265 (177)	<0.001
Pivotal study is RCT	29 (91%)	5 (46%)	0.004
Primary endpoint in pivotal study			
Overall survival	19 (59%)	0 (0%)	<0.001
Progression-free survival	7 (22%)	3 (27%)	
Time to progression	1 (3%)	1 (9%)	
Response rate	5 (16%)	7 (64%)	
Number of patients in safety population	980 (978)	453 (220)	0.006
Timelines			
Total assessment time in days	315 (77)	393 (84)	0.005
Active assessment time in days	197 (17)	201 (10)	0.809
Clock stop time in days	118 (68)	192 (76)	0.004
Accelerated assessment, n (%)	6 (19%)	0 (0%)	0.312
Procedures			
Scientific advice, n (%)	25 (78%)	8 (73%)	0.698
SAG-O meeting, n (%)	9 (28%)	8 (73%)	0.014
Consensus vote, n (%)	28 (88%)	6 (55%)	0.034
Appeal procedure, n (%)	0 (0%)	1 (9%)	0.256

Means (standard deviations) are reported unless specified otherwise. Comparison testing with Wilcoxon rank-sum tests for continuous variables and Fisher exact test for categorical variables.

For most products, the use of CMA was proposed during the MA procedure. There was one request by an applicant for CMA during an oral explanation at day 120. Nine proposals for CMA were made by the CHMP: for one product CMA was proposed by CHMP around day 150, for six medicines on or after day 180, and for one product during an appeal procedure (timing for one product is missing). In these nine cases, CHMP members had doubts about the positive benefit-risk balance of the product for granting a standard MA. In four out of nine CMA proposals, the requested indication for standard MA was narrowed down to a subpopulation for which less comprehensive data was available, but for which the benefit-risk profile was deemed positive.

In terms of procedures, companies perceived no major differences between CMA and standard MA. However, they noted more frequent requests for additional data during the CMA procedure, including the provision of interim results of pivotal trials that were ongoing during the procedure. Requests for additional data were considered as a reason for the observed longer clock-stop times.

The role of scientific advice varied between CMA procedures. No centralised scientific advice was taken for four products that were granted CMA. In two of these cases, MAHs noted that, in hindsight, they should have taken centralised scientific advice in order to anticipate on a potential CMA outcome. For two other products, MAHs did not adhere to scientific advice and filed the data despite negative advice of regulators.

Discussion

This study assessed how the CMA pathway has been used by companies and regulators for oncology medicines in the period 2006-2013. In line with the regulation, we observed that data on oncology medicines that were granted CMA was less comprehensive than data on oncology medicines that were granted standard MA. However, the use of CMA to authorise oncology medicines with smaller data packages was accompanied with more challenging MA procedures, as reflected by longer assessment times, no accelerated decision-making and less consensus among CHMP members to provide a positive opinion. Reasons for the observed procedural complexities are requests for additional data during the MA procedure and the fact that discussions on CMA (and post-marketing obligations) often only start when serious concerns about granting a standard MA are not alleviated after secondary evaluation (between day 120 and day 180). A lack of sufficient incentives for companies to request CMA upfront due to perceived problems with reimbursement probably contribute to this.

Limitations and further research

The present study focused only on oncology medicines and as such covered 11 out of 20 medicines that were granted CMA in the period 2006-2013. Given the specific characteristics of the oncology field, including a strong focus on targeted therapies and staggered authorisation strategies (Tafuri et al. 2010; Trotta et al. 2011), it may be difficult to extrapolate the outcomes of our study to the granting of CMA for other indication areas such as human immunodeficiency virus (HIV), influenza or multiple sclerosis.

We observed a trade-off in MA procedures between the amount of data available for MA and the complexity of the procedure, but do not know whether this trade-off is specific for the European regulatory context. We therefore suggest conducting a similar analysis on oncology medicines that were authorised in the United States, comparing accelerated approval with standard approval.

Our study merely focused on the MA process and did not consider the trajectories of medicines after authorisation. Previous research observed that products authorised under the CMA procedure do not show an increased number of safety issues in the post-marketing phase

(Boon et al. 2010; Arnardottir et al. 2011). We are currently conducting a study focusing on the characteristics of post-marketing obligations and the time to conversion to standard MA. Furthermore, interview respondents mentioned challenges with reimbursement as one of the reasons for not requesting CMA upfront. In light of this finding we are currently performing an analysis of the association between CMA status and reimbursement decisions for the oncology medicines in our sample. Finally, the trajectory before starting authorisation could be taken into account by investigating to what extent medicines that are granted CMA also have shorter development timelines.

The interviews reconstructed the MA procedure of individual medicines but there may have been recall and hindsight bias among interview respondents in the description of the MA process, especially as the granting of CMA was often described as an unexpected outcome. This concern might be mitigated by triangulating the company interviews with interviews conducted with regulators.

Conclusion

CMA is given to oncology medicines with less comprehensive data available upon MA, compared with oncology medicines that receive standard MA. The MA procedures resulting in CMA are challenging, possibly because CMA use is often initiated relatively late during the MA procedure. Companies do not seem to have sufficient incentives to request CMA upfront, which leads in a substantial number of cases to a situation in which regulators initially use standard evaluation criteria for data assessment. In these cases, the option of CMA is only discussed once there is initial consensus that a standard MA cannot be granted. As a consequence, the use of CMA for oncology medicines is sometimes perceived as a 'rescue' option by regulators and companies rather than as a prospectively planned pathway to grant early access to medicines that show promising effects, but for which comprehensive data is not yet available.

Acknowledgements

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3.4 Timing of submission, development status, and outcomes of paediatric investigation plans

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Background

The Paediatric Regulation, which came into force in January 2007, aims to increase the safe and effective use of medicines in children by requiring the conduct of paediatric studies and the development of appropriate formulations for paediatric age-groups. Under the regulation, companies are required to submit a paediatric investigation plan (PIP) or a product- or class-specific waiver to the Paediatric Committee (PDCO) at the EMA *before* submitting a marketing authorisation application (MAA) for a new medicinal product. The PDCO can decide that studies proposed in a PIP should start immediately (i.e. during the clinical development phase of the product) or can grant a deferral to all or a subset of studies until after marketing authorisation (MA). The regulation requires submission of PIPs *'not later than upon completion of human pharmacokinetic (PK) studies'* (EC 2006) such that the performance of paediatric studies fits into the overall clinical development programs of pharmaceutical companies and does not delay MAA for other populations.

However, companies have raised concerns over the appropriateness of PIP submission deadlines for three main reasons (Joos et al. 2011; Annex 6). First, there is still considerable uncertainty about the benefit-risk profile of the product upon completion of human PK studies, which increases the likelihood that downstream modifications need to be made to the proposed study designs. It can be expected that this uncertainty is higher for Article 7 products (i.e. a PIP/waiver for a product not yet marketed in the EU) as compared with Article 8 products (i.e. a PIP/waiver for a product already marketed in the EU). Secondly, many products fail between the end of phase I and marketing authorisation, which may result in the drafting and conduct of PIPs for products that will never actually reach the market. Finally, the Food and Drug Administration (FDA) requests paediatric development plans after phase II, which creates misalignment between paediatric development of products that are to be marketed in both the US and the EU.

Objectives

The primary aim of this study was to identify factors that contribute to the early availability of information on the use of medicines in children (i.e. the completion of at least one paediatric study). The secondary aim was to provide insight into the number of downstream modifications and redundant PIPs (i.e. PIPs for which the development plan has been terminated).

Methods

PIP cohort

We conducted a cohort study by including all PIPs and full waivers that were agreed upon by the PDCO in the period 2007-2010 (n=558). Publicly available decisions on the first agreement of a PIP or waiver were retrieved from the EMA website or, if missing, requested from EMA.

PIP characteristics

For each PIP we collected the following data: procedure number; active substance; therapeutic area; MAH; first decision date; number of modifications to PIP since first decision; full deferral (yes/no); number of indications to be studied; number of clinical studies; number of non-clinical studies; number of quality studies; total number of studies.

We classified active substances by products that were marketed in the EU before and

after 2007, because we expected that there would be more uncertainty about the benefit-risk profile of those products that were still under development when the PIP was agreed upon as compared with those products that were already marketed at that time. Because of classification ambiguity, we excluded the following from this analysis: PIPs for vaccines (n=25), allergen extracts (n=100), diagnostics (n=1), purified products (n=1) and nutrition products (n=2).

Outcome measure

We received a list of all Article 46 procedures up to March 2014 from the EMA to assess whether or not at least one of the proposed studies in the PIP had been completed. Procedures were linked to PIPs and time to Article 46 decision was computed as the absolute difference between the first decision date on the PIP and the first completed Article 46 procedure. Since there are currently only a number of products that have successfully applied for a patent extension (EC 2013), we use successful completion of paediatric studies as reflected in Article 46 procedures as a surrogate measure. An advantage of this measure is that it directly captures all research efforts related to the PIP. A disadvantage is that an Article 46 procedure does not necessarily imply that all PIP efforts will be completed in the future (due to termination of development).

Survey

We collected additional information on the cohort of PIPs and waivers through a short survey among 42 EFPIA member companies that was sent out in April 2014 (see Annex 10). We specifically asked companies to indicate the number of PIPs and waivers for which the development program for adults had since been terminated. For a subset of Article 7 products that did not receive a full deferral we also asked additional information on timing of PIP submission (early: phase I/phase II; late: end of phase II/phase III/initial MA), and status of the product (development for adults terminated; marketed for adults; still under development; under review for MA). We considered only PIPs that received a partial deferral, as we expected it to be most likely that these PIPs would have had Article 46 outcomes.

Analyses

We performed time-to-event analyses to quantify Article 46 outcomes for PIPs, and calculated crude incidence rates to study the association of outcomes with various determinants.

Results

PIP Cohort

In the period 2007-2010, the PDCO agreed on 385 PIPs and 173 product- or class-specific full waivers. For the 385 PIPs, a median number of three (Interquartile range [IQR]: 1-5) studies was requested of which 74.8% were clinical studies. As of March 2014, a median number of one modification (IQR: 0-3) was made to these PIPs.

After a median follow-up of 4.4 years, 18.2% of the 385 PIPs had at least one Article 46 outcome. The incidence rate of Article 46 outcomes was higher when PIPs underwent at least one modification. We also observed a positive association with the number of clinical studies as well as the total number of studies. The incidence rate of an Article 46 outcome was higher when a product was already marketed before 2007, but the incidence rate ratio comparing products marketed before and after 2007 did not reach statistical significance (Table 1).

Table 1: Determinants of Article 46 outcomes

	Number of PIPs	Article 46 outcomes	Incidence rate ratio
Full or partial deferral			
No	55	9	ref
Yes	330	61	1.31 (0.65 - 3.00)
Total number of studies*			
≤ 2 studies	219	29	ref
> 2 studies	155	38	1.67 (1.00 - 2.80)
Number of clinical studies*			
≤ 1 studies	227	27	ref
> 1 studies	147	40	2.04 (1.22 - 3.45)
Number of non-clinical studies*			
No study	272	48	ref
At least 1 study	102	19	0.99 (0.55 - 1.72)
Number of quality studies*			
No study	271	49	ref
At least 1 study	103	18	0.94 (0.51 - 1.64)
Number of conditions studied*			
1 condition	335	57	ref
> 1 condition	39	10	1.47 (0.67 - 2.90)
Marketed before 2007†			
No	165	33	ref
Yes	91	26	1.39 (0.80 -2.40)
Number of modifications			
No modification	175	7	ref
At least 1 modification	210	63	6.30 (2.89 - 16.32)

**Data on number of studies and conditions is missing for 11 PIPs.*
† Based on subset of cohort due to classification ambiguity (see methods).

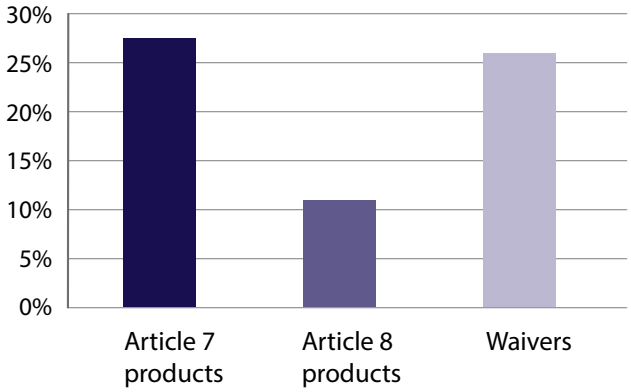
Survey

Additional data regarding PIP submissions were provided by 21 companies (response rate: 50%). These companies had submitted 83 PIPs for Article 7 products, 56 PIPs for Article 8 products, and 78 waivers, comprising 38.9% of all PIPs and waivers agreed on by the PDCO in the period 2007-2010. The development program was terminated for 28% of PIPs for Article 7 products, for 11% of PIPs for Article 8 products and for 26% of PIPs for products that received a full waiver (23% of all PIPs and full waivers, 21% of all PIPs). Of Article 7 products that did not receive a full deferral, 15% of the PIPs were terminated (Figure 1).

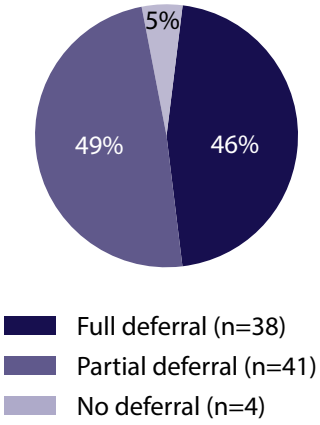
Of all PIPs for Article 7 products that did not receive a full deferral, approximately two-thirds were submitted during or after phase II studies in adults. We were not able to relate timing of PIPs to Article 46 outcomes because we could only link data on timing to individual PIP numbers in 17 cases. Of these 17 PIPs, two PIPs had an Article 46 outcome.

Figure 1: Timing and status (as of April 2014) of PIPs based on survey data

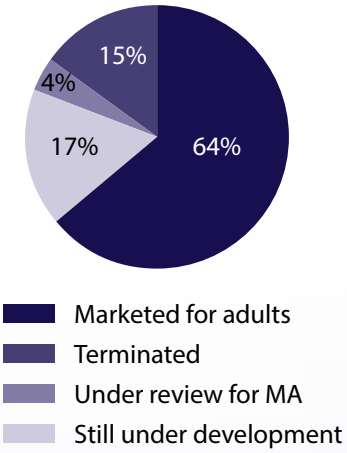
(1) Percentage of development programs in adults terminated (n=217)



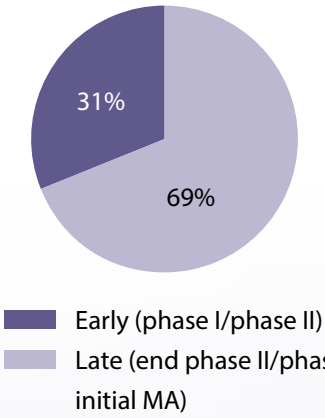
(2) Deferrals for PIP for Article 7 product (n=83)



(3) Status of Article 7 products (n=47)



(4) Timing of Article 7 PIP submissions (n=39)



(1) Percentage of development programs in adults terminated according to product type as of April 2014 (n=217). (2) Types of deferrals reported by companies for all PIPs for Article 7 products, 2007-2010. (3) Status of all Article 7 product PIPs without a full deferral as of April 2014. (4) Timing of submission of Article 7 product PIPs without full deferral. Missing data regarding the timing of PIP submission accounts for the differences in total PIPs (n=47 for status; n=39 for timing).

Discussion

Main findings

This study identified factors that contribute to the early availability of paediatric data. Furthermore, we provided some estimates of redundancy in the regulatory system due to modifications to PIPs and termination of development programs in adults. Our results indicate that PIPs with subsequent downstream modifications were more likely to have Article 46 outcomes, suggesting that agreed upon PIPs are changed more often once companies

initiate the actual conduct of paediatric studies. We also found that 23% of all agreed upon PIPs were abandoned due to termination of the development program in adults. This percentage is higher for Article 7 products as compared with Article 8 products, and is especially high for Article 7 products that received a full deferral.

The estimates provided in this study give an indication of redundancy in efforts by companies and regulators in preparing PIPs that need to be modified at a later stage and in drafting and conducting studies for products that will not be marketed due to the termination of development programs. To reduce redundancy, one could further explore alternative ways of submitting PIPs during early stages of development, including proposals to reduce the level of detail in initially submitted PIPs and staggered approaches to PIP submission as recently suggested by several stakeholders (Micheaux 2011; EC 2013). Such proposals could take into account the observed differences in the likelihood of early availability of data between Article 7 and Article 8 products. Moreover, we found that two-thirds of all PIPs are already submitted during phase II or later (Figure 1) which is in line with previous findings (Rocchi et al. 2011). This seems to suggest that there is already flexibility in the regulation to submit PIPs during various moments in the development plan, although part of the observation may also be explained by the fact that in the early period of the regulation many products that needed a PIP were already late in development.

Limitations

Our study has a number of limitations. First, we only included the PIPs and waivers agreed by the PDCO between 2007 and 2010. Given that the implementation of the Paediatrics Regulation happened in January 2007, this means that there might have been learning effects (for companies as well as the EMA and PDCO) during the first year(s). Therefore, care should be taken when extrapolating our results to more recent years, although the total number of PIPs submitted in 2007 is relatively low compared to the subsequent years. Furthermore, a large number of PIPs in our sample was not completed at the time of data collection. Therefore, the total number of modifications per PIP could increase in the coming years.

Second, despite the fact that we had a reasonable response rate on the survey concerning termination of product development, only limited additional data were available for the subset of Article 7 products that received a full deferral. As a consequence, we are missing information on the timing and status of most PIPs and could not determine an association between the timing of PIP submission during companies' development programs and early availability of data on Article 46 outcomes.

Third, we used all completed Article 46 procedures at EMA to determine whether or not a study from a PIP had been completed. However, an Article 46 procedure also needs to be submitted for a paediatric study sponsored by the MAH that was not part of the PIP, and also to report on studies that have been discontinued. As a consequence, there may have been some overestimation in the number of reported Article 46 outcomes. However, there is no reason to assume that this overestimation differs between the observed PIP characteristics in our study. Moreover, other regulatory output measures next to Article 46 outcomes are available including changes to SmPCs and rewards for PIP completion in the form of a six month patent extension. It is important to conduct future time-to-event analysis on these outcome measures to keep track of the availability of information on medicine use in children.

Conclusion

The results of this study suggest that some efforts of companies and regulators while preparing and assessing PIPs become redundant due to downstream modifications, or because

adult development is terminated after the PIP is agreed upon by the PDCO (21% of all PIPs). Further in-depth analyses and discussions among stakeholders is necessary to determine the exact level of redundancy in recent years, whether or not this level is acceptable for stakeholders, and how it can be effectively reduced. One suggestion would be to use a staggered approach for PIP submission, potentially taking into account differences between Article 7 and Article 8 products in their likelihood of early completion. Based on the results of this study, we believe that there is room for increasing the efficiency of the Paediatrics Regulation without negative consequences for the availability of information on the safe and effective use of new medicines in children.

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3.5 Pharmaceutical industry resources required for compliance with European pharmacovigilance requirements

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Background

A major reform of the regulatory framework for post-marketing surveillance of medicines came into force in the EU in July 2012. This legislation - called the new pharmacovigilance legislation - was projected to improve public health through better post-marketing monitoring of medicines, while simultaneously resulting in substantial cost savings for the European pharmaceutical industry. The legislation has been called *'the biggest change to the regulation of medicines since 1995'* (EMA 2014) and provided clearly defined rules and responsibilities for all stakeholders; simplification of tasks; decreased duplication of efforts; and targeted administrative simplification, and it resulted in adapted requirements for virtually all parts of pharmacovigilance activities (EMA 2014). The EMA has recently published a one-year evaluation of the implementation of the new legislation (EMA 2014), and the EMA remains responsible for both implementation and evaluation of the implementation process. However, it is also important to assess the impacts of the new legislation from an independent academic perspective (see Chapter 5), and such an evaluation can complement the evaluations performed by the EMA itself.

The survey described in Chapter 2 indicated several areas of pharmacovigilance that were seen as being in need for improvement. Furthermore, the resources needed to comply with all EU post-marketing requirements have not been systematically assessed previously, and such an assessment is important for future evaluations of the impact of the regulation.

Objectives

The aim of this study was to assess the company resources needed for pharmacovigilance activities, and to assess the impact of the new Pharmacovigilance Legislation for MAHs in the EU.

Methods

Survey

Based on methods previously applied by Ridley et al. (Ridley et al. 2006) to measure the costs of post-approval safety in the United States, we created a survey that consisted of 24 questions to measure the resources used by pharmaceutical companies regarding the following pharmacovigilance activities in the EU (Annex 11):

- Handling of individual adverse event cases;
- Periodicsafetyupdatereport(PSUR)/periodic benefit-risk evaluation report (PBRER) reporting;
- Safety department operations;
- Safety surveillance activities;
- Safety-related label changes;
- Post-authorisation safety studies ([PASSs], used for a separate analysis presented in Chapter 3.6).

Companies were asked to report the number of full-time equivalents (FTEs) required to perform all activities listed above for the year 2013. We further asked companies for the number of PSURs/PBRERs submitted; risk-management plans (RMPs) submitted; safety variations submitted; and expedited adverse drug reaction (ADR) reports submitted to at least one European Economic Area (EEA) country in 2011 and 2013. We also asked for the number of all PASSs

Table 1: Pharmaceutical companies that participated in the survey

AbbVie	Bristol Myers Squibb	J&J	Novo Nordisk
Almirall	Celgene	Lilly	Pfizer
AstraZeneca	Chiesi	Lundbeck	Roche
Bayer	GSK	Menarini	Sanofi
Bial	Janssen	MSD	

In total, 19 companies (representing ~50% of the total European pharmaceutical market) provided data.

companies had completed since January 2007, as the legislation was projected to impact all these pharmacovigilance activities.

The legislation came into force on the 1st of July 2012. Asking for data for 2011 and 2013 therefore allowed comparison of the impact of the legislation on several indicators. The survey was piloted in January 2014 (by three different companies) and the final version was sent to EFPIA member companies (n=42) as well as AESGP member companies (n=13). Respondents were given the option either to fill out a PDF or to submit the data through an electronic questionnaire. Responses were anonymised by a third person such that the researchers were blinded to company names during extraction and analysis.

Results

Sample characteristics

In total, 19 companies provided data regarding the resources required for compliance with pharmacovigilance requirements in the EU (Table 1; response rate 35%). 14 of the respondents belong to the top 20 pharmaceutical companies in Europe as ranked by 2013 sales at ex-factory prices, representing 47.5% of the total pharmaceutical market in the EEA. Combined with the sales of the five smaller companies in our sample, this means that our sample represents over 50% of the total European pharmaceutical market (data regarding size of market provided by EFPIA; data not shown).

The companies marketed a variety of products: 89% of companies marketed new chemical entities (NCEs), 68% biologicals, 53% over-the-counter (OTC) products, 16% biosimilars, and 32% generics. One company marketed only OTC products, two companies marketed only NCEs and one company marketed only biologicals. All other companies marketed various types of products. The companies employed an average of 329 FTEs for all pharmacovigilance activities (median 186; data from 18 respondents) (Table 2). The substantial difference between the median and average number of FTEs indicates large variability among companies due to differences in total company size or due to differences in mix of product portfolios.

Table 2: Pharmacovigilance activities of respondents for the year 2013

	Mean	Median	Number of respondents
Total FTEs per company for all pharmacovigilance activities*	329	186	18

** FTEs per activity were added up per company (n=16) or provided as a total (n=2).*
Not all respondents provided complete data.

PSUR/PBRER reporting

The average time required to prepare and submit one PSUR in 2011 was 306 hours (n=12, median=265, Figure 1). In 2013, the average time required to prepare and submit a single PBRER was 487 hours (n=12, median=423). Companies submitted an average number of 61 PSURs (n=12, median=28) to at least one EU country in 2011. In 2013, the average number of PBRERs reported to at least one EEA country decreased to 36 (n=17, median=21, Figure 2). The total number of reports submitted decreased by 35% per company on average, while the average time required to prepare and submit one report increased by 59%.

EU RMPs

Between 2011 and 2013, the average number of EU RMPs submitted by companies to at least one EEA country increased from 9 (median=5) to 19 (median=11) per company (n=17, Figure 2).

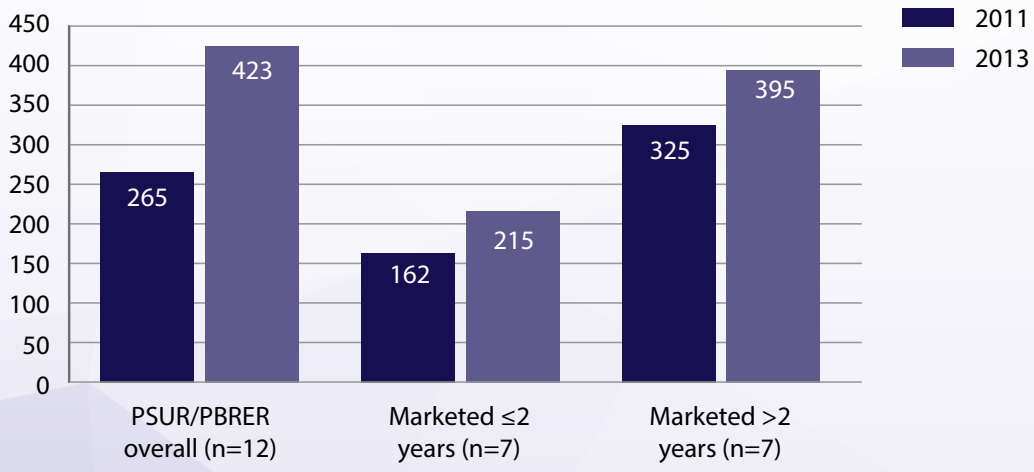
Impact on workload

We asked all companies to indicate the impact of the new pharmacovigilance legislation on workload. One company indicated a mixed impact, meaning that the workload increased in some areas but decreased in other areas. All other companies (95%) indicated an increase in workload at the company (Table 3). We also asked respondents whether they hired additional staff as a result of the increase in workload. 84% of the companies that responded said that they hired additional staff, either in-house or outsourced. On average, 14 additional FTEs were hired per company.

Areas experiencing the biggest impact from the new legislation

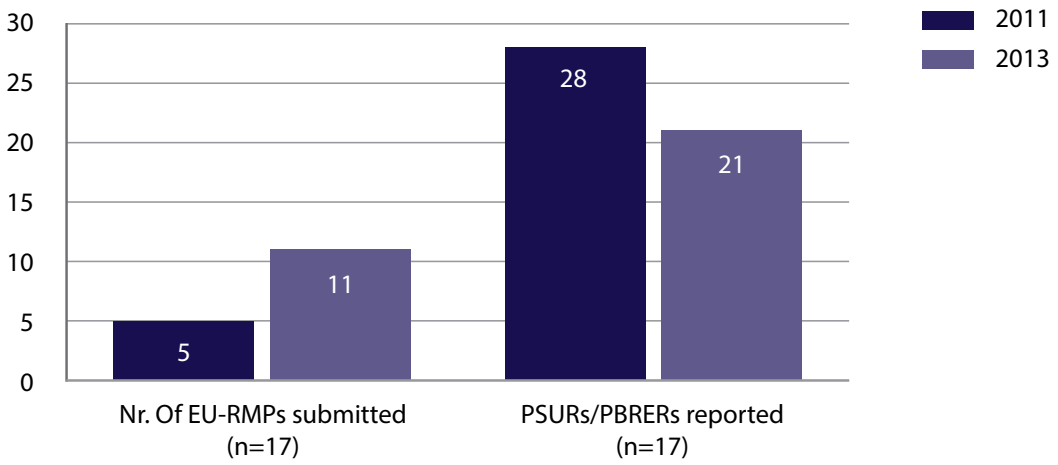
Finally, we asked respondents to indicate which areas of pharmacovigilance had seen the biggest impact from the new legislation, by means of an open-ended question. Table 4 summarises the different pharmacovigilance activities that were named most often by respondents, and shows that the introduction of the pharmacovigilance system master file and the new PBRER format were reported by 74% of all responding companies.

Figure 1: Time required to prepare and submit one PSUR/PBRER (median hours)



Data reported in median hours per PSUR/PBRER. 12 respondents provided data about overall hours required for a single PSUR/PBRER; seven respondents also differentiated according to time on market.

Figure 2: Number of EU RMPs and PSURs/PBRERs submitted in ≥1 EEA country (median per company)



Not all companies provided complete data.

Discussion

Main findings

A year after the introduction of the new Pharmacovigilance Legislation, 95% of the companies that participated in our survey reported an increase in workload within their companies with regard to pharmacovigilance activities. Furthermore, the majority of companies have hired additional staff in response to this increased workload. The introduction of the new legislation was expected to reduce the burden for pharmaceutical companies in pharmacovigilance activities and to simplify efforts. The results of our survey – although preliminary – indicate that it is unlikely that substantial cost savings have been achieved so far for the pharmaceutical companies included in our sample. Given that we have data for the year 2013 and that the legislation came into force mid-2012, it can be assumed that at least part of the observed increase in workload was related to the implementation phase of the new requirements and could be a temporary increase in total workload. Therefore, it

Table 3: Impact of new pharmacovigilance legislation on workload

	Response	Number of respondents
Overall change in workload		
Increase	95%	19
Decrease	0%	19
Mixed (some areas increase, others decrease in workload)	5%	19
Companies that hired additional staff	84%	17
Average nr. of additional FTE hired	14	13

Table 4: Areas of pharmacovigilance with biggest impact from new legislation

PhV areas that saw biggest impact of new legislation:	% of respondents	n
Pharmacovigilance system master file	74%	19
New PBRER format	74%	19
Risk-management plans	63%	19
Reporting of non-serious ADRs	32%	19
Article 57 requirements	26%	19
PRAC	16%	19

PRAC: Pharmacovigilance Risk Assessment Committee.

would be important to monitor the impact of the new legislation in coming years as well to further assess the actual impact on company resources in the long run. Moreover, it is of interest to relate the costs to public health benefits attained.

The Impact Assessment of the new legislation, published by the European Commission in 2008, foresaw a number of changes for pharmaceutical companies (EC 2008). It was expected that the total number of PSURs that needed to be submitted would decrease due to simplified requirements and that the number of RMPs per company would increase (EC 2008). Our data confirm the increase in the median number of RMPs submitted by companies (five per company in 2011, 11 per company in 2013, Figure 2) and a modest decrease in the median number of PSURs/PBRERs submitted per company: 28 PSURs per company in 2011 and 21 PBRERs in 2013 (Figure 2). Compared with these median figures, the averages for both years show a steeper decline, indicating that differences for individual companies might be larger (61 PSURs in 2011, 36 PBRERs in 2013). None of these data are corrected for total product portfolio.

When looking at the number of hours required to prepare and submit one PSUR/PBRER, we observe an increase from a median 265 hours per PSUR in 2011 to a median 423 hours per PBRER in 2013 (Figure 1). Although there will undoubtedly be a learning effect present, given the new PBRER format to which companies will need to become accustomed, this nonetheless indicates that the total cost savings expected from simplifying PSUR requirements as foreseen in 2008 (from 61 PSURs per company to 36 PBRERs per company on average) are offset by the changes to the PSUR format – now a PBRER – that result in an increase of the time spent to prepare a single report (from a median of 306 hours per PSUR to 487 hours per PBRER): the number of reports submitted annually decreased by 35% yet the hours required to prepare a single report increased by 65%.

The 18 companies that reported the total number of FTEs working in pharmacovigilance for their companies employed on average 329 FTEs to comply with all European pharmacovigilance requirements (Table 1). In a survey of the US pharmaceutical industry, Ridley et al. found that the mean number of FTEs employed by US pharmaceutical companies for post approval safety requirements was 298 per company (Ridley et al. 2006). The Ridley et al. sample included 11 companies that made up 71% of the total US pharmaceutical market, which means that this study also included large pharmaceutical companies. The size of the total pharmacovigilance function (in terms of FTEs employed per company) that we found is comparable to the size reported for large US pharmaceutical companies.

Limitations

Our study has a number of limitations that warrant careful interpretation of the results discussed in this case study. First, our response rate was 35% of all companies we invited to participate in our study. When looking at company size, however, our study included 14 out of the 20 largest European companies, and the companies included in our study represent >50% of the total European market. We cannot extrapolate our results to the entire European pharmaceutical industry since smaller companies are underrepresented in our sample. There is also large variability in our data. Part of this variability can be attributed to total company size, but we cannot exclude the possibility that a number of respondents have under- or over-reported the total number of FTEs working in different pharmacovigilance functions, as we are working with self-reported survey data.

Conclusion

A survey of 19 pharmaceutical companies regarding the impact of the new pharmacovigilance legislation indicates that one year after the legislation came into force, the vast majority of participating companies report an increase in total workload. Although short-term learning effects will be present - and companies might become more efficient in adapting their activities to the new requirements in the coming years - careful monitoring is warranted in the coming years of company activities and the impact on workload of the new legislation.

Acknowledgements

The results in this case report originate from Bouvy et al. (full manuscript in preparation). We gratefully acknowledge help from Sandra Rodrigues in collecting the responses from all participating companies. Furthermore, we would like to thank all participating companies for their efforts, as well as the discussions about the results with the participants at the Escher Workshop in May 2014. We also would like to thank Isabelle Stoeckert and Sarah Montagne at Bayer; and the EFPIA PRAC Task Force for their input.

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3.6 The cost-effectiveness of post-authorisation safety studies (PASSs) for new active substances in Europe

Jacoline C Bouvy, Marc A Koopmanschap, Marie L De Bruin

Background

A new medicine is allowed to enter the EU market only when regulatory authorities deem its benefit-risk profile to be positive. However, uncertainties regarding a medicine's benefits and risks usually remain after marketing authorisation, especially for products that have not been authorised in the EU before. A RMP summarises a product's important identified and potential risks as well as any missing information at market entry, so that it can be determined whether only routine pharmacovigilance activities are needed or whether additional pharmacovigilance activities are warranted. Routine pharmacovigilance activities need to be performed for all authorised products and include ADR reporting and submitting of PSURs to regulatory authorities. For some products, additional pharmacovigilance activities need to be performed as well. This usually means a post-authorisation safety study (PASS) that needs to be performed by the MAH. Types of PASS that could be requested by regulatory authorities in order to generate more information regarding the medicine's benefit-risk profile include registries, database studies, surveys, and clinical trials. These studies require company and regulatory resources for execution and assessment. Therefore, it is of interest to determine their added value - as determined by their incremental cost-effectiveness - over routine pharmacovigilance activities only.

Objectives

The aim of this study was to assess the cost-effectiveness of PASSs that were requested at market entry for centrally approved new active substances that received a positive opinion in 2007.

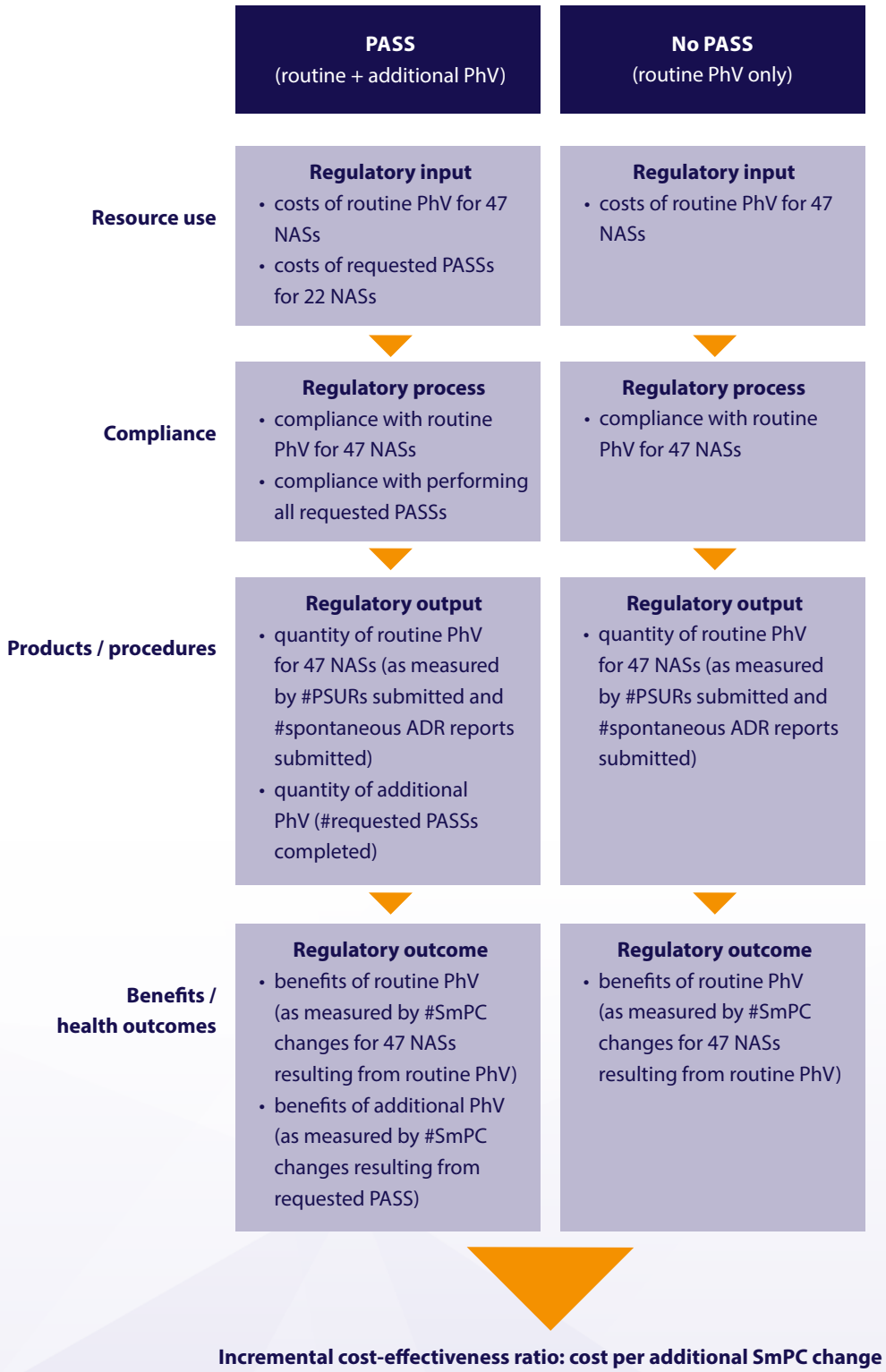
Methods

Regulatory scenarios

A cost-effectiveness analysis is always comparative to enable determination of the added value of an intervention, such that it can be determined how much is gained when compared with what is already being done. With regard to the cost-effectiveness of PASSs for new active substances, this means that two scenarios are compared: (1) PASS and (2) no PASS (Figure 1). The PASS scenario considered in this study consisted of the actual situation as it occurred for new active substances in 2007: for some of these products only routine pharmacovigilance activities were required, whereas a proportion required additional pharmacovigilance activities (i.e. a PASS). Under the no-PASS scenario, we assumed that, for all new active substances receiving a positive opinion in 2007, only routine pharmacovigilance activities would have been required.

The effectiveness endpoint in our analysis was the occurrence of new safety information in a product's SmPC. We created a cohort of all centrally approved new active substances in 2007. All requested PASSs for this cohort were described by Blake et al. (Blake et al. 2011) and 31 PASSs were requested for 22 of the 47 new active substances. Products were followed up until 31 December 2013. All safety information that was added to each product's SmPC during these years was recorded. Furthermore, as part of the EPAR, the EMA publishes a document titled *'Procedural steps taken and scientific information after the authorisation'* for every centrally approved product (www.ema.europa.eu). We used this document to collect all safety-related changes of the SmPC (type IA, IB, and type II variations) for each new active substance in

Figure 1: Regulatory scenarios to determine the added value of PASSs



NAS: new active substance;
All regulatory inputs, processes, outputs, and outcomes relevant to the evaluation are listed for both regulatory scenarios (see Chapter 5). We did not include regulatory processes/compliance in our evaluation. As the analysis was comparative, we could exclude all elements that are identical under both regulatory scenarios (i.e. the costs and quantity of routine PhV activities) without quantification.

our cohort. From the information listed under 'Summary', we categorised the source of the safety information that resulted in the label change as spontaneous ADR reports; clinical observational studies (including requested PASSs); clinical interventional studies (including requested PASSs); change in the context of use (dosing/extension of indication); class effect; or other sources. Using this information enabled us to determine the number of SmPC changes that resulted from a requested PASS.

PASS costs

We sent out a survey to 55 pharmaceutical companies (42 EPFIA members and 13 AESGP members) to measure the costs of conducting PASSs (see Chapter 3.5). The survey (see Annex 11) asked the companies to report the type and number of PASSs they had completed and that started after 1 January 2007. We collected the following characteristics for each PASS: type of study; length of study (if applicable: number of months between inclusion of first and last patient); start date (month + year of inclusion of first patient); and total costs (including insurance costs, study facility costs, contract research organisation [CRO] costs, total employee costs, and any other relevant costs). We used the study characteristics provided by the companies in the survey (study type, duration in months) to estimate the costs of PASSs for the new active substances 2007 cohort.

13 companies provided information about at least one PASS (response rate 24%) and in total information about 86 PASSs was reported. The level of detail provided by the pharmaceutical companies differed and not all studies included a cost estimate (56 out of 86 studies). We used a conversion rate (30 April 2014, 1 EUR = 0.72 USD; 1.22 GBP; 0.82 CHF; 0.11 SEK) to convert all cost estimates to euros (Table 1). Due to the variability in the level of detail provided about the studies, we categorised the 86 studies into the following types: clinical trial; registry/prospective observational study; database/retrospective observational

Table 1: Costs of PASS

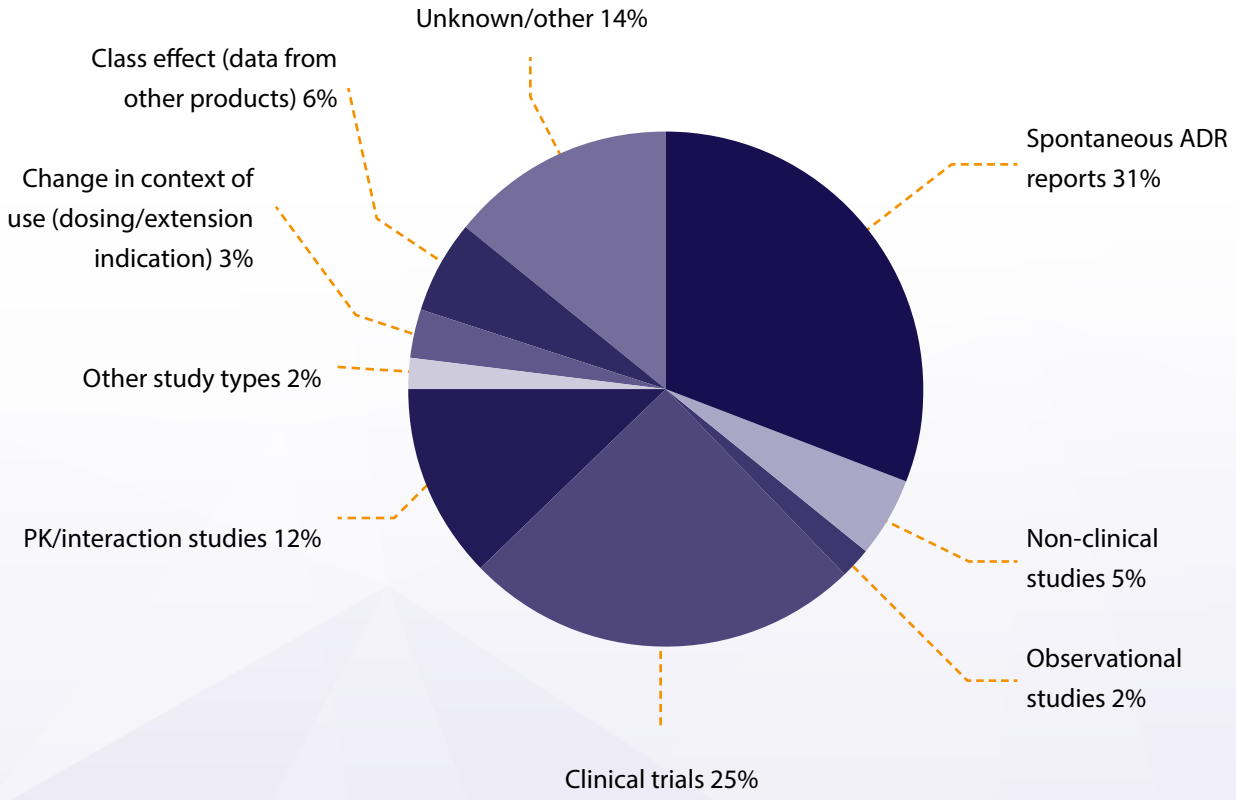
PASS reported	Total # studies	With costs	Mean costs	Median costs	Lowest cost estimate	Highest cost estimate	Mean duration (months)
Clinical trial	7	6	€ 8.3 mil	€ 7.1 mil	€ 183,000	€ 18 mil	22 (23)
Registry / prospective observational	14	8	€ 5.4 mil	€ 1.0 mil	€ 136,000	€ 20 mil	51 (47)
Database / retrospective observational	54	36	€ 921,000	€ 328,000	€ 42,000	€ 6.3 mil	17 (13)
PK / interaction study	5	2	€ 853,000	€ 853,000	€ 476,000	€ 1.2 mil	23 (23)
Survey	4	3	€ 96,000	€ 54,000	-	-	-
Pragmatic trial	1	0	-	-	-	-	-
Other	1	1	€ 35,000	€ 35,000	-	-	-
TOTAL	**86**	**56**					

Data originated from survey of pharmaceutical companies. These cost estimates were used to calculate the costs of the PASS that were requested for the 2007 cohort.

study; PK/interaction study; survey; pragmatic trial; and other study types (Table 1). We differentiated the study types based on designs that would incur different costs, since clinical trials will generally be more expensive than observational studies and prospective observational studies will generally be more expensive than retrospective observational studies.

Although cost per patient is often used to determine the total costs of studies, we did not have access to the number of patients that were included in the requested PASSs. We did have information available regarding the duration of all PASSs as this was listed in the paper by Blake et al. (Blake et al. 2011). Therefore, we used the duration of the studies (as measured in months) to estimate the total study costs. We divided the median cost per study type by the median number of months per study type in order to estimate the median cost per month of the different study types. We calculated the estimated costs of the 2007 PASSs by multiplying the number of months planned with the median cost per month (€307,000 for a clinical trial, €21,000 for a registry, €26,000 for a database study, €37,000 for a PK study). We used a fixed cost estimate of €54,000 for a survey and €35,000 for 'other study type'. We had no cost information regarding pragmatic trials, but there was no pragmatic trial among the sample of 22 PASSs either.

Figure 2: Sources of safety variations for all NASs approved in 2007 (n=334)



Observational studies include database studies and registries. Paediatric trials are included in the clinical trials, Paediatric PK studies are included under PK/interaction studies. Percentage of requested PASSs resulting in an SmPC change: 4% (13 SmPC changes in total). Study types: four observational studies, four PK/interaction studies, five interventional studies.

Table 2: Characteristics of 2007 PASSs for NASs

Product	Type	Planned duration (months)	Safety variation
Sitagliptin	Database	60	No
Sitagliptin	Trial	60	No
Sitagliptin	Trial	10.5	Yes
Sitagliptin	Trial	10.5	Yes
Telbivudine	Survey	6	No
Telbivudine	Trial	12	Maybe
Telbivudine	Registry	6	No
Lenalidomide	Registry	54	No
Retapamulin	PK study	0.5	Yes
Eculizumab	PK study	3	Maybe
Eculizumab	Registry	60	Maybe
Melatonin	Registry	24	No
Hydroxycarbamide	Registry	120	No
Mecasermin	Registry	60	No
Methoxy polyethylene glycol-epoetin beta	Trial	48	No
Nelarabine	Registry	120	No (not completed)
Aliskiren	PK study	2	Yes
Epoetin alfa	Registry	6	Maybe
Epoetin alfa	Trial	19	No
Epoetin alfa	Registry	6	No
Maraviroc	Registry	108	Maybe
Anidulafungin	Trial	30	No
Anidulafungin	Trial	42	No
Trabectedin	Trial	3	No
Fluticasone furoate	Trial	19	Yes
Fluticasone furoate	Trial	24	Yes
Epoetin zeta	Survey	12	No
Epoetin zeta	Registry	5	No
Epoetin zeta	Trial	14	No
Raltegravir	Registry	60	Maybe
Raltegravir	PK study	1.5	Yes

Planned duration and study type was reported by Blake et al. (Blake et al. 2011). In seven cases, a reference to the requested PASS was found in the text of the safety variation. In another six cases, a potential reference to the requested PASS in the text of the safety variation was found but could not be verified based on publicly available information.

Results

Cost-effectiveness

In total, we found 334 safety variations by 1 January 2014, for 41 out of the 47 new active substances that were approved in 2007. Spontaneous ADR reports were the source of 31% of all variations; clinical interventional studies contributed to 25% of all variations; and observational studies resulted in only 2% of all safety variations (Figure 2).

Five of the 47 products had at least one safety variation (seven variations in total) for which we could verify the requested PASS as the source of the safety variation. For another six variations, we suspect that the requested PASS was the source of the safety variation but we were unable to verify this based on publicly available information. When combined, this resulted in 13 SmPC changes for which the requested PASS was likely to be the safety variation source (Table 2). We estimated the total costs of the 31 PASSs in the range[1] of €84 million to €126 million in total (Table 3).

The incremental effects of full regulation are 13 SmPC changes (seven definite and six probable) that would not have happened if only routine pharmacovigilance would have been requested for the 47 products in our cohort. The estimated total costs ranged from €84 million to €126 million. Using both the lower and upper ranges for the incremental effects (seven and 13 SmPC changes; €84 million and €126 million) we estimated an incremental cost-effectiveness ratio of PASSs for the 2007 new active substances of €6.5 million to €18.0 million per additional SmPC change (Table 3).

Planned duration and study type were reported by Blake et al. (Blake et al. 2011). In seven cases, a reference to the requested PASS was found in the text of the safety variation. In another six cases, a potential reference to the requested PASS in the text of the safety variation was found but could not be verified based on publicly available information.

Discussion

Main findings

For 22 out of 47 new active substances that received a positive opinion in 2007 at least one PASS was requested by the CHMP. After six years of follow-up (until 31 December 2013) about half (52%) of all requested PASSs resulted

Table 3: Cost-effectiveness results

Regulatory Scenario	Costs (PASSs)	Effectiveness (SmPC changes)	Incremental cost-effectiveness ratio (lower range)	Incremental cost-effectiveness ratio (upper range)
Full regulation	€ 84 – € 126 mil	334	€ 6.5 million per SmPC change	€ 18 million per SmPC change
Limited regulation	0	321-327		

The range of study costs was calculated by applying 20% lower and upper limits to the point estimate of €105 million for all 31 PASSs. The range of total number of SmPC changes was derived as there were seven SmPC changes that were deemed to be the result of a requested PASS and another six SmPC changes (13 total) that were scored as probably the result of a requested PASS.

[1] *The costs were estimated at 105 million euros. The range was calculated by ±20%.*

in a change to the product's SmPC, which accounts for 9.5% of all post-marketing safety variations for these products. The total costs of conducting the 31 PASSs were estimated to be in the range of €84 and €126 million. Combining these estimates resulted in an incremental cost-effectiveness ratio of €6.5 million to €18.0 million per additional SmPC change.

Limitations

Our study has several limitations. First, we had access only to publicly available information regarding the results of the 31 requested PASSs and it is possible that we misclassified some of the sources of the type IA/IB/II safety variations based on the procedural information we used. Furthermore, we did not have access to the cost data of the actual 31 requested PASSs. In order to accommodate the uncertainty regarding the cost estimates we report only a broad range of the total estimated costs of all of the studies, but we cannot exclude the possibility that the actual costs of these studies were higher or lower than we estimated. We also did not perform sensitivity analyses to assess this uncertainty other than using upper and lower ranges for both the cost and effects estimates. Finally, we did not include any other costs - such as regulatory costs or societal costs - in our analyses.

With respect to the effects, it should be noted that PASSs are often requested to reduce uncertainties about safety concerns of medicines. As a consequence, one of the intended effects of a PASS is to prove safety, rather than to identify previously unlisted ADRs. It is known that this type of knowledge (proven safety) is less frequently reflected in EU SmPCs (Warnier et al. 2014). Our effectiveness endpoint (SmPC changes) is therefore not sensitive enough to pick up all intended effects of PASSs, resulting in an underestimation of possible effects.

Our results assessed the cost-effectiveness of PASSs for all new active substances that entered the market in 2007. We cannot extrapolate our results to new active substances that were approved in other years, as the total number of SmPC changes and types of PASSs requested are to a large extent dependent on the type of product. Furthermore, it is possible that in other years the total number of PASSs that were requested differed as well. We did not translate the SmPC changes into actual health outcomes (in terms of quality-adjusted life years gained), therefore we are not able to comment on the impact on public health. Furthermore, we do not know what level of cost-effectiveness would be acceptable to society regarding the incremental costs per SmPC change and therefore we cannot conclude whether or not the incremental effects of PASSs outweigh their incremental costs.

Conclusion

Although the majority of requested PASSs in 2007 resulted in a change to the product's label, PASSs that are specifically requested by regulatory authorities are not the main source of new safety information listed in the SmPC within the post-marketing setting, but the costs of conducting these studies appear substantial. Ways to increase the efficiency of PASSs, as well as the societal value of pharmacovigilance activities should be explored.

Acknowledgements

The results in this case report originate from Bouvy et al. 2014 (full manuscript in preparation). We would like to thank all participating companies in the survey for their efforts, as well as discussions about the results with participants at the Escher Workshop in May 2014. We also would like to thank Isabelle Stoeckert and Sarah Montagne at Bayer; and the EFPIA PRAC Task Force and discussions with Kevin Blake at EMA for their input.

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4 DEALING WITH REGULATORY UNCERTAINTY AROUND MARKETING AUTHORISATION

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4.1 Introduction

Decision-making during marketing authorisation application (MAA) procedures is complex and requires science-based judgments of vast amounts of data. Good regulatory practice should aim for high-quality decision-making that is, amongst other things, predictable, consistent and transparent (WHO 2014). A complicating factor in achieving this goal is that regulations cannot cover every possible situation that may be encountered during MA. Innovative technologies or products targeting novel targets are especially difficult to regulate, as the established framework of laws, guidelines and procedures is generally less well-equipped to deal with novelty. Regulators therefore need a certain amount of flexibility to apply existing regulatory instruments to a wide variety of products. However, flexibility may also lead to uncertainty about which standards and procedures will be applied to products in development. This 'regulatory uncertainty' may influence the behaviour of both companies and regulators.

A detrimental effect of regulatory uncertainty is that it may adversely influence incentives for the development of new medicines (Dickson and Gagnon 2004; DiMasi et al. 2010; Budish et al. 2013; Stern 2014). When companies experience uncertainty about standards and procedures in a particular therapeutic area, they may be less likely to invest in this area or may play safe and spend resources on studies or procedures that are ultimately regarded of limited value when obtaining MA. What is more, with high regulatory uncertainty, regulators may become overly risk-averse in the assessment of products (Eichler et al. 2013). Uncertainty on the part of regulators could also lead to inconsistencies in the application of regulation, with potential consequences for MA outcomes and assessment times. An example of this is the 'familiarity effect' which indicates that under conditions of uncertainty, regulators will consider the products and claims of well-known applicants more credible, which leads to variation in assessment times between applicants (Carpenter and Ting 2005).

Ultimately, both companies and regulators benefit from a robust and predictable decision-making process (Liberti et al. 2009). Therefore, this chapter aims to provide insight into regulatory uncertainty by asking two questions: first, under what conditions is regulatory uncertainty likely to be present; and second, how can it be reduced? The chapter focuses specifically on regulatory uncertainty in the application and use of MA procedures. It draws from case-studies on conditional marketing authorisation (CMA) and the mutual recognition/decentralised procedure (MRP/DCP), which were presented in Chapter 3.2 and Chapter 3.3. We conclude with a number of considerations for dealing with regulatory uncertainty in the use of MA regulation.

4.2 Regulatory uncertainty

We define regulatory uncertainty in the application of MA regulation as the perceived inability of regulators and companies to predict and select the course and outcome of an MA procedure (cf. for general definitions: Milliken 1987; Hoffmann, Trautmann, and Schneider 2008). This includes uncertainties about regulatory decision-making on the content of MAAs, i.e. uncertainties about how scientific data will be assessed, as well as on the structure and format of the procedure, including timelines, responsibilities and administrative issues. Decision-making on the content of MAAs is not merely a binary decision to grant or refuse a marketing authorisation but also covers decisions on indication areas, claims in labelling and post-marketing commitments, amongst others.

Regulatory uncertainty can be differentiated from technological uncertainty, i.e. uncertainty about the performance or mechanism of action of a medicinal product (Eichler et al. 2013). The two are, however, related in that technological uncertainty usually leads to regulatory uncertainty, particularly when developing and evaluating innovative products for which specific standards have not been established. For instance, DiMasi et al. observed significant variation in the development success rates of antibiotics (high) and central nervous system (CNS) medicines (low). (DiMasi et al. 2010) They attributed this variation to differences in the level of uncertainty about the underlying scientific knowledge base (technological uncertainty) resulting in a lack of specific guidance and evaluation standards for MAAs (regulatory uncertainty). However, even when technological uncertainty is virtually absent, regulatory uncertainty may occur, for example around the introduction of new regulation or when existing regulation is complex. The introduction of the Paediatric Regulation in 2007 introduced, for example, uncertainties about the interpretation of key terms in the regulation; requirements for the conduct of studies; and pay-offs for completed Paediatric Investigation Plans (see also Chapter 3.4)[1].

Due to inherent variability between products, uncertainty is an integral part of regulation. However, since predictability of MA procedures facilitates efficient and consistent regulatory decision-making, there is a strong case to reduce this uncertainty. In order to do so, generic as well as tailor-made measures can be employed. Generic measures apply to entire sets of products at once, and aim for consistent and equal application of regulation across these products or for providing clarification on what should be the content of MAAs, for example through the provision of evidentiary standards in written guidelines. They may also deal with inconsistencies in the structure and format of MA procedures, for example through the introduction of decision-making tools, adoption of standard operating procedures or staff training. Recent examples of such efforts include pilots for the introduction of structured benefit-risk assessment (Zafiropoulos et al. 2012; EMA 2014a) and the promotion of 'good review practices (GRevP)' (WHO 2014).

Tailor-made measures deal with regulatory uncertainty surrounding individual products. This is mainly done through the provision of information and clarification on what should be the content of MAAs. Tailor-made measures usually take the form of question-and-answer sessions and dialogues between regulators and

[1] *Since we focus on regulatory uncertainty in the application of MA regulation, we refrain from analysing this case further.*

companies. Since part of this form of guidance can also be provided through generic measures, the regulatory system needs to strike a balance between the two. In recent years this balance has shifted towards an increased use of tailor-made measures (scientific advice) as opposed to generic measures (written guidance). This may well be a consequence of a shift away from a blockbuster model towards a targeted therapy approach that focuses on rare diseases and specific patient populations (Trusheim et al. 2007; Tambuyzer 2010; Milne et al. 2014). It can be expected that the resulting increase in variation in therapeutic approaches has made it more difficult to establish generic guidance for entire sets of products.

To increase our understanding of regulatory uncertainty, we focus in the next section on the occurrence of regulatory uncertainty in a situation of relatively high technological uncertainty (CMA procedure) and relatively low technological uncertainty (MRP/DCP).

4.3 Case study examples

Conditional marketing authorisation

The CMA regulation was created in 2006 to accommodate the wishes of patients for early access to medicines that fulfil an unmet medical need (EC 2006a). CMA can be granted based on limited clinical data, but only on four conditions: that medicines show a positive benefit-risk balance; that they fulfil an unmet medical need; that the benefit to public health of immediate availability outweigh the risks; and that more data will be generated after MA. Within the context of the case study on the use of CMA for oncology medicines (Chapter 3.3) we identified several sources of regulatory uncertainty.

A first source of regulatory uncertainty that we observed is uncertainty about the interpretation of key terms in the CMA regulation. This type of uncertainty is particularly observable in the use of evaluation criteria for CMA, especially the evaluation of the benefit-risk balance and the level of unmet medical need of a product. CMA can only be granted to medicines that show a positive benefit-risk balance, which implies that the same evaluation criteria need to be applied by regulators as those for standard MAs. Several interviewees noted that this situation creates uncertainty about the exact evidentiary standard that would be sufficient for obtaining a CMA. It seems that in the absence of clarity about these standards, opportunities to apply CMA are sometimes narrowed down, while it also becomes challenging to apply the procedure efficiently. For instance, companies found it difficult to predict under what conditions the use of surrogate endpoints would be accepted or the extent to which early results of ongoing studies would play a role in the MA procedure. To illustrate this, we observed a case of a product for a rare cancer type where the company claimed that efficacy data on objective response rate (as a surrogate endpoint) should be considered as a clinically meaningful endpoint. Since there was no regulatory precedent, an important issue during this MA procedure was to reach agreement on the acceptability of this endpoint. This resulted in a relatively long and complex procedure with advice taken from the Scientific Advisory Group on Oncology on this matter and an additional oral explanation from the company relatively late in the procedure. It is difficult to extrapolate from this case, but we observed similar challenges in other CMA procedures due to lack of clarity about the interpretation of evaluation criteria, which may have contributed to the observed longer assessment times for these products (Chapter 3.3).

A complicating factor and second source of regulatory uncertainty is that specific guidelines for CMA eligible products often do not exist, as CMA is intended to regulate innovative products that fulfil an unmet medical need, i.e. products for an indication area in which no or

a limited number of therapies is available. This often results in the joint occurrence of technological and regulatory uncertainty, making the outcomes of the MA procedure difficult to predict. In one of the MAs investigated in our study, regulatory uncertainty was for instance reflected in a discussion between regulators and the European Commission on the specific wording of the therapeutic indication. The CHMP proposed granting a standard MA to a targeted therapy with an indication that contained a qualifying claim, stating that for some patients with a gene-negative status the benefit was not fully confirmed. This indication was, however, not accepted by the European Commission, necessitating additional discussion on the benefit-risk balance of the product and, finally, a proposal to grant a CMA late in the MA procedure.

A third source of uncertainty stems from overlap in scope between the CMA and standard MA procedure. When a product fulfils an unmet medical need, and treats a severely debilitating or life-threatening disease, it may qualify for a MA via the standard as well as the CMA pathway. Overlap between the two pathways results in a situation where companies try to keep both options open as long as possible by not requesting CMA upfront (only 2 out of 11 products). This happens despite the fact that, in theory, CMA would allow for early market access and initial revenues while studies are still ongoing. However, it seems that uncertainties about the chances of reimbursement for products authorised via the CMA pathway discourages companies from requesting CMA upfront to such an extent that some companies did not make an upfront CMA request even when they already knew that it was unlikely that data would be sufficient to obtain a standard MA. As a consequence, the procedures for these products became challenging, because the option of CMA was discussed only once initial consensus had been reached that a standard MA could not be granted. Over time, this has led to a situation in which the perception of the CMA pathway has become one of a 'rescue option'. It seems, therefore, that uncertainties about the pay-off of choosing a particular regulatory strategy have had a pronounced influence on the successful introduction and use of the CMA pathway.

Mutual recognition/decentralised procedure

During the mutual recognition and decentralised procedure (MRP/DCP), companies can obtain an MA in multiple Member States at once, based on recognition by national authorities of a first assessment performed by one Reference Member State. Within the context of the case-study on the MRP/DCP pathway (Chapter 3.2), we identified a number of sources of regulatory uncertainty in the application of this procedure.

First, as is also seen during the CMA procedure, companies experience uncertainties about the interpretation of key terms in the MRP/DCP regulation. Member States can disagree with the assessment of a Reference Member State on the grounds of a 'potential serious risk to public health' (PSRPH). However, it is difficult to predict when a PSRPH arises. Despite detailed guideline explaining the nature of PSRPHs (EC 2006b), many points of disagreement between member states can potentially be categorsed as a risk to public health. Furthermore, there seem to be differing perspectives on this matter between Member States. To reduce this uncertainty, a list has been created containing objections that will not usually be considered as grounds for a PSRPH (EC 2006b). Only a limited number of procedures currently end in a CMDh referral (see Chapter 3.2). Also, the frequency of PSRPHs leading to CMDh referrals has been decreasing over the years, occurring in 1.6% of the procedures in 2013 versus nearly 15% in 2006 (data on file). These numbers indicate that learning takes place at the level of regulatory agencies and companies on what qualifies as an PSRPH, although the outcome may also be explained partly by

companies anticipating PSRPH objections and running several parallel procedures, or withdrawing their applications in one or more member states to prevent referral procedures.

A second source of uncertainty is introduced by the flexibility on the part of applicants to choose between the centralised procedure and DCP/MRP for a group of generic and non-prescription medicines. Like the use of CMA, this introduces uncertainty about the expected pay-off when choosing a particular pathway. Choosing the centralised procedure opens up a possibility for obtaining a marketing authorisation in all EU member states at once. This may be a favourable option for generic medicines that have harmonised summaries of product characteristics (SmPCs) across Europe. However, a choice to follow the centralised procedure may come at a price, as the policies of non-prescription medicines differ in various European countries. For example, in the UK two categories of non-prescription medicines exist: pharmacy-only medicines (POM), available without a prescription under supervision of a qualified pharmacist; and general sales list (GSL) medicines available without a prescription, from outlets such as a chemist or supermarket (Aronson 2009). In the Netherlands three categories exist, including medicines that may be sold by qualified pharmacists only; those sold by pharmacists or chemists; and general sales products that may also be sold at outlets such as supermarkets (CBG 2014). As Member States have different categorisations of non-prescription medicines, consensus-seeking between member states may increase the likelihood that regulators err on the side of caution and grant a restricted marketing authorisation, which could have negative commercial consequences for the company. Therefore, companies often opt for a decentralised procedure (although this option is not possible for products already authorised via the centralised procedure when companies want to apply for a 'switch' from prescription to non-prescription status). While opting for multiple decentralised procedures is more cumbersome, it provides a possibility for tailoring the application to different approaches towards self-medication in the various Member States. Therefore, non-prescription companies may prefer a non-harmonised (and thus less predictable) situation, which provides flexibility for adjusting strategies to individual countries or regions, rather than a harmonised but restrictive (and predictable) situation. This is not optimal, and several proposals have been made to improve the workings of the MRP/DCP for the non-prescription sector. It has been suggested that separate versions of product information documents could be created for non-prescription and prescription-only products, which could be assessed in a single procedure. Alternatively, a single product information document could be created containing several subsections, some of which could then be completed in different ways according to national legal status. This would be analogous to the so-called 'blue box', which is a country-specific part of labelling and packaging that includes additional information to satisfy specific national requirements for the product, for example on reimbursement status or specific warning pictograms (CMDh 2014). While this would provide flexibility, it also conflicts with the idea of harmonised product information and may make it more challenging to reach a single benefit-risk assessment for products where use differs between countries.

A final source of regulatory uncertainty concerns timelines for obtaining MA. As lengthy national authorisation processes demonstrate, these are not always adhered to in practice even when strict regulatory deadlines exist, for example the maximum time of 30 days to national approval following a positive outcome in the case of the MRP/DCP. This seems very much in contrast to the situation at the centralised European level, where adherence to assessment deadlines is high. Apart from differences in assessment times, there are also

considerable differences between Member States in timelines for implementation of European decisions. Reasons for such differences are likely to be related to differences in resources available at national regulatory agencies in the various member states and the existence of specific national requirements. Thus, even if regulations are clear, situations may exist that lead to a failure to adhere to these regulations, causing unpredictable delays in the access to medicines.

4.4 Dealing with regulatory uncertainty

Completely resolving the aforementioned sources of regulatory uncertainty is neither possible nor always desirable. Uncertainty about how to apply MA regulation is integral to regulatory processes and the two case studies show that it occurs in situations of both high and low technological uncertainty. Guidance on the content, format and structure of MA procedures cannot cover all potential decision-making options that regulators and companies face during the development and evaluation of medicines. Also, regulators are mostly 'reactive', i.e. they do not develop products but base their decisions on data generated by companies. As a result, many concerns and questions about medicines may become apparent only after regulators receive a dossier (Melchiorri et al. 2013). This is especially the case with joint occurrences of technological and regulatory uncertainty, where lack of knowledge and experience precludes *a priori* guidance on some aspects of product development. In these situations regulatory norms and novel products co-evolve, i.e. they are developed simultaneously, as has been observed in the development of advanced therapies and biosimilars.

Although certain forms of uncertainty may always persist, there are good reasons to search for ways of reducing regulatory uncertainty. To do so, both generic and tailor-made measures can be used that aim to provide critical information or to improve consistency in the application of regulation. The provision of critical information seems especially applicable for the regulation of novel products or novel targets, or for the introduction of novel regulatory pathways and/or instruments. Improving consistency in the application of regulation is applicable for complex regulation and decision-making procedures, or when there is a lack of knowledge or experience by companies and regulators about the application of these procedures. Below we provide two main considerations when dealing with uncertainty.

Early dialogue for innovative products

Examples from the CMA procedure demonstrated that given high regulatory uncertainty there are benefits to providing more clarity on pathway use before starting the MA procedure. This may pre-empt challenging and complex MA procedures with unexpected outcomes and lengthy assessment times (see also Chapter 3.3). In the current regulatory system, this can be achieved only through measures that are tailored towards individual products. In this respect, the scientific advice instrument provides a formal and neutral setting for scientific review of data and for dialogue between regulators and companies about these data. Obtaining early scientific advice and complying with advice have been linked to an increased chance of obtaining a positive MA (Eichler et al. 2010; Regnstrom et al. 2010; Putzeist et al. 2011). Possibilities could therefore be explored to extend the mandate of this policy instrument which, in light of this chapter, seems especially important for innovative medicines that treat unmet medical needs.

Strengthening the role of scientific advice for innovative products is also a key priority in the current adaptive licensing pilot that provides a safe harbour environment for

interaction between regulators and companies on experimental medicines (EMA 2014b). Dialogue in this environment allows for a more iterative 'question and answer session' to discuss an optimal pathway towards MA during early stages of development, involving a wider array of stakeholders including payers, reimbursement agencies and patient representatives. Such an approach addresses concerns that the current scientific advice procedure is too much of a 'one-way street', whereas for truly innovative products a real dialogue may be more appropriate (Eichler et al. 2012). For such a strategy to work it is, however, particularly important to better understand how companies and regulators explicate regulatory and technological uncertainties during scientific advice and to establish whether or not there is willingness to follow and adhere to this advice. Effective strategies to reduce regulatory uncertainty can be implemented only with improved clarity on this matter.

Instead of increasing the opportunities for tailor-made advice, another route to reduced uncertainty would be to further develop and refine written guidelines for product categories. However, given the trend towards medicines development for small indication areas and rare diseases, this is likely to be a challenging and resource-intensive effort, unless it is accompanied by more homogenous evidentiary standards for larger groups of products as an alternative way to reduce uncertainty. For instance, *in extremis* one could think of a regulatory system in which all oncology products are granted market access only after showing benefit on overall survival. Although this would largely decrease regulatory uncertainty, it would also require substantial changes to the regulatory system and would most likely delay access to promising and potentially life-saving medicines. This extreme example illustrates, however, the need to strike a balance between tailor-made measures (dialogue) and generic measures (written guidance) when determining and communicating evidentiary standards. Striking this balance is as much a political as a scientific decision.

The case studies also provide hints that flexibility in the application of regulation may lead to lower predictability of the course and outcome of the MA procedure. However, despite this association it may not always be wise to instantly reduce regulatory uncertainty, especially not during early stages of development. For example, the difficulty for regulators during scientific advice is to give their view on requirements for marketing authorisation when many relevant data have not yet been generated. Strict and potentially binding advice on further development of the product may in this case close a window of opportunity for product development, which may not be in the interest of patients and public health. A similar argument can be made with respect to the development of guidelines for an emerging therapeutic area. Although written guidelines will reduce uncertainty for development in that therapeutic area, they may also limit the opportunity for innovative development. Besides finding a balance between the application of generic and tailor-made measures, a major challenge is therefore to find the appropriate moment for the application of these measures. This moment may well differ between individual products and therapeutic areas.

Consistent application of regulation

Even when high technological uncertainty limits the predictability of decisions on the content of MAAs, it may still be possible to reduce uncertainty about the format and structure of MA applications and procedures. Attempts by regulators to make benefit-risk assessments of both prescription and non-prescription medicines more consistent and transparent, through the development of decision making models, are promising in this respect (Phillips et al. 2011; Mt-Isa et al. 2014; Brass et al. 2011). The EMA is currently piloting

the use of effects-tables, which aim to provide insight into the assessment of benefit-risks and uncertainties in scientific data. Ongoing activities to create 'good review practice (GRevP)' also contribute to continuous quality improvement by making regulatory review procedures more consistent (WHO 2014).

Increased experience of regulators and companies in the application and use of regulation may also lead to more consistency in the application of regulation. This was, for instance, illustrated by a reduction in the number of CMDh referrals over time. However, care should be taken here as a more predictable system due to increased experience does not necessarily signal efficient use of regulation. We showed that there are situations in which companies adapt to the regulatory environment in unintended ways. For example, they may avoid particular regulatory options (e.g. not requesting CMA upfront, and running various parallel procedures in a limited number of member states in a MRP/DCP), or they may adopt a 'wait-and-see approach' so as to maximise chances of obtaining a standard MA. In these cases, the system may have become more predictable and less uncertain over time, yet may not necessarily achieve its goals of providing timely access to promising medicines.

To prevent these adverse effects, instruments to improve consistency in the application of regulation should be accompanied by ongoing monitoring and evaluation of these instruments as further discussed in Chapter 5. Such efforts could contribute to uncovering why regulatory uncertainty occurs and whether or not the direction in which it is reduced is desirable. This is especially important, as regulatory uncertainty is a perceptual rather than an objective phenomenon. As a consequence, some uncertainties may be shared by many, while others are unique to some companies (e.g. SMEs). It goes without saying that measures to reduce uncertainty should be sensitive to these differences.

4.5 Conclusion

This chapter provides insight into the concept of regulatory uncertainty to show that – alongside technological uncertainty – regulators and companies may experience uncertainties about the course and outcome of MA procedures. Regulatory uncertainty has become prominent in recent years due to greater variation in medicines development (e.g. in oncology) and the creation and use of multiple MA pathways to accommodate this variation. In order to reduce this uncertainty it is necessary to increase mutual understanding on how current regulation is applied. Two measures are key to this. First, constructive and timely dialogue between stakeholders is needed to increase mutual understanding on directions of medicines development and the content of MAAs from early phases of development onwards. This is especially important for regulating innovative medicines that treat unmet medical needs, as for these medicines regulatory uncertainty is expected to be high. Second, further efforts to increase consistency in decision-making should be encouraged and embedded in broader efforts to monitor and evaluate regulatory instruments. Both of these measures will contribute to the creation of a regulatory environment that is conducive for learning, which ultimately contributes to public health through facilitating responsible innovation.

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5 THE EVALUATION OF REGULATORY INSTRUMENTS

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5.1 Introduction

The regulatory system for medicines is intended to protect public health, by ensuring that only medicines of sufficient quality, safety, and efficacy are allowed to enter the market, while simultaneously seeking to promote public health, by facilitating patient access to needed therapies without unnecessary delay. It strives to achieve these goals via a large set of individual regulatory instruments, all of which describe certain conditions or requirements related to the quality, safety, and efficacy of medicines. These conditions could require actions both before as well as after marketing authorisation of medicines. Different types of regulatory guidance, including directives, guidelines, notes for guidance, or other types of regulatory requirements could all be considered a regulatory instrument.

Despite the regulatory system's aims, stringent regulatory requirements have been identified as one of the reasons for the increase in costs of pharmaceutical research and development (R&D) (Scannell et al. 2012; Munos 2013). Therefore, the opportunity costs[1] of new regulatory requirements should be considered (Eichler et al. 2013) in the development of these regulatory instruments but until now, these have not usually been taken into account (Bouvy 2013). Since the regulatory system uses public resources to regulate private sector activities, an assessment is needed as to whether or not the regulation of these activities is justified. In addition, the size of public and private resources required to attain the regulatory system's objectives (such as public health gains) needs to be determined, as well as how efficient regulatory functions are in achieving these objectives (Ratanawijitrasin and Wondemagegnehu 2002).

'Revisability' is a required condition for the accountability of healthcare policy-making (Daniels and Sabin 2008) and means that if a healthcare policy is evaluated and then subsequently found not to be achieving its goals, it should either be revised, or replaced by a better policy, or removed. This concept of revisability could be extended to regulatory instruments as well and would mean that if a regulatory instrument is not functioning as intended, there are grounds for adaptation, replacement, or even removal from the regulatory system (Prieto et al. 2012). Currently, evaluations of regulatory

[1] *Opportunity cost: the (monetary) value of the best alternative not chosen. In the case of opportunity costs of regulatory requirements, this means that given a finite budget for R&D, all resources that a company has to spend on complying with regulatory requirements for generating evidence of quality, safety, and efficacy for one product cannot be spent on anything else, e.g. the development of other medicines.*

instruments are performed without clear policy consequences and, thus far, regulatory requirements have hardly ever been removed from the regulatory framework, even if a strong case for removal could be made with little or no impact on the safety of medicines (Scannell et al. 2012).

In this chapter, we present a framework for the evaluation of regulatory instruments. This framework outlines different aspects that could be subjected to an evaluation, and we discuss a number of methodological considerations as well. The results of the case studies described in Chapter 3, along with other reports and scientific publications, are used as illustrative examples. We conclude with a number of considerations that need to be taken into account for the embedding of evaluations within the regulatory framework for medicines in Europe.

5.2 A framework for the evaluation of regulatory instruments

Components of the evaluation of regulatory performance

Based on a logic model approach (Schalock and Bonham 2003) we have identified four components of regulatory instruments that can to be addressed in an evaluation (Figure 1):

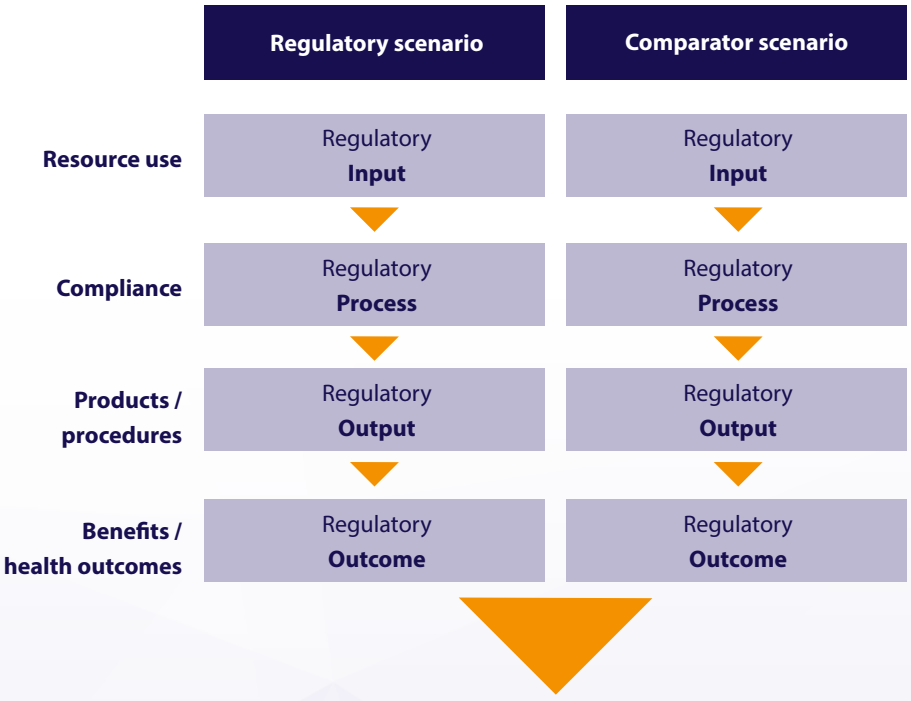
- Regulatory **inputs**: the resources required for the instrument to function as part of the regulatory system. These include the required regulatory resources at regulatory agencies as well as resources for pharmaceutical companies – for example, costs of performing studies that are outlined by a regulatory instrument (e.g. a guideline for performing clinical trials) and the costs of assessing the results of these studies by regulatory authorities.
- Regulatory **process**: the activities or processes that take place as a result of the instrument being part of the regulatory system, both at pharmaceutical companies and regulatory authorities. Compliance with a regulatory instrument is a regulatory process component and relates to the extent to which the activities of pharmaceutical companies are in line with the requirements set out by a regulatory instrument.
- Regulatory **outputs**: the outputs that are directly produced by the instrument. This includes, for instance, the number of procedures completed or medicines evaluated by a regulatory instrument. For example, the outputs of a guideline that requires a certain clinical trial to be performed for new medicinal products can be measured as the total number of clinical trials performed by pharmaceutical companies according to the specific guideline.
- Regulatory **outcomes**: the (societal) benefits that follow indirectly from the instrument's outputs. This includes, for example, morbidity/mortality averted as a result of the regulatory instrument.

An instrument's *direct* regulatory **outputs** always need to be translated into its *indirect* societal benefits, such as public health impacts, in order to determine the **outcomes** of a regulatory instrument. Although all regulatory components can be studied separately, a *comprehensive* evaluation of a regulatory instrument – such as a periodic evaluation of a major legislative reform – would have to include all of these components. In the regulatory science literature, few comprehensive assessments have been described thus far. Studies have assessed the resource use resulting from requirements related to post-approval safety (Ridley et al. 2006); the functioning of a regulatory instrument's process (Arlett et al. 2014); or compliance with a specific regulatory instrument such as pregnancy prevention programmes (Crijns et al. 2011). Other studies have focused on regulatory outcomes such as direct healthcare professional communications (DHPCs)

issued (Mol et al. 2010; Piening et al. 2012); or have compared the regulatory pathways used for different types of medicines (Putzeist et al. 2013). Additionally, several studies have assessed the impact of regulatory instruments on outcomes – such as the effect of risk communications on medicine use (Piening et al. 2012); or the cost-effectiveness of regulatory instruments (Bouvy et al. 2012; Bouvy et al. 2013).

The case studies reported in Chapter 3 are all partial evaluations of different regulatory instruments. The case study reported in Chapter 3.6 on the cost-effectiveness of PASSs has included most of the elements described above (See Chapter 3.6, Figure 1): the analysis considered resource use (inputs); the number of studies performed as a result of the instrument (outputs); and the outcomes of the regulatory instrument as determined by changes to a product's label as a consequence of a PASS resulting in new safety information (outcomes). Furthermore, the evaluation is also comparative, as we assessed the regulatory inputs, outputs, and outcomes of the regulatory system in an alternative scenario without the regulatory instrument (see Chapter 3.6 for more details).

Figure 1: A Framework for the evaluation of regulatory instruments



Determining the added value of a regulatory instrument requires comparison to the regulatory system without the regulatory instrument, so that a comparative analysis is possible. Regulatory cost-effectiveness analysis involves using a non-health outcome endpoint. Regulatory cost-utility analysis involves expressing health outcomes in quality-adjusted life years (QALYs).

Regulatory outcomes can be defined as any outcome related to the procedure. When a non-health outcome is used as the endpoint, such as new safety issues identified or number of dear healthcare professional communications (DHPCs), a cost-effectiveness analysis can be performed. When the regulatory outcome is a QALY, a cost-utility analysis can be performed.

Methodological considerations

Comparator selection

Although the outputs or outcomes of a regulatory instrument can be assessed in isolation, a comparative analysis is required if one wants to determine the added value of the instrument, as we are usually interested in the impact of an intervention on a certain outcome as compared with an alternative course of action. In practice, this means that the outputs and/or outcomes of the regulatory instrument need to be compared with the outputs and/or outcomes of the regulatory system for medicines without the instrument (Figure 1). In some cases, comparisons with other regulatory settings (e.g. different countries or regions) or comparisons of different years could be considered, but usually a comparison to a hypothetical regulatory scenario needs to be made (Bouvy 2013).

The need to select a comparator for a regulatory instrument has several implications. Although experimental settings are possible to evaluate healthcare interventions (such as a clinical trial to assess the efficacy of a medicine), this option will generally not be available for regulatory instruments, because it is usually not possible to exempt certain products or patient groups from a regulatory measure. A baseline measurement (with regard to outputs and public health outcomes) from before the instrument is implemented ideally serves as a comparator for the evaluation in such cases. However, when no baseline measurement is available, the comparator would be a (hypothetical) no-regulation scenario in which the instrument would not exist and the outputs of the instruments will be assumed to be non-existent.

In the study on the cost-effectiveness of PASSs described in Chapter 3.6 we designed this comparator – a (hypothetical) no-regulation scenario – as follows. We used the cohort of all new active substances that were approved in 2007 (n=47). For about half of these products, at least one PASS was requested at market entry. We assumed that if only routine pharmacovigilance activities had been required, none of these PASSs would have been conducted, and thus any new safety information resulting from these requested PASSs would not be available. Subsequently, we found 334 safety variations for 41 of the 47 new active substances, and we found that for seven variations, one of the requested PASSs was the source of the safety variation (furthermore, in another six variations we deemed it likely that a requested PASS was the source of the safety variation). Therefore, we assumed that under a no-regulation scenario, where none of these PASSs would have been requested, these 13 variations would not have been available. The differences between the two regulatory scenarios with regard to the regulatory outcomes (as measured in safety variations) are the 13 safety variations that were a direct result from one of the requested PASSs.

Linking of regulatory outputs to regulatory outcomes

The (public health) outcomes of a regulatory instrument are generally related to a change in the effectiveness, quality or safety of medicines (Ratanawijitrasin and Wondemagegnehu 2002), which subsequently could result in a decrease or increase in either disease burden or incidence of adverse drug reactions in clinical practice. In order to establish an association between regulatory outputs and outcomes, a mechanism needs to be established that translates outputs into societal benefits, because a high level of compliance with regulatory processes, and the regulatory outputs themselves, are not sufficient on their own to assume positive health outcomes. Establishing such a mechanism clearly is generally difficult, especially when several years pass between the implementation and evaluation of the regulatory instrument, an issue that has also been recognised for the evaluation of the effectiveness of risk minimisation activities (Prieto et al. 2012). For example, in the case study on the

cost-effectiveness of PASSs (Chapter 3.6), we found 13 SmPC changes that we could verify as being the result of the requested PASS. However, we did not translate these regulatory outcomes into public health benefits.[2]

Another consideration that is often overlooked when linking regulatory outputs to outcomes is that the health impact of a regulatory instrument is determined in large part by the *frequency* or volume of medicine use in the population. Two medicines could have the same rare, but severe, adverse drug reaction, but still have very different total impacts on public health if one of the medicines has a low volume of use and the second a high volume. Furthermore, the outcomes of regulatory instruments are frequently driven by changes in the behaviour of healthcare professionals and/or patients. In the case of the new pharmacovigilance legislation this could mean that better information regarding adverse drug reactions is available so that doctors and/or pharmacists can take actions to prevent an adverse drug reaction from occurring in a patient. In case of the Paediatric Regulation, adverse events could be prevented due to better information on appropriate dosing and prescribing in children. Currently, a substantial gap can exist between the regulatory world and clinical practice, despite the fact that the *effectiveness* of many regulatory instruments is largely determined by what happens in clinical practice.

In the impact assessments that were performed for both the new pharmacovigilance legislation and the Paediatrics Regulation, the potential positive health benefits of implementing the regulations were calculated. However, in both cases, secondary sources (i.e. literature estimates) were used to estimate health impacts. A study from the US was used for the estimation of the costs of adverse drug reactions in the European population occurring outside a hospital setting, and this study was extrapolated to the European setting (EC 2008). This means that data in the impact assessment cannot be used as a baseline measurement for a future evaluation of the new pharmacovigilance legislation. Although the use of secondary data sources such as published studies or data from other regions such as the US is understandable, given the lack of readily available primary data sources for the European setting, the reliance on secondary data in impact assessment makes the performance of a high-quality evaluation of the legislation in question problematic. In order to overcome this issue, the public health estimates for future impact assessments should be made in such a way that they could be replicated at the time of a formal evaluation with more recent data. For example, if databases are used for predictive calculations then the same databases should preferably be used (including identical study methods) at the time of an evaluation.

Impact assessments by the European Commission are published several years before regulatory reforms are finalised. This means that in the case of the new pharmacovigilance legislation, adaptations in regulatory requirements were not taken into account in the initial impact assessment. The consequences of this can be seen in the case study on the resources required for compliance with European pharmacovigilance requirements (Chapter 3.5). The impact assessment predicted that the company resources required for PSURs would decrease as a result of simplifications to the PSUR requirements. The survey did find that, on average, the

[2] *If we had wanted to perform a cost-utility analysis of PASSs, we would have had to translate SmPC changes into their impact on safety and/or effectiveness of the medicines in clinical practice, in terms of the number of QALYs gained. Doing so was beyond the scope of the study, but previous studies (Bouvy et al. 2012, Bouvy et al. 2013) have demonstrated the feasibility of such an approach.*

annual number of PSURs submitted to regulatory authorities decreased for companies. What was not foreseen in the impact assessment, however, was that the format and contents of the PSUR would be adapted as well. Since 2012, companies have to submit a PBRER, which replaced the old PSUR format. As a consequence, the number of hours that companies have to spend on preparing and submitting one report (i.e. a PSUR in 2011 and a PBRER in 2013) has increased by about 60% on average. Therefore, any cost savings resulting from the simplifications that were foreseen in the impact assessment are offset by the change from the PSUR to the PBRER format. This particular issue could be addressed by performing a baseline measurement as close as possible to the date of implementation of new regulatory instruments, with the sole purpose of creating a baseline measurement for future comparison with a follow-up measurement.

Appropriate measurement of resource use

In order to measure the regulatory efficiency or (cost-)effectiveness of regulatory instruments, not only do the public health impacts of the instrument need to be determined, but the resource use generated by the instrument also needs to be measured. However, no standardised methods currently exist for measuring regulatory resource use. Furthermore, it is also important to determine whether any changes in resource use are resulting from the regulatory instrument. Measuring resource use in an appropriate way means that, first of all, the costing perspective (company perspective, regulatory agency perspective, healthcare perspective or societal perspective) needs to be determined. We would argue that resource use resulting from regulatory instruments should be measured from a societal perspective, such that not only costs directly related to regulatory processes and outputs ('direct regulatory costs') are considered but also all costs indirectly related to regulatory outcomes ('indirect regulatory costs'). Examples of direct regulatory costs include the number of studies performed as required by the instrument, or the resource use of regulatory agencies as a result of the regulatory instrument. An example of an indirect cost is the cost of hospitalisation due to an ADR. Some of the challenges involved in measuring resource use are illustrated by the case study on company resources required for compliance with the new pharmacovigilance regulation (Chapter 3.5), which demonstrated that measuring resource use at the company level results in significant variation.

Measuring the resource use of regulatory instruments allows for a regulatory cost-effectiveness analysis. Such studies (Bouvy et al. 2012; Bouvy et al. 2013) allow the estimation of a regulatory instrument's incremental cost-effectiveness ratio, which makes explicit the added resources required to increase public health through the instrument. Recently, a group of European regulators argued that opportunity costs of studies should be a factor considered in regulatory decision-making regarding the appropriateness of regulatory requirements and evidentiary standards (Eichler et al. 2013). In order to achieve this, regulatory cost-effectiveness analyses are needed.

Definition of regulatory success

Before a regulatory evaluation is performed, a definition is needed of what will constitute success or failure of the instrument. This requires an ex-ante decision rule on the level of effectiveness or efficiency, as well as acceptable levels of resource use that are desired at a predefined time following implementation of a regulatory instrument. We propose that desired values for all components of the evaluation of a regulatory instrument (i.e. input, process, output, and outcome) should be defined before an instrument is implemented, such that the results of an evaluation can subsequently result – or not result – in policy actions. Therefore, the objectives of the instrument should be defined

in such a way that they are identifiable, quantifiable and measurable at the intended time of evaluation.

The new pharmacovigilance legislation was projected to save between 500 and 5000 lives annually, and to result in €245 million annual cost savings (EC 2008). Suppose, however, that an evaluation undertaken after five or ten years subsequently indicated no cost savings but rather an increase in costs, and a lower (but still positive) public health impact. Without a definition of 'regulatory success' of a regulatory instrument ex-ante, it is not clear what the policy implications of such an evaluation would be. Furthermore, it could be questioned whether it is cost-effective to perform a resource-intensive regulatory evaluation when its results will not subsequently be used to inform policy decisions.

5.3 Embedding regulatory performance evaluations

In this section we will identify a number of themes that go beyond the methodological considerations for performance evaluations, and which rather look at how such evaluations can better be embedded in the regulatory system. These considerations are based on discussions with experts, our experience with conducting the case studies described in this report, and on recent reports and literature.

The need for a joint effort by stakeholders

Buy-in from all of the different stakeholders will be paramount in successfully embedding regulatory evaluation in the regulatory system. In some cases, this may also mean that the group of stakeholders involved needs to be broadened. Furthermore, the nature and extent of stakeholder involvement can vary according to the type of regulatory instrument under evaluation. In addition, token involvement of stakeholder groups is a serious risk and should be recognised early on and resolved. Although stakeholder involvement is required both for the design of methods for regulatory evaluation and for its subsequent embedding in the regulatory system, it has particular importance for the definition of regulatory success. How regulatory success or failure is defined will to a large extent depend on the perspective of the stakeholder, and it is quite possible that objectives for different stakeholders will be divergent or even conflicting. Therefore, reconciling these different views – or at least making them transparent – should be part of the design and interpretation of any policy evaluation, including evaluations of regulatory instruments.

Data sharing

Access to data is essential for performing evaluations of regulatory instruments but the required data are often not publicly accessible and, in particular, data regarding relevant public health outcomes for the European population are generally unavailable. This is currently a major limitation for the performance of regulatory evaluations. Moreover, the required data sources are fragmented: some data are in the possession of pharmaceutical companies, whereas other information can be held by health insurance companies or regulatory agencies. In the case of the analyses we conducted on the paediatric investigation plans in Chapter 3.4, combining the results of a company survey with a listing of Article 46 procedures from EMA was instrumental. Given the fragmented nature of all data that need to be brought together for regulatory evaluations, joint efforts of all stakeholders will be required at the European level.

Consensus on methodology

No standard methods for performing high-quality evaluations of regulatory instruments for medicines currently exist. Yet the development of such methods – and their subsequent use – is an essential condition for the accountability

of regulatory systems. Furthermore, innovation in this area is urgently needed, given that the involvement of several stakeholders (e.g. regulatory agencies, health care professionals, pharmaceutical companies and patients) is crucial when gathering all data required for systematic and high-quality evaluations of regulatory instruments. A potential future direction could be to design a set of principles for the evaluation of regulatory instruments that is more specifically tailored to the field of medicine, along the lines of the Commission Impact Assessment Guidelines and Evaluation Standards. Furthermore, developments in other areas of research, such as HTA and governance studies, could also be explored for examples of best practice.

Independent platform

In order to safeguard the accountability and objectivity of evaluations of regulatory instruments, we believe it is important that the development of regulatory instruments is separated from their evaluation, and the evaluation should not be performed by the authority that is also responsible for the implementation of the instrument. Furthermore, evaluations should preferably be conducted in a context where different stakeholders have equal roles and are represented in a transparent and appropriate manner. Such evaluations should be planned and organised in a prospective fashion. Therefore, we propose that both the development of methods for the evaluation of regulatory instruments and the evaluations themselves should be performed by independent organisations or consortia that work closely with regulatory agencies, healthcare professionals, pharmaceutical companies and patients. Future public-private partnerships, for example within the context of the Innovative Medicines Initiatives, could explore the opportunities and requirements for such joint activities and infrastructure.

Timing for evaluations – continuous monitoring and time assessments

One of the key challenges for evaluations of regulatory instruments is the appropriate timing of studies. If an evaluation is undertaken too early it may not be able to access the right data, and insufficient time may have passed for the regulatory instrument to be fully implemented. Moreover, sometimes data sources cannot yet be accessed, or output or outcome data may not have yet been collected. At the other end of the spectrum, evaluations that are performed too late may no longer be able to sufficiently inform policy debates. Within this context, it may be of value to identify a set of regulatory instruments that are monitored on a more continuous basis. This could, for example, take the form of a bi-annual or monthly publication of a set of key metrics. In many cases, the focus will be on process or output measures in such monitoring exercises, although one can envision that these will be complemented by a full assessment, which also includes outcomes, on a more intermittent basis. These monitoring activities could be part of the portfolio of an independent platform such as the one described above.

Focus on the post-marketing space

In the next decade, we expect a move towards a regulatory system in which the focus for evidence generation and evaluation will be more equally distributed across the pre- and post-marketing space, and this move is driven by two main developments. First, there is an increased willingness from both regulatory authorities and pharmaceutical companies to explore more adaptive modes of regulation and licensing. Second, there is increasing recognition of the link between marketing authorisation and subsequent reimbursement of a medicinal product. This shift could also have implications for the evaluations of regulatory

instruments: the data that need to be collected for regulatory evaluations would be found in more places (e.g. different HTA agencies); more and different stakeholders would be involved (e.g. stronger role of payers, patient organisations and clinicians); diversity in the application of regulatory instruments would increase (e.g. having implications for the comparability of different cases); the types of studies used for evidence generation would be broadened (e.g. pragmatic trials, adaptive designs); and regulatory outputs would become more diverse (e.g. staggered and/or conditional approval procedures).

5.4 Conclusion

In this chapter, we have proposed a framework that could be used for the evaluation of regulatory instruments. This framework encompasses a number of novel requirements for regulatory evaluations and recommends that evaluations should always be comparative; it requires that explicit policy mechanisms translating regulatory outputs into public health effects need to be identified; and it stipulates that envisioned effects of the regulatory instrument should be determined (in a measurable manner) before the instrument is implemented. Although impact assessments are performed for major regulatory reforms before implementation, they are not performed in a systematic manner and the policy consequences of subsequent evaluations are not made clear. Therefore, significant improvements could be made to impact assessments for regulatory reforms of the regulatory system for medicines in Europe.

The field of drug regulatory science is relatively young (Gispen-De Wied and Leufkens 2013) and still very much in development. Nonetheless, a more coordinated and joint approach could greatly improve – and speed up – the development of standardised methods for evaluation studies. Furthermore, different stakeholders will need to work together to provide all necessary data for performing such regulatory evaluations. Therefore, we see an important role for a platform that could firstly work on the development of methods for the evaluation of regulatory instruments and secondly perform systematic analyses of regulatory instruments in an independent manner.

Ultimately, systematic evaluations of regulatory instruments will not merely improve the accountability and legitimacy of the European regulatory system for medicines, but will also contribute to identifying an optimal balance between facilitating innovation on the one hand and achieving a high level of public health on the other hand. When regulatory instruments are designed with a strong emphasis on incorporating available evidence, and are periodically subjected to appropriate and high-quality evaluations, societal trust in the regulatory system can be strengthened. This requires a regulatory system that is evidence-based, explicit about its aims, and efficient in achieving its policy objectives. The case studies that are presented in Chapter 3 demonstrate that high-quality and scientifically rigorous regulatory evaluations are possible, and can provide stakeholders with the right data that can guide evidence-based policy making and ultimately can contribute to improving the regulatory system for medicines.

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6 CONCLUDING REMARKS AND RECOMMENDATIONS

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In the last decade the regulatory system for medicines has seen considerable change. Although the overall system seems well equipped to safeguard public health, its ongoing evolution means that continuous reflection is needed on whether or not it is achieving its aims in the best way possible. This report contributes to such reflection by investigating a number of specific regulatory areas, and recommendations have been made for each of these areas in the preceding chapters.

By way of conclusion, we highlight three main messages and high-level recommendations that emerge from this report, namely:

1. Discrepancies between the initial objectives of legislation and the effects of regulatory instruments in actual practice should be addressed;
2. Learning during implementation of legislation can make regulatory instruments more effective;
3. Regulatory science studies can help to assess real-world outcomes of the system and to identify opportunities for improvement.

> Discrepancies between the initial objectives of legislation and the effects of regulatory instruments in actual practice should be addressed

In some instances it can be questioned whether or not a priori objectives (for example, public health objectives) are being achieved, and if regulatory instruments are providing 'value for money'. The case studies in this report have evaluated a number of direct regulatory outcomes, such as safety-related label changes, that are important predictors for indirect public health outcomes of regulatory instruments (see Chapter 5). We identified several cases where a gap seems to exist between initial objectives and real-world effects of regulatory instruments. These include the following:

- The conditional marketing authorisation route is meant to provide early access to medicines, provided that benefits to public health outweigh the risks inherent in the requirement for additional data. However, the case study on conditional marketing authorisation (CMA) found that, in practice, the use of CMA for oncology medicines is often perceived as a 'rescue' option by regulators and companies, rather than as a pathway to grant early authorisation to medicines that show promising effects (Chapter 3.3). Furthermore, total time needed for the CMA was longer than for standard market authorisation and applicants voiced concerns about subsequent HTA procedures and reimbursement decisions.
- Data presented in Chapter 3.5 indicates that the annual number of periodic safety update reports (PSURs) submitted to regulatory authorities has decreased, as was intended, after the introduction of the new pharmacovigilance legislation. What was not taken into account in the impact assessment on the draft legislation, however, was that since 2012 companies have to submit

a periodic benefit-risk evaluation report (PBRER). The results from a survey of pharmaceutical companies indicated that the number of hours spent by companies on preparing and submitting one report (i.e. a PSUR in 2011 and a PBRER in 2013) has increased by about 60% on average, offsetting the foreseen change to simplified requirements. Although these are self-reported data from companies, and the legislation is relatively recent, these data indicate that a gap between the original impact assessment and actual practice might exist.

- For the medicines included in the study on the cost-effectiveness of newly requested post-authorisation safety studies (PASSs), 52% of all requested PASSs resulted in a change to the SmPC (Chapter 3.6). This accounts for 9.5% of all post-marketing safety variations for these medicines and led to an incremental cost-effectiveness ratio of €6.5 million to €18.0 million per additional SmPC change. Whether or not this substantial investment was expected by the legislator, or effectively converted into societal value, is unclear at the moment.

As a first step, the way in which formal (impact) assessments of regulatory instruments are conducted should be strengthened. Better baseline measurements are needed for ex ante impact assessments of legislation. These measurements should take into account amendments by Parliament and Council on the draft legislation – often occurring during or after conducting the impact assessment. This model of ex ante and updated impact assessments is also mentioned in EC Impact Assessment Guidelines (EC 2009). Apart from ex ante assessment, there is need for periodic re-assessments, in order to evaluate whether or not regulations are achieving their (pre-determined) objectives.

Any formal evaluation of a regulatory instrument should include the different actors involved (e.g. regulators, companies, patient organisations, prescribers) in the design of the assessment. Strengthening the role of interested parties to provide input is also something that is mentioned in the draft Commission Evaluation Policy Guidelines. It is important to assess how this new policy evaluation guideline will be implemented in practice. Moreover, data sources needed for evaluations are often fragmented and reside with various partners. In order to monitor the performance of the system, including the perceived complexity of procedures and the 'regulatory burden', prospective databases will need to be set up. All of the above will require additional efforts from regulatory agencies; companies; the European Commission; and other organisations, and may have implications for internal monitoring and evaluation activities; staff training; and standard operating procedures (SOPs) in organisations.

Learning during implementation of legislation can make regulatory instruments more effective

We can increase the effectiveness of regulatory instruments by reflecting on the interpretation and implementation of the primary legislation. Companies state that they experience difficulties with the burden of some more recent regulatory requirements (e.g. new variations regulation and pharmacovigilance requirements) because they make internal company procedures more complex and lack alignment with similar regulatory requirements in other regions. Some of this can be resolved by adjusting how legislation is implemented, without compromising public health or the objective of the legislation. For example:

- The case study on paediatric investigation plans (PIPs) in Chapter 3.4 gives an indication of redundancy in efforts by companies and regulators in preparing and reviewing

PIPs. Many PIPs need to be modified at a later stage, and studies are sometimes drafted and conducted for products that will not be marketed due to the termination of development programs (21% of all agreed-upon PIPs were abandoned due to the termination of the development program in adults). Addressing this issue could alleviate the workload of regulators (including PDCO) and companies.

- There appears to be a lack of clarity about how 'a positive benefit-risk balance' in conditional marketing authorisation should be interpreted. Examples in Chapter 4 revealed that uncertainty for regulators and companies exists about what level of evidence would be sufficient for obtaining a CMA, compared with a 'standard' marketing authorisation. Currently, companies do not seem to have sufficient incentives to request CMA upfront, which can lead to a situation in which regulators initially use standard evaluation criteria for assessment, adding to the uncertainty around benefit-risk assessment for medicines eligible for a CMA.
- The national phase of the mutual recognition procedure or decentralised procedure (MRP/DCP) can be improved (see Chapter 3.2). Delays in issuing national marketing authorisations have been known about for years, however the topic still warrants further attention.

Providing better or more detailed written guidance on the interpretation of legislation can address some of the issues described above. Furthermore, altering the timelines for the submission of key documents should be explored. For example, one could explore alternative ways of submitting PIPs during early stages of development. An option could be a reduction in the level of detail within initially submitted plans (i.e. a staggered approach), which would still fit the requirements of current legislation while making sure public health is safeguarded.

Another way to make implementation more effective would be to optimise the interactions between regulators and companies. The value of better-timed and more frequent interactions is highlighted in several case studies. For example, in the study on CMA we can see that a more open dialogue (e.g. through scientific advice) between applicant and regulator about the pros and cons of a CMA, and a common understanding of the interpretation of the benefit-risk balance, could add value.

A staggered approach for PIP submissions would require more open and more frequent interactions between regulators and companies. Intensified interactions can also help to address unintended complexities of requirements early on. An example of an area where this could be of particular relevance is the recent implementation of the new variations regulation. Although the topic was highlighted in the survey in Chapter 2, recent changes in regulation made it unsuitable for study and the issues appeared to be more of an administrative nature, with appropriate data sources lacking at the moment. However, the topic is recommended for future analysis and discussion. In the area of MRP/DCP, it remains to be seen what the underlying reasons are for the delays in national approval. There may be various factors responsible for this delay, including discussions on packaging, brand names, quality of translations of the product information or merely workload at the national competent authority.

> Regulatory science studies can help to assess real-world outcomes of the system and to identify opportunities for improvement

Insight into the use and performance of the regulatory system is needed, through performing monitoring, analysis and evidence-based

assessments. Important opportunities for learning about the system can result, for example from analysing how previous marketing applications were handled; the implementation of regulatory requirements; and the way in which regulatory authorities, companies, patients, and HTA bodies interact (De Jong et al. 2013). The current report gives examples on how learning in the regulatory system can be improved:

- Stakeholder surveys, such as the one conducted in Chapter 2, provided a quick and easy-to-use method for identifying areas for further discussion and research. This understanding of what 'users' of the system perceive as issues helped to target research on the most relevant topics.
- Several studies used a multidisciplinary approach. In the study on conditional marketing authorisation (Chapter 3.3), a quantitative analysis of publicly available data was combined with semi-structured interviews with persons involved in specific dossiers in order to achieve in-depth insight into the functioning of this pathway. In the study on the costs and effects of PASSs, more traditional regulatory science approaches (such as an assessment of which studies have generated SmPC changes) were combined with economic analysis methods. By combining methods coming from different disciplines, insights can be obtained that reveal the reasoning behind regulatory action.
- In Chapter 5, we discussed what kinds of data could be collected for future studies and the type of data that are currently missing. The impact of medicines regulation on public health outcomes has rarely been studied. This is a difficult area for analyses as it requires the combination of a variety of data sources and often requires collecting data in a prospective manner.

In order to strengthen this kind of evaluation of the regulatory system, two elements would have to be put in place.

First, the conducting of regulatory science studies should become an integral part of the system. This requires setting up a research infrastructure with adequate expertise and resources, with arrangements for access to data and with suitable governance to ensure the independent conduct of studies. Comparisons with other regulatory areas, such as the US, should also be part of such studies. An independent regulatory platform can play a valuable role here. To bring this about, certain topics could be taken up by partnerships such as the Innovative Medicines Initiative.

Second, an appropriate follow-up process would have to be put in place to ensure that lessons are drawn from the evidence collected. Therefore, consensus is crucial between parties, at the moment of implementation of new regulatory instruments, on how data on will be collected and how success will be measured. This should involve making a clear distinction between the scientific evidence; its evaluation and appraisal; policy options; and their potential impact.

By addressing the issues highlighted above, and by strengthening 'learning' in the regulatory system, we believe we will be able to move towards the ideal of a 'learning regulatory system': a system that is constantly adapting in order to remain efficient and up-to-date, and to protect and promote public health.

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ACKNOWLEDGEMENTS

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In particular, the individuals listed below have provided reviews of chapters and input on content, and have participated in discussions and constructive critiques to make this report meaningful and useful.

- Kevin Blake (EMA)
- Ton de Boer (Utrecht University)
- Hubertus Cranz, Christelle Anquez-Traxler and colleagues at AESGP
- The European Medicines Agency, which hosted a discussion session on preliminary results
- Sue Forda (Lilly), Sabine Atzor (Roche), David Jefferys (Eisai), Sarah Montagne (Bayer), Isabelle Stoeckert (Bayer) and members of the Scientific, Regulatory and Manufacturing Policy Committee of EFPIA
- Tidde Goldhoorn and colleagues at the Dutch Ministry of Health, Welfare and Sport (VWS)
- Escher IRC members:
  - Eric Abadie
  - Mary Baker
  - Alasdair Breckenridge
  - Bruno Flamion
  - Bert Leufkens
  - Marjolein Weda
- Jorg Janssen, Marjan Akkermans, Hiliana Fienig, Ruth Wong, Wieteke Wouters and colleagues at TI Pharma
- Susan Janssen, Joëlle Hoebert and colleagues at the Dutch National Institute for Public Health and the Environment (RIVM)
- Ingrid van de Kamp (Flexos)
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- Pär Tellner and colleagues at EFPIA
- Niels Vermeer (Utrecht University/Dutch Medicines Evaluation Board)

ANNEXES

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Annex 1 - About Escher

Escher is TI Pharma's multi-stakeholder platform for regulatory innovation. It initiates and conducts research on regulatory and HTA topics to advance the development of medicines that address unmet needs. Escher aims to promote scientific research and the international debate needed to optimise guidance, policy and regulations for the development of medicines and medical technology. It does so by partnering with stakeholders in the pharmaceutical sector: government agencies, academic institutions, companies and non-governmental organisations (NGOs). Escher operates independently, and this independence is assured by its governance and through transparency in the way it works.

Governance

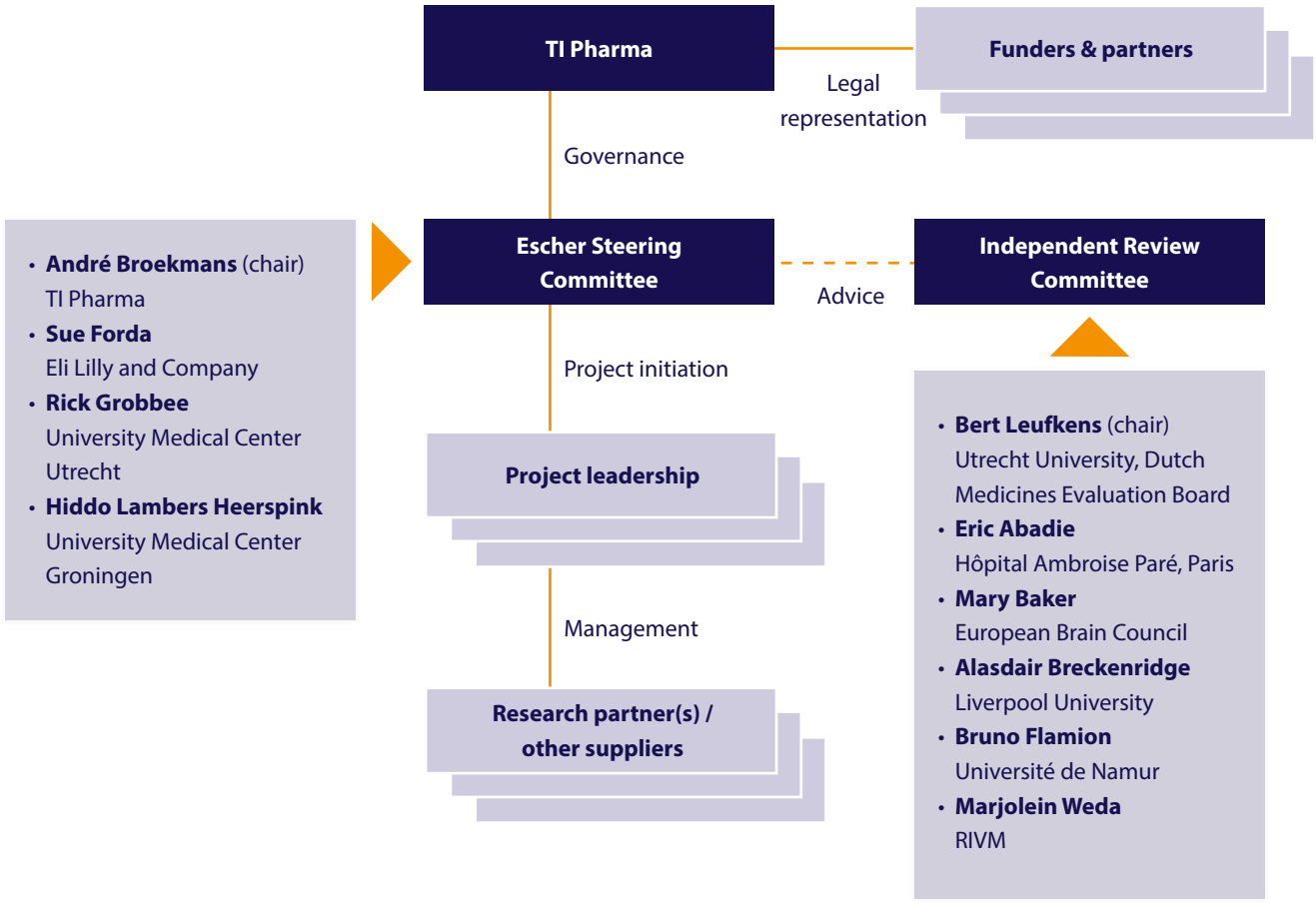
The highest governing body of Escher is the Escher Steering Committee, which consists of individuals with a background in regulatory sciences and with experience in various settings (academia, companies and government). The current composition of the Escher Steering Committee is as follows: André Broekmans, TI Pharma (chair); Sue Forda, Lilly; Rick Grobbee, University Medical Center Utrecht; and Hiddo Lambers Heerspink, University Medical Center Groningen.

The Escher Steering Committee decides whether and how a project should be executed. Depending on the nature of a specific project, a project leadership team is formed to oversee a particular project.

An Independent Review Committee (IRC) advises the Escher Steering Committee on the quality and scientific robustness of studies. Its membership consists of experts and leaders in the field of regulatory science. The current composition of the IRC is as follows: Bert Leufkens, Utrecht University & Dutch Medicines Evaluation Board (chair); Eric Abadie, Hopital Ambroise Paré; Mary Baker, European Brain Council; Alasdair Breckenridge, Liverpool University; Bruno Flamion, Université de Namur; and Marjolein Weda, Dutch National Institute for Public Health and the Environment (RIVM).
Figure 1 below illustrates the governance of Escher.

For more information visit:
www.escher.tipharma.com

Figure 1: Escher governance



Annex 2 - Project organisation

The project is set up as an independent research project under the umbrella of Escher, the TI Pharma platform for regulatory innovation. Activities have been funded by a research grant to TI Pharma from EFPIA and AESGP. The work was carried out by Utrecht University and Exon Consultancy.

Ways of working and communication within the project are determined by project governance (Figure 1). The main responsibilities of each party are shown below.

Project Steering Committee

The Project Steering Committee represents all parties involved in the project and is the highest decision making body. It is responsible for ensuring that the project meets overall requirements as laid down in the project agreements.

The Committee consists of the following people:

- André Broekmans, TI Pharma/Escher (chair)
- Pär Tellner, EFPIA
- Hubertus Cranz, AESGP
- Ton de Boer, Utrecht University
- Pieter Stolk, Exon Consultancy

Project Management (Exon Consultancy)

Project Management provides an interface between all parties in the project. It coordinates activities with the Research Partner (Utrecht University), organises external communication and manages the reporting process.

Jean Philippe de Jong acts as the Project Manager.

Research Partner (Utrecht University)

The Research Partner is responsible for conducting a set of scientific analyses for the project. It writes reports and scientific publications and presents findings about its analyses at meetings. Marie L. De Bruin is the Principal Investigator on behalf of the Research partner.

Independent Review Committee

The Independent Review Committee (IRC) advises on the scientific quality of the work. It is not responsible for the contents of reports and publications. The IRC consists of the following people:

- Bert Leufkens, Utrecht University, Dutch Medicines Evaluation Board (CBG-MEB) (chair)
- Eric Abadie, Hopital Ambroise Paré
- Alasdair Breckenridge, Liverpool University
- Bruno Flamion, Université de Namur
- Marjolein Weda, Dutch National Institute for Public Health and the Environment (RIVM)
- Mary Baker, European Brain Council

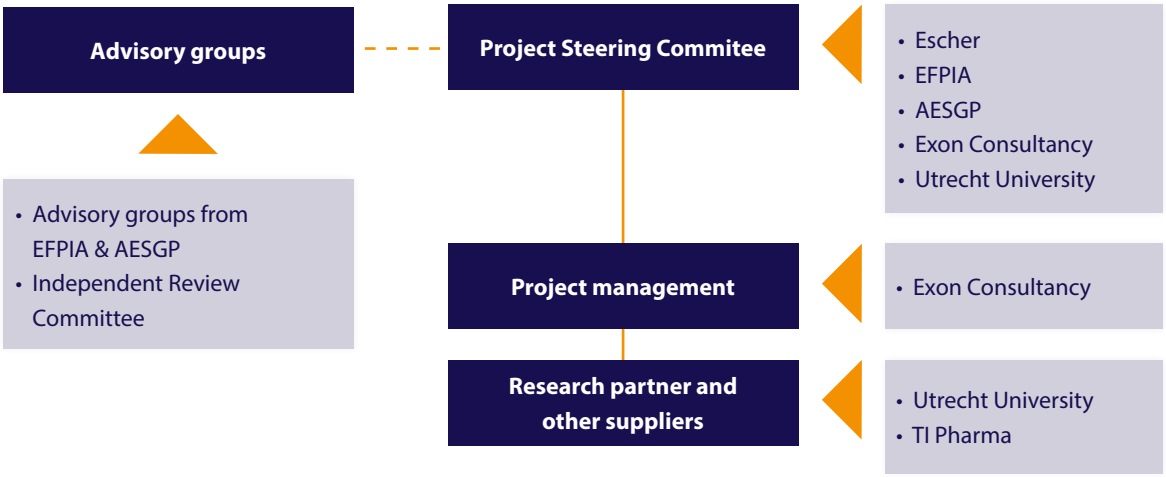
Advisory groups from EFPIA and AESGP

Advisory groups support the project by providing input on project content. Drafts of the report were shared with EFPIA and AESGP in order to remove confidential information or to correct factual errors. Interpretation of the data and analyses was the sole responsibility of Escher and its Research Partner.

TI Pharma

TI Pharma is the legal representative for Escher, supporting the governance structure and facilitating the project with administrative (finance & legal) and communications activities.

Figure 1: Project governance



Annex 3 - Workshop program

Title: Towards a Learning System: How to Address Current Regulatory Challenges?
Date: 13 May 2014
Location: Academiegebouw, Domplein 29, Utrecht, The Netherlands

Introduction

The workshop presented interim results from the project. Participants were selected key persons with a broad regulatory experience from regulatory agencies, academia, companies, patient organisations and public sector stakeholders. The goals of the workshop were to provide participants with new insights into the functioning of the regulatory system and to generate input for the project's further analyses. The workshop provided ample room for discussion and an opportunity to exchange ideas on regulatory science and reform.

Workshop approach

The morning programme was plenary: presentations on four case studies on regulatory challenges (decentralised procedure/mutual recognitional procedure [DCP/MRP], conditional marketing authorisation, paediatric investigation plans and pharmacovigilance) followed by reflections and discussion in order to strengthen the analyses and suggest ways forward.

The afternoon programme built on the morning programme and consisted of a combination of plenary presentations and interactive break-out sessions with a facilitated poster-session setting. The afternoon focused on two cross-cutting themes related to regulatory learning: 'evidence and evaluation of regulatory system performance', and 'learning to use new regulatory pathways'. The output from the sessions was a list of structured and prioritised suggestions on how to move towards a more learning regulatory system.

Agenda

Monday, May 12, 2014

18.00-19.00: Welcome drinks
19.00-22.00: Dinner

Tuesday, May 13, 2014

08.30-09.00: Registration, coffee & tea
09.00-09.05: Opening & Introduction - André Broekmans
09.05-09.20: Introduction to the project 'Improving the EU system for marketing authorisation: Reviewing regulatory deficiencies and inefficiencies' - Jean Philippe de Jong
09.20-09.30: Introduction of case studies: evidence on regulatory challenges - Marieke De Bruin
09.30-09.50: Presentation case study DCP/MRP - Hans Ebbers
09.50-10.10: Presentation case study conditional marketing authorisation - Jarno Hoekman
10.10-10.20: Reflection from stakeholders
10.20-10.45 Discussion - Moderator: André Broekmans
10.45-11.15: Break

11.15-11.35: Presentation case study paediatric investigation plans - Jarno Hoekman/Jacoline Bouvy
11.35-11.55: Presentation case study pharmacovigilance - Jacoline Bouvy
11.55-12.05: Reflection from stakeholders
12.05-12.30: Discussion - Moderator: André Broekmans
12.30-13.30: Lunch
13.30-13.45: Introduction to parallel sessions: how to move towards a more learning regulatory system? - Jean Philippe de Jong
13.45-14.45: Parallel session 1a: Evidence and evaluation of regulatory system performance

Group A; Bert Leufkens, chair; Pieter Stolk, facilitator; Jacoline Bouvy, monitor
13.45-14.45: Parallel session 1b: Learning to use new regulatory pathways

Group B; Alasdair Breckenridge, chair; Jean Philippe de Jong, facilitator; Jarno Hoekman, monitor
14.45-15.00: Break
15.00-15.45: Parallel session 2a: Learning to use new regulatory pathways

Group A; Bert Leufkens, chair; Jean Philippe de Jong, facilitator; Jarno Hoekman, monitor
15.00-15.45: Parallel session 2b: Evidence and evaluation of regulatory system performance

Group B; Alasdair Breckenridge, chair; Pieter Stolk, facilitator; Jacoline Bouvy, monitor
15.45-16.00: Break
16.00-16.10: Plenary report from session 2a: Learning to use new regulatory pathways - Bert Leufkens, Jean Philippe de Jong
16.10-16.20: Plenary report from session 2b: Measuring the performance of regulatory instruments - Alasdair Breckenridge, Pieter Stolk
16.20-16.30: Closing - André Broekmans
16.30-17.30: Drinks

Participants

Alasdair Breckenridge	Liverpool University
Angelika Joos	MSD
Bert Leufkens	Dutch Medicines Evaluation Board, Utrecht University
Birte van Elk	Dutch Medicines Evaluation Board
Bruno Flamion	University of Namur
Christelle Anquez	AESGP
Christine Eising	Novartis Consumer Health
Eric Abadie	Euremed Consulting
Filip Babylon	Apotheek Babylon, PRAC
Giovanni Tafuri	Italian Medicines Agency

Glenn Carpenter	Johnson & Johnson
Hans Hillege	University of Groningen, CHMP
Hiddo Lambers Heerspink	University Medical Center Groningen
Hubertus Cranz	AESGP
Isabelle Stoeckert	Bayer
Kora Doorduyn	Dutch Medicines Evaluation Board
Larry Liberti	Centre for Innovation in Regulatory Science
Marit Elenbaas	Dutch Ministry of Health, Welfare and Sport
Marjolein Weda	Dutch National Institute for Health and the Environment
Pär Tellner	EFPIA
Pieter Stolk	Exon Consultancy
Sabine Atzor	Roche
Stephen Champion	GSK
Sue Forda	Eli Lilly
Tidde Goldhoorn	Dutch Ministry of Health, Welfare and Sport
Ton de Boer	Utrecht University
Wim Wientjes	International Diabetes Federation

Escher organising committee

Andre Broekmans	TI Pharma
Hans Ebbers	Utrecht University
Jacoline Bouvy	Utrecht University
Jarno Hoekman	Utrecht University
Jean Philippe de Jong	Exon Consultancy
Marie L. De Bruin	Utrecht University, Dutch Medicines Evaluation Board
Wouter Boon	Utrecht University

Annex 4 - Survey / Identifying areas in the regulatory system in need of improvement

Introduction

Your company is kindly invited to participate in a survey for the Escher Project '*Improving the EU system for marketing authorization: Reviewing regulatory deficiencies and inefficiencies*'. The survey asks companies to identify specific areas in need of improvement and to share examples/cases of issues within these areas. The survey will be used to guide the topic selection for the project.

Instructions

The survey will take a couple of hours to complete. The survey consists of three parts:

- Part 1: respondent's profile;
- Part 2: grade regulatory areas according to the need of improvement;
- Part 3: share cases/examples of issues within these areas.

Specific instructions will be given for each part. The deadline for submitting the survey is in two weeks: November 6, 2013. We understand this is a short time frame. If it will pose a problem, please contact me about this.

If multiple persons have been involved in filling out the survey, please keep an internal record of that, so that we can contact relevant persons at a later stage.

Confidentiality

Information will be treated in a confidential manner. Without prior permission, results will not be published in a way that could lead to identification of persons, products or companies. If you have major concerns about confidentiality, please anonimize information accordingly.

Please do not hesitate to contact the Escher Project if you have questions about the survey or the project.

(j.ph.dejong@escher-project.org)

Part 1: Respondent's profile

1. CONTACT PERSON

a. Name

b. Function and areas of activities:

c. Contact details (telephone and email):

2. COMPANY

a. Name:

b. SME: ❒ Yes ❒ No

c. Product types:

- ❒ New chemical entities
- ❒ Generics
- ❒ Over the counter medicines
- ❒ Biologicals/medicines derived from biotechnology processes
- ❒ Biosimilars
- ❒ Advanced therapies (ATMP)
- ❒ Herbal medicinal products
- ❒ Other

Part 2: Grade areas according to the need of improvement

In part 2 of this survey you are requested to grade areas within the regulatory system for marketing authorization according to the need of improvement.

Instructions

- Grade areas on a 4-point scale: from 1, no need for improvement, to 4, high need for improvement.
- If you grade with 3 or 4, please specify the need for improvement in a few sentences
- If you cannot grade an area, you can leave the question blank
- In the next pages, areas within the regulatory system are structured according to three phases in the marketing authorisation process (the list is based on regulatory areas as identified on EMA website):

Grade areas in the pre-authorisation phase according to the need of improvement:

If you grade with 3 or 4, please specify. **1 = no need, 4 = high need**

Scientific guidelines: Quality

1	2	3	4
❒	❒	❒	❒

Scientific guidelines: Biologicals

1	2	3	4
❒	❒	❒	❒

Scientific guidelines: Non-clinical

1	2	3	4
❒	❒	❒	❒

Scientific guidelines: Clinical efficacy and safety

1	2	3	4
❒	❒	❒	❒

Scientific guidelines: Multidisciplinary

1	2	3	4
❒	❒	❒	❒

EudraCT Database/EU Clinical Trials register

1	2	3	4
❒	❒	❒	❒

Presubmission meetings

1	2	3	4
❒	❒	❒	❒

SME guidance

1	2	3	4
❒	❒	❒	❒

Scientific advice (including protocol assistance)

1	2	3	4
❒	❒	❒	❒

Qualification of novel methodologies procedure (opinion or advice)

1	2	3	4
❒	❒	❒	❒

Grade areas in the authorisation phase according to the need of improvement:

Centralised authorisation procedure

1	2	3	4
❒	❒	❒	❒

National authorisation procedures

1	2	3	4
❒	❒	❒	❒

Decentralized procedure

1	2	3	4
❒	❒	❒	❒

Mutual recognition procedure

1	2	3	4
❒	❒	❒	❒

Compassionate use

1	2	3	4
❒	❒	❒	❒

Accelerated assessment

1 2 3 4

❒ ❒ ❒ ❒

Conditional marketing authorization

1 2 3 4

❒ ❒ ❒ ❒

Marketing authorization under exceptional circumstances

1 2 3 4

❒ ❒ ❒ ❒

Orphan designations

1 2 3 4

❒ ❒ ❒ ❒

Authorisation procedure for 'normal' products (compared to the 'special' procedures mentioned above: Compassionate use; Accelerated assessment; Conditional marketing authorization; Marketing authorization under exceptional circumstances; Orphan designations)

1 2 3 4

❒ ❒ ❒ ❒

Dossier format

1 2 3 4

❒ ❒ ❒ ❒

Submission of applications

1 2 3 4

❒ ❒ ❒ ❒

Withdrawal of applications

1 2 3 4

❒ ❒ ❒ ❒

Rapporteur/(Co)-Rapporteur appointment

1 2 3 4

❒ ❒ ❒ ❒

Assessment of applications

1 2 3 4

❒ ❒ ❒ ❒

CHMP opinions

1	2	3	4
❒	❒	❒	❒

Assessment reports

1	2	3	4
❒	❒	❒	❒

EPARs

1	2	3	4
❒	❒	❒	❒

Summary of product characteristics (SmPC)

1	2	3	4
❒	❒	❒	❒

Product information requirements (label/packaging leaflet)

1	2	3	4
❒	❒	❒	❒

Other areas in the authorisation phase (e.g. linguistic review, article 58 applications)

1	2	3	4
❒	❒	❒	❒

Other areas in the authorisation phase (e.g. linguistic review, article 58 applications)

1	2	3	4
❒	❒	❒	❒

Grade areas in the pharmacovigilance phase according to the need of improvement:

Periodic Safety Update Reports (PSURs)

1	2	3	4
❒	❒	❒	❒

Assessment reports

1	2	3	4
❒	❒	❒	❒

Pharmacovigilance inspections

1	2	3	4
❒	❒	❒	❒

EudraLex/EudraVigilance

1	2	3	4
❒	❒	❒	❒

Individual case safety reports

1	2	3	4
❒	❒	❒	❒

Post-authorization safety studies (PASS)

1	2	3	4
❒	❒	❒	❒

Risk-management plans

1	2	3	4
❒	❒	❒	❒

Urgent safety restrictions

1	2	3	4
❒	❒	❒	❒

Post authorization measures (PAM) (e.g. SOB, ANX, MEA, LEG,REC)

1	2	3	4
❒	❒	❒	❒

Other areas in the pharmacovigilance phase:

1	2	3	4
❒	❒	❒	❒

If you grade with 3 or 4, please specify

1	2	3	4
❒	❒	❒	❒

Other areas in the pharmacovigilance phase:

1	2	3	4
❒	❒	❒	❒

Grade other (non-pharmacovigilance) areas in the post-authorisation phase according to the need of improvement:

Variations (e.g. type IA/IB/II/unforseen (article 5) variations

1	2	3	4
❒	❒	❒	❒

Extension applications

1	2	3	4
❒	❒	❒	❒

Renewals

1	2	3	4
❒	❒	❒	❒

Annual re-assessment

1	2	3	4
❒	❒	❒	❒

Cessation

1	2	3	4
❒	❒	❒	❒

Sunset clause

1	2	3	4
❒	❒	❒	❒

Referrals (e.g. safety referrals (articles 107i, 20, 31), paediatrics referrals (article 29), harmonization referrals (articles 13, 29(4), 30)

1	2	3	4
❒	❒	❒	❒

Article 46 paediatric study

1	2	3	4
❒	❒	❒	❒

Product defects

1	2	3	4
❒	❒	❒	❒

Sampling and testing (of the quality of Centrally Authorised Products)

1	2	3	4
❒	❒	❒	❒

Transfer of marketing authorization

1	2	3	4
❒	❒	❒	❒

Other areas in the post-authorisation phase(e.g. article 61 (3) notifications, parallel distribution, GMP inspections, certificates of medicinal products, falsified medicines)

1	2	3	4
❒	❒	❒	❒

Other areas in the post-authorisation phase(e.g. article 61 (3) notifications, parallel distribution, GMP inspections, certificates ofmedicinal products, falsified medicines)

1	2	3	4
❒	❒	❒	❒

Cross-cutting areas

In the next pages, you are requested to grade areas that cut across the three phases of the marketing authorisation process.

Grade regulatory areas related to the types of products according to the need of improvement

New chemical entities

1	2	3	4
❒	❒	❒	❒

Generics

1	2	3	4
❒	❒	❒	❒

Over the counter medicines

1	2	3	4
❒	❒	❒	❒

Biologicals/medicines derived from biotechnology processes

1	2	3	4
❒	❒	❒	❒

Biosimilars

1	2	3	4
❒	❒	❒	❒

Advanced therapies (ATMP)

1	2	3	4
❒	❒	❒	❒

Herbal medicinal products

1	2	3	4
❒	❒	❒	❒

Other type of product:

1	2	3	4
❒	❒	❒	❒

Other type of product:

1	2	3	4
❒	❒	❒	❒

Grade disease areas with compulsory centralized procedure according to the need of improvement

HIV/AIDS

1	2	3	4
❒	❒	❒	❒

Cancer

1	2	3	4
❒	❒	❒	❒

Diabetes

1	2	3	4
❒	❒	❒	❒

Neurodegenerative disease

1	2	3	4
❒	❒	❒	❒

Auto-immune and other immune dysfunctions

1	2	3	4
❒	❒	❒	❒

Viral disease (other than HIV)

1	2	3	4
❒	❒	❒	❒

Grade other disease areas in the regulatory system according to the need of improvement

Geriatric medicines

1	2	3	4
❒	❒	❒	❒

Paediatric medicines

1	2	3	4
❒	❒	❒	❒

Pandemic influenza

1	2	3	4
❒	❒	❒	❒

Antimicrobials

1	2	3	4
❒	❒	❒	❒

Orphan medicines

1	2	3	4
❒	❒	❒	❒

Other disease areas.

1	2	3	4
❒	❒	❒	❒

Other disease areas.

1	2	3	4
❒	❒	❒	❒

Grade other cross-cutting areas in the regulatory system according to the need of improvement

Development of the regulatory framework (e.g. consultation of experts, public consultation, impact analysis, hearings, appeal procedures, harmonization, ICH)

1	2	3	4
❒	❒	❒	❒

Innovative drug development methods (e.g. nanotechnology, personalized medicine, biomarkers, statistical methods/trial design)

1	2	3	4
❒	❒	❒	❒

Public communication (e.g. EMA website, direct healthcare professional communication, notifications)

1	2	3	4
❒	❒	❒	❒

Interaction with companies (e.g. in person, meetings, oral explanations, letters, notifications)

1	2	3	4
❒	❒	❒	❒

Division of labor and coordination (e.g. between EMA committees, between EMA and Member States)

1	2	3	4
❒	❒	❒	❒

Administration/reporting (e.g. databases, formats, templates, quality review of documents, forms)

1	2	3	4
❒	❒	❒	❒

ICT/telematics

1	2	3	4
❒	❒	❒	❒

Knowledge and expertise (e.g. scientific, regulatory, therapeutic area)

1	2	3	4
❒	❒	❒	❒

Patient/stakeholder involvement

1	2	3	4
❒	❒	❒	❒

Consistency and objectivity (e.g. conflicts of interests)

1	2	3	4
❒	❒	❒	❒

Transparency and accountability (e.g. confidentiality, transparency measures, release of trial data, data exclusivity)

1	2	3	4
❒	❒	❒	❒

Harmonization (e.g. between Member States, between EU and other regions)

1	2	3	4
❒	❒	❒	❒

Complexity of the regulatory system

1	2	3	4
❒	❒	❒	❒

Costs/funding of the system (including fees)

1	2	3	4
❒	❒	❒	❒

Decision/assessment instruments (e.g. benefit-risk methodology)

1	2	3	4
❒	❒	❒	❒

New regulatory pathways (e.g. adaptive licensing)

1	2	3	4
❒	❒	❒	❒

Other cross-cutting areas in the regulatory system:

1	2	3	4
❒	❒	❒	❒

Other cross-cutting areas in the regulatory system:

1	2	3	4
❒	❒	❒	❒

Part 3: Cases/examples of issues

In this section you are invited to share cases/examples of issues within regulatory areas in need of improvement.

Instructions

- Please describe up to five high priority cases/examples of regulatory issues.
- The project has so far identified four broad regulatory areas where reform is desirable: pharmacovigilance, paediatrics regulations, conditional approval and variations. We suggest you provide cases/examples of issues related to these areas. However, cases/examples related to other areas are welcome too.
- Provide as much detail as possible.
- Be as concrete as possible and do not use abbreviations or (internal) jargon.
- In the next pages, we provide a list of questions that can help you to generate a comprehensive account of a case/example.
- At the end of the list of questions about a case/example, you can either provide an additional case/example, or exit the survey.
- It is also possible to use your own format to describe cases/examples. You can use the first question ('describe the problem') to enter your description or send your cases/examples of regulatrory issues directly by email to: j.ph.dejong@escher-project.org.

Describe the problem

a. What areas of the regulatory system were involved? (See part 2 of the survey (in the pdf document); please specify in terms of Directives, regulations, procedures, instruments etc.)
b. What was the nature of the problem? (e.g. in terms of deficiency, redundancy, efficiency, flexibility, specificity, consistency, transparency, complexity, timelines etc.)
c. Which parties were involved? (e.g. companies, authorities, patients, other stakeholders; specify in terms of teams, committees, subgroups etc.)
d. When did the problem occur? (Period, development phase)
e. How has the situation developed since?

Describe the causes of the problem

a. What are main causes and what are aggravating or mitigating factors? (In the regulatory framework itself, its development or its execution/implementation;; and from outside the regulatory system)
b. How do you expect the situation will develop without changes to the regulatory system?

Describe the impact of the problem

a. Who or what was affected? (e.g. in terms of products, companies, patients, other stakeholders; please specify)
b. What effects did the problem have? (on public health, companies, economy, society)
c. What is the severity and scope of the impact?

Describe solutions for the problem

a. What is the desired situation?
b. What action has been taken do far?
c. What are possible strategies to reach the desired situation? (And what are opportunities and barriers)
d. What do you consider the most feasible strategy?

Describe what data is needed

a. On which aspects of the case/example is more data needed?
b. What kind of data is needed?
c. Where can this data be found and who are experts to consult?

Annex 5 - Prioritised list of regulatory areas

Rank	Topic	Mean score	n
1	Paediatric medicines	3.44	25
2	Variations (e.g. type IA/IB/II/unforseen (article 5) variations	3.29	31
3	Other areas in the pharmacovigilance phase	3.29	21
4	Costs/funding of the system (including fees)	3.20	25
5	Article 46 paediatric study	3.19	21
6	Transparency and accountability (e.g. confidentiality, transparency measures, release of trial data, data exclusivity)	3.17	24
7	Harmonisation (e.g. between Member States, between EU and other regions)	3.14	28
8	New regulatory pathways (e.g. adaptive licensing)	3.14	21
9	Conditional marketing authorisation	3.09	22
10	Accelerated assessment	3.08	24
11	Risk-management plans	2.97	30
12	Mutual recognition procedure	2.97	29
13	ICT/telematics	2.95	19
14	Decentralised procedure	2.93	28
15	Other disease areas	2.88	8
16	Over-the-counter medicines	2.87	15
17	Product information requirements (label/packaging leaflet)	2.86	28
18	Development of the regulatory framework (e.g. consultation of experts, public consultation, impact analysis, hearings, appeal procedures, harmonization, ICH)	2.84	25
19	Complexity of the regulatory system	2.81	21
20	Decision/assessment instruments (e.g. benefit-risk methodology)	2.78	23
21	Antimicrobials	2.78	9
22	Other areas in the authorisation phase (e.g. linguistic review, article 58 applications)	2.74	39
23	Assessment of applications	2.72	29
24	Summary of product characteristics (SmPC)	2.71	28
25	Other cross-cutting areas in the regulatory system	2.71	14
26	Individual case safety reports	2.71	24
27	Administration/reporting (e.g. databases, formats, templates, Quality Review of Documents, forms)	2.67	21
28	National authorisation procedures	2.63	30
29	Compassionate use	2.60	20
30	Innovative drug development methods (e.g. nanotechnology, personalized medicine, biomarkers, statistical methods/trial design)	2.59	22
31	Biosimilars	2.57	14

Rank	Topic	Mean score	n
32	Division of labor and coordination (e.g. between EMA committees, between EMA and Member States)	2.57	21
33	Scientific advice	2.56	32
34	Interaction with companies (e.g. in person, meetings, oral explanations, letters, notifications)	2.56	27
35	Post-authorisation safety studies (PASS)	2.52	23
36	Post authorisation measures (PAM) (e.g. SOB, ANX, MEA, LEG,REC)	2.50	24
37	Referrals (e.g. safety referrals (articles 107i, 20, 31), paediatrics referrals (article 29), harmonization referrals (articles 13, 29(4), 30)	2.50	22
38	EudraCT Database/EU Clinical Trials register	2.46	28
39	Other type of product	2.43	14
40	Periodic safety update reports (PSURs)	2.41	29
41	Public communication (e.g. EMA website, direct healthcare professional communication, notifications)	2.41	29
42	Centralised authorisation procedure	2.40	30
43	Assessment reports	2.37	29
44	Knowledge and expertise (e.g. scientific, regulatory, therapeutic area)	2.36	25
45	Renewals	2.34	29
46	Rapporteur/(Co)-Rapporteur appointment	2.33	27
47	Other areas in the post-authorisation phase (e.g. article 61 (3) notifications, parallel distribution, GMP inspections, certificates of medicinal products, falsified medicines)	2.33	33
48	Neurodegenerative disease	2.33	15
49	Scientific guidelines: clinical efficacy and safety	2.29	34
50	Other pre-authorisation areas (e.g. GCP inspections, invented name)	2.29	41
51	Extension applications	2.29	24
52	New chemical entities	2.29	21
53	Cancer	2.27	15
54	Consistency and objectivity (e.g. conflicts of interests)	2.26	19
55	Submission of applications	2.26	31
56	EudraLex/EudraVigilance	2.23	26
57	EPARs	2.21	28
58	Patient/stakeholder involvement	2.21	19
59	Sunset clause	2.21	24
60	Presubmission meetings	2.18	33
61	Auto-immune and other immune dysfunctions	2.15	13
62	Authorisation procedure for 'normal' products (compared to the 'special' procedures mentioned above: Compassionate use; Accelerated assessment; Conditional marketing authorization; Marketing authorization under exceptional circumstances; Orphan designations)	2.15	27

Rank	Topic	Mean score	n
63	Viral disease (other han HIV)	2.14	7
64	Qualification of novel methodologies procedure (opinion or advice)	2.14	22
65	Marketing authorisation under exceptional circumstances	2.11	18
66	Orphan medicines	2.10	20
67	Advanced therapies (ATMP)	2.08	12
68	Cessation	2.06	18
69	Scientific guidelines: Multidisciplinary	2.00	30
70	Orphan designations	2.00	25
71	Herbal medicinal products	2.00	4
72	Pandemic influenza	2.00	6
73	Scientific guidelines: Quality	1.97	33
74	CHMP opinions	1.96	28
75	Annual re-assessment	1.94	17
76	Assessment reports	1.93	29
77	Scientific guidelines: Biologicals	1.93	27
78	Pharmacovigilance inspections	1.92	26
79	Transfer of marketing authorisation	1.92	24
80	Generics	1.90	10
81	Diabetes	1.90	10
82	Biologicals/medicines derived from biotechnology processes	1.89	19
83	Scientific guidelines: Non-clinical	1.88	32
84	Dossier format	1.87	30
85	Product defects	1.80	20
86	HIV/AIDS	1.80	5
87	Urgent safety restrictions	1.79	19
88	Geriatric medicines	1.78	18
89	Withdrawal of applications	1.62	26
90	Sampling and testing (of the quality of centrally authorised products)	1.56	16
91	SME guidance	1.29	7

- *The table is ranked according to mean score;*
- *'Mean score' is mean of respondents that scored the area. 1 indicates no need for improvement and 4 indicates a high need for improvement;*
- *'n' is number of respondents that scored the area.*

Annex 6 - Summaries of comments on 12 high priority regulatory areas

Note to reader

The summaries below describe comments that were made through our survey of EFPIA and AESGP member companies (see Chapter 2.2). It should be noted that we specifically asked for comments on areas in need of improvement, and not for a balanced view on topics. We have included only comments that were made by more than one respondent, and have tried to interpret comments as little as possible. Text in quotation marks denotes quotes that best captured issues mentioned. Comments are taken at face value: we did not perform a thorough factual check or further analysis of the background of comments made. Some issues mentioned, for example in the area of transparency, have undergone considerable changes since respondents filled out the survey at the end of 2013. The comments below should not be seen as a formal statement by any respondents, company, EFPIA or AESGP.

1. Paediatric medicines

General

Many respondents feel that the current regulatory system for paediatric medicines is too 'complex' and 'burdensome' and 'does not satisfactorily address the goal of bringing more medicines to children'. According to respondents, the problems with the current regulatory system are 'multi-factorial' and include the type of studies that are requested; the timelines of submission of paediatric investigation plans (PIPs); the role of the Paediatric Committee (PDCO); and administrative issues. Respondents believed 'there is an opportunity with the revision of the Paediatric Regulation in 2017 to try to get this right'.

Requested studies

Respondents believed that the regulatory processes could be better 'adapted according to the specifics of the disease and product in question'. Respondents felt that the 'scope of studies requested should be limited to the disease indication instead of the potential use of a product'. Also, there should be a 'clearer delineation between paediatric needs in the indication being explored for adults and a voluntary opportunity to look beyond for other indications'. In addition, respondents thought that the 'size of information' that is requested in PIPs should be more flexible. In some cases, the 'PDCO's requirements for development efforts' are being perceived as 'rather extensive and going beyond the planned development path of the product'. Respondents noted that 'it should not be requested to start phase 1 study in children without having received approval in adults for diseases for which there are already existing therapies in children'.

Companies experienced that because 'the extent of studies required by the PDCO to be included in a PIP is increasingly demanding, it is becoming a challenge to complete paediatric

programmes in time for applying for a supplementary protection certificate (SPC) extension'. As a consequence, 'completed PIPs may not always lead to rewards'. Furthermore, companies believed that conducting extensive paediatric studies might 'delay new products being available for adults'.

A possible solution for situations 'where large paediatric studies are not feasible' would be to 'utilise extrapolation of adult data and innovative trial designs'. Furthermore, it was suggested that a solution should be found for situations in which 'necessary studies are impossible or highly impracticable in a particular paediatric age segment', e.g. in situations where recruitment of sufficient children is problematic. There could also be more 'flexibility and pragmatism' with respect to changing paediatric plans when it becomes clear that they are not feasible.

Timelines

Respondents believed that the required timing for the submission of the initial paediatric investigation plans is too 'early in development (i.e. after finalisation of PK/PD studies/end [or] phase 1)'. The reality of drug development is that investigation plans have to be adapted during development: 'early submission of detailed PIPs thus means that modifications have to be submitted in a high proportion of cases'. As the 'resource investment for every single PIP is considerable' and because 'product failures are very common' in the early phases, early PIP submission is considered 'inefficient'. An additional challenge is that the 'early commitment in EU' makes it difficult 'to plan global paediatric programs'.

Respondents suggested reconsidering the 'timing of the submission (of PIPs) to allow the applicant to better define the details of the relevant paediatric programme at an appropriate time during development', e.g. 'at end of phase 2'. This could also lead to a better alignment 'with the equivalent submission in the US'. 'A stepwise approach could be considered, starting with a PIP restricted to high level aspects, which could later be supplemented', and 'adjusted for therapeutic areas', 'as more data is generated through product development'.

PDCO

It was suggested by respondents that the 'PDCO should recommend and not decide': 'decisions should be made by the CHMP as it is for other EMA committees'. Or that, 'alignment between PDCO requirements and CHMP position should be clearly defined and ensured'. Furthermore, companies would like to have a more informed communication on what the 'PDCO requests' in terms of paediatric studies. Also 'since paediatric drug development is a very complex area, with many open questions', respondents felt that the 'opportunities to interact with the PDCO before and during the PIP review process' are currently too 'limited' and too 'formal'. A solution could be to 'create meeting opportunities with PDCO experts prior to PIP submission'.

Administrative burden

Finally, companies experienced a 'high administrative' burden with little 'added value' with regard to the procedure for 'PIP modification' and 'compliance checks'.

2. Variations (e.g. type IA/IB/II/unforeseen [Article 5] variations)

Note to reader

Since companies responded to the survey, the EMA has issued clarifying guidance concerning variation categories C.I.11 and C.I.13, which addresses some of the concerns raised below.

General

Respondents believed that the Variations Regulation ([EC] No 1234/2008) 'is in general acceptable, but that the implementation of it has been so rigid that the overall scope about simplification and reduced administrative workload has been bypassed'. Respondents felt that currently, 'more complexity is added, leading to an increasing number of variation classifications, with descriptions of conditions and documentation requirements often difficult to comprehend and open to diverging national interpretation'. 'A much more pragmatic and flexible approach is needed,' amongst others by 'a reduction of the number of different variation classifications and better possibility to group variations, also leading to cost reductions'.

On a higher level, respondents identified a 'need to revise the European Commission consultation process to update the variation guidance in order to guarantee the best integration of expertise of both agencies and companies. With the current process, companies had very little impact on the evolutions of this key guideline despite a massive investment of expert time to make proposals'. Respondents thought that the practical application of the legislation and the accompanying guidance 'should be reviewed to ensure that it is meeting the Commission's goals of reducing the administrative burden and duplication of costs'.

Classification of variations

The introduction of new variation classes (C.I.11 and C.I.13) in 2013 has led to a classification of submissions that is, according to respondents, 'arguably not justified by the level of review required'. For example, 'any Article 46 submission' of paediatric study reports 'or any submission of a final clinical study report as part of a post approval measure is now a type II variation'. This is also the case where the report 'does not significantly alter benefit-risk' or 'impact the product information'. Respondents commented that this new classification 'will require increased industry resources and will entail significant increases in the fees paid to EMA'. It was felt that classification should be more risk-based and 'should better reflect assessment burden and risk to patient'. For example, respondents reported cases where there have been 'requests for type II variations when no significant impact on the quality, safety or efficacy of the concerned medicinal product'.

Besides having issues with the criteria for classifying variations themselves, respondents also reported that 'additional clarification and harmonisation in the interpretation the variations guideline is still necessary'. Respondents reported that 'the guidance is 'unclear,' 'in particular the new classifications categories C.1.11 and C.1.13'. This has led to 'unclear' or 'inconsistent advice' from authorities and the rejection of applications 'due to incorrect classification'.

Grouping of variations

Respondents also experienced a lack of consensus between Member States regarding the administrative procedures concerning the acceptability of grouping of variations and the requirements regarding documentation, such as 'the necessity of providing original documents'. This 'creates a lot of administrative paperwork'. A related issue is the complexity that arises when 'variations are run in parallel or in groups and the potential consequences of that on quality review documents'. A misalignment here 'may have major consequences on production processes'. 'More flexibility for grouping different changes into one variation' and better guidance could help 'to reduce administrative burden' and reduce fees.

Timelines

Also with respect to timelines there appeared to be differences between member states. For example, respondents noted that 'deadlines to answer questions regarding type II variations vary from 60 days, up to six months'. In addition, respondents noted that existing timelines are not always met, leading to delays, for example in gaining national approvals with respect to MRP/DCP variations.

Quality

Respondents also commented on several issues related to quality. For example, respondents thought that 'there is a strong need for improvement in the EU to align with the concepts of ICH Q8-11' with respect to 'quality-related variations classification (especially for biologics)'. Furthermore, respondents reported that the 'new variations regulation is unspecific with regard to changes to primary or secondary reference standards', 'creating uncertainty for the MAHs'. Respondents 'expect clear classification for changes to reference standards'.

A final issue mentioned by respondents was that 'one of the objectives of the revision to the Variations Regulation was to facilitate continuous improvement, including Quality by Design, across a product's life-cycle by introducing a more flexible regulatory framework for those companies who have introduced risk-management and quality systems. This has not yet been achieved'.

3. Other areas in the pharmacovigilance phase

Note to reader

Since companies responded to the survey, the communication between MAH and Pharmacovigilance Risk Assessment Committee (PRAC), has been revised, addressing some of the issues mentioned by companies.

General

Some respondents believed that several requirements in the new pharmacovigilance framework are misbalanced 'from a public health versus burden/information value perspective'. An example provided related to the pharmacovigilance system master file (PSMF) in which it is required to list 'all market research activities ongoing and completed in the last two years, whereas it has little to do with pharmacovigilance and patient safety.' It was suggested that a 'better sense of proportionality should be introduced' and that 'the EU should be encouraged to a more pragmatic and value added approach to their requirements'. Another

general concern expressed by respondents was that the implementation of administrative requirements could have been more efficient, for example with respect to how companies were requested to provide input for the very detailed EudraVigilance Medicinal Product Dictionary (EVMPD) database and the Article 57(2) / ISO IDMP standards.

Signal management

Respondents thought that the current 'specifications for signal detection include some low-yield activities which remove focus from the ones more likely to identify true safety issues'. Respondents wanted more clarity on the requirements with respect to how to manage safety signals, for example 'in good pharmacovigilance practices (GVP) Module IX with respect to data mining of individual case study report databases' and the 'threshold for inclusion of a safety signal in the PBRER'.

PRAC

Some respondents thought that communication with the PRAC 'is complex and not smooth, due to too many players (PRAC, CHMP, internal company players) combined with need for rapid decision making'. For example, respondents suggested that 'transparency of PRAC decisions might be premature as final scientific decision lies with the CMD/CHMP two weeks later'. Furthermore, respondents felt that there is currently a 'very late notification to MAHs on emerging concerns with tight timelines for response preventing high-quality deliverables'. Respondents found it especially important that a 'MAH is always informed in advance, before a company product is visible in agenda, minutes or other PRAC publications'. For example, with respect to 'new signals detected from EU spontaneous reporting systems - the MAH gets informed only when the signal is published in the PRAC agenda. It will be very helpful if the Product Team Leaders inform the MAH in advance of the PRAC discussion'. Respondents believed that 'more possibilities to interact with PRAC would be valuable in order to talk with regulators about safety'.

4. Costs/funding of the system (including fees)

General

Respondents experienced that 'costs of regulation for the pharmaceutical industry have heavily increased over the last years', e.g. in relation to fees.

Public funding

Respondents thought that 'as the activities of regulators constitute not only a service to industry but also a public health service, consideration should be given to some level of community/public contribution to their costs, particularly in respect of pharmacovigilance activities'. The impression is now that 'the legislator continuously increases the burden on industry while its relative contribution to the funding of the centralised system decreases'. Respondents questioned 'whether it is appropriate that services to protect public health should be 100% funded by industry'.

Fee structure

Respondents experienced a lack of 'transparency' with respect to how fees are 'linked to the services provided' by authorities. Examples of this are that 'for new charges more clarity is needed

why these fees should be paid,' and that the 'costs for mutual recognition procedures/decentralised procedure/national procedures are not harmonised, and that there are very high costs in some countries'. Besides having a transparent cost structure, fees should also 'be in proportion to the effort required from the reviewer'. The feeling was that 'fees have become dissociated from the amount of work needed or benefit obtained'. For example, 'for well-established over-the-counter (OTC) medicines like e.g. aspirin/paracetamol etc. the fee structure does not reflect the lower level of work associated with such molecules'. Furthermore, respondents cautioned that 'as new EMA fees are introduced, duplicate charging by Member States for the same activities must be avoided'. Various examples given by respondents related to the new pharmacovigilance and variation regulations (see below).

Pharmacovigilance

Respondents believed that 'the planned introduction of EMA fees for pharmacovigilance activities will likely lead to significant increases in the regulatory fees paid by marketing authorisation holders' and that this 'in many cases is disproportionate to the work to be conducted'. Furthermore, it appeared to respondents that 'industry is expected to pay fees that fully fund new requirements under the Pharmacovigilance legislation' and that this should be more balanced: 'pharmacovigilance must (also) be publicly funded where the activity is in the interests of broad public health'. Also 'referral fees (pharmacovigilance) need some community/national competent authority contribution for referrals invoked by them'.

Variation

Respondents expected that 'recent changes to variations requirements will likely lead to significant increases in the regulatory fees paid by marketing authorisation holders', which do 'not always provide value for money'. Respondents think that currently 'too many minor variations require fees'. Examples of fees deemed inappropriate by respondents are: 'Article 46 submission for which we have to pay a full variation type II fee,' 'fees for variations that impact only one Concerned Member State (CMS) in European procedures', 'new variation fees for changes to risk-management plans', and 'group variation fees'.

Orphan medicines

Respondents felt that for some development areas with important benefits for public health the regulatory costs could be further reduced. For example: 'development of medicinal products for orphan indications are a common goal of the EU but is extremely cost intensive. Scientific advice should be free of charge for all companies independent of the size of the company'.

5. Article 46 paediatric study

General

Article 46 of the Paediatric Regulation requires MAHs to submit a report of any MAH-sponsored study involving the use in the paediatric population of a medicinal product within six months of the end of a study. According to respondents this 'leads in the current setting (e.g. for studies that are included in a paediatric investigation plan) to a duplication of assessments, unnecessary procedures

(time, workload), and increased costs'. Respondents felt that there is a 'need to evaluate the overall cost-effectiveness of this process, also because they considered 'it is questionable if individual Article 46 studies on their own can be evaluated and add to the understanding of the product'. Respondents suggested that it would make 'more sense to make an interpretation of the data if all studies are finalised'.

Variations

Respondents thought that 'Article 46 paediatric study applications should not be submitted as a type II variation by default' as is required by 'the revised variation classification guidelines', because of the accompanying 'additional time & financial burdens', which 'goes against the spirit of the variations regulations'. Respondents suggested that 'submission as type IB should be possible if there is no change of benefit-risk' or if there is 'no impact on product information'. In addition, respondents suggested that 'it should be possible to submit multiple related paediatric studies in a single variation (not separate variations, as currently required)'.

Timelines

'The new variation framework requires that individual studies approved within a PIP are to be submitted within a 6 month timeframe'. Respondents noted that this 'timeframe can be challenging to meet', especially for vaccines and in case of studies conducted outside the EU. Respondents suggested that 'the reporting timeframe should be aligned with that for studies in adults (12 months)'.

Assessments

Respondents noted that in some cases 'assessment reports and CHMP conclusions for Article 46 applications are not received in due time (several months delay)'. Furthermore, respondents suggested that 'assessment of data should be avoided if a future assessment is foreseen (e.g. in a variation application)'.

6. Transparency and accountability (e.g. confidentiality, transparency measures, release of trial data, data exclusivity)

Note to reader

Considerable developments have taken place on the topic of transparency since respondents filled out the survey in 2013. EMA is in the process of drafting a new policy on transparency which should be finalised in October 2014. As a consequence, practically all the statements made by respondents on this topic are out-dated and would not provide a valuable contribution. Therefore, we did not include them in this summary.

7. Harmonisation (e.g. between Member States, between EU and other regions)

General

Respondents noted the importance of harmonisation on two levels: between EU member states, and between the EU and other regions. For instance, respondents thought that 'timelines and other requirements should not depend on the regulatory route' and believed that 'significant interaction between agencies (e.g. FDA, EMA, Member State agencies) facilitates mutual alignment on

conclusions and makes a joint approach more likely'.

Member States

Respondents observed that 'there is still a lack of harmonisation and consistency between Member States' requirements which can present challenges to applicants/MAHs', 'particularly in the OTC setting'. It could help if 'new regulations and directive provisions are to be promptly reflected into guidelines and Q&A'. Furthermore, respondents thought that the 'lag time between implementation of changes in EU legislation and its adoption by member states needs to be improved'.

ICH

According to respondents, 'opportunities for improving alignment with processes and requirements of other major regulators (particularly US FDA) should be pursued' and 'EU requirements are to be focused on global usability'. Respondents highlighted the International Conference on Harmonisation (ICH) as an important instrument to improve harmonisation between regions: 'The ICH process has provided significant benefits through the harmonisation of regulatory guidance and requirements in key areas in the three ICH regions. The work of ICH should continue to ensure that existing ICH guidance is maintained and updated, and to adopt new guidance in new areas'. Respondents felt that 'consideration should also be given to broadening the scope of ICH to additional countries/regions, to help ensure that harmonised approaches can be applied more globally'.

Development plans

Respondents believed that 'there is a need for global harmonisation of development plans,' and thought that it is unfortunate that 'there is currently no transparency in the conversations held between EMA and other regulatory agencies, mainly FDA'. 'In a world of global development, it would be helpful if more global approaches could be agreed between agencies'.

Regulatory requirements

Many different regulatory areas or the way they are applied in practice are mentioned by respondents as in need of harmonisation, including paediatric requirements; interpretation of variation applicability and requirements; quality guidelines; interpretation of the good manufacturing practice (GMP) regulations; harmonisation of the clinical efficacy and safety guidelines; alignment of PBRER reporting periods; biosimilars; legal status; and dossier requirements.

8. New regulatory pathways (e.g. adaptive licensing)

General

Respondents did not agree as to whether legislative changes for new regulatory pathways are needed or desirable. Whereas some respondents welcomed, for instance, 'adaptive' pathways, other respondents maintained: 'Do not include more pathways. The current ones are sufficient' and suggested a 'wider use of conditional/adaptive authorisations and accelerated assessment in diseases with high unmet need'. Also, respondents cautioned that 'new regulatory pathways will only be useful if they are considered in a holistic approach including

health technology assessment (HTA) and payers'. Furthermore, the importance of 'understanding the business needs for new pathways' is stressed, as is the importance of 'understanding and contributing as an industry to the practical implementation of new pathways'.

Adaptive licensing

Several respondents thought that 'a new expedited and/or adaptive approach would be welcome in Europe', but also noted that 'adaptive licensing has been discussed for a long time with very little action'. Respondents believed that 'we need an analysis on the need, feasibility and the potential features of an adaptive licensing concept and how this can be best achieved at regulatory, health economic and political level while involving patients perspectives,' including 'considerations for alignment with the FDA'.

Existing pathways

Although some respondents felt that 'there is currently no legal basis for adaptive licensing' others thought that it should 'include appropriate use of the regulatory tools we currently have (i.e. within the existing framework)'. For example, some respondents thought that 'the conditional approval pathway could be more flexible and be rather similar to what is part of current adaptive licensing proposals,' and therefore suggested an 'assessment of existing pathways'.

HTA

Respondents believed that 'it is critical that the continuum of drug development, authorisation and access is considered: so-called "adaptive licensing" requires "adaptive development" and will be of little or no benefit if access (i.e. HTA and payer decisions) is not also appropriately "adapted"'. Some respondents thought that 'when so many issues are uncertain for adaptive licensing, not least HTA and payer attitudes: avoid a new pathway increasing the complexity of the EU regulatory framework'. Other respondents suggested there should be a 'relationship with payers at an early stage of development'.

9. Conditional marketing authorisation

General

Respondents valued the current procedure for conditional marketing authorisation as an 'option', but also believed that it has not been functioning as intended: 'generally, it is used to "rescue" potential negative outcomes rather than a prospectively-planned approval approach'. Furthermore, respondents thought that the procedure is 'underused' and it 'should be applied more often'. Especially, 'with the current post-approval systems in place, the procedure could be further expanded'.

Criteria

According to respondents, one of the reasons for the underutilisation of the procedure is 'the very strict criteria for use'. In addition, respondents observed 'that the practical application/implementation to some extent narrows down the flexibility set in the legislation'. Respondents highlighted two criteria as problematic: the indication and the benefit-risk.

Respondents noted that, according to the guidelines, conditional authorisation is currently applicable

only for the first indication of a product, i.e. 'excluding additional new indications' and extensions. For respondents, this 'seems counterintuitive and possibly unethical if the second indication is for a life-threatening disease with an unmet medical need, but just happens not to be the first indication'. Respondents felt that a 'clear mechanism is required for new [subsequent] indications to obtain a conditional approval' 'in areas of high unmet needs'.

The second criterion considered problematic was the benefit-risk: 'the guidance refers to 'established' benefit-risk and this is not the approach of the draft text when the guidance was being formulated. The conditional marketing authorisation should be based on reasonable evidence that there is a positive benefit-risk profile, to be confirmed with post-authorisation commitments'. Moreover, respondents noted that 'there are differing views among national agencies about the level of data needed in order to make a benefit-risk assessment, and this may prevent early access to medicines which have a promising benefit-risk profile'. In summary, respondents thought that the current application of 'the criterion for a positive benefit-risk balance is rigid' and not fully transparent.

Market access

Some respondents felt that the current procedure has 'limited added value due to delayed access'. 'It should be noted that if this type of approval is allocated, market access procedures require alignment'; 'there needs to be a better understanding and acceptance of conditional marketing authorisations by all stakeholders, to ensure that the potential benefits of access to innovative medicines is not undermined by other restrictions (e.g. in pricing and reimbursement)'.

Adaptive licensing

Several respondents expressed 'a need for more "adaptive" approaches to development, authorisation and access to innovative medicines. Conditional marketing authorisations may be one vehicle in the current framework to help achieve this'. Respondents suggested that, 'the regulation could be revised to expand the scope to allow conditional approval (maybe under strict supervision or in strictly defined populations) to novel medicines where clinical activity in the overall population has not yet been established'. However, respondents also noted that 'while the legislative framework seems to provide for a high degree of flexibility, it should be reviewed as to whether it is still fully fit for purpose for adaptive development programs'. Here too, respondents noted that there needs to be discussion about the position of HTA bodies.

10. Accelerated assessment

General

Respondents generally believed that this pathway is 'underused'. 'In 2012, of 59 new medicines approved by EMA only one used the accelerated assessment procedure,' which 'raises questions around whether the procedure is being used to its full potential'. Respondents noted that 'even when requested it is often declined and/or revoked during the assessment phase' and suggested that 'maybe a different approach to accelerated assessment needs to be

considered, such as rolling submission and more flexibility with regard to issuing and responding to questions, rather than having all questions and responses at single pre-defined time points'. As a general issue, some respondents believed that 'all existing legal frameworks to support earlier patient access should be reviewed'.

Qualification hurdle

Respondents felt that 'there appears to be a high hurdle for EMA acceptance of accelerated assessment requests' and that use of the accelerated assessment procedure 'is being discouraged by EMA and CHMP'. A reason for this was, according to respondents, that 'very few products are regarded as having 'major public interest' or being 'therapeutic innovation' by CHMP'. Acceptance 'seems to be achievable only under exceptional circumstances (pandemics, etc.)'. Furthermore, respondents note that the 'reduction in review time is considered as almost "not feasible"' by regulators. There 'appears little interest by EU regulators to accelerate review timelines, compared to e.g. FDA'.

Broaden scope

Respondents suggested that the scope of the accelerated assessment procedure could be broadened: 'Accelerated assessment could be applied in more cases considering systems of other regions (e.g. priority review, fast track, breakthrough therapy mechanisms in US)'. Respondents provided several examples of this: 'An orphan indication should always automatically qualify for accelerated assessment due to the probably high unmet medical need and urgency for availability of new treatment for patients'. In addition, the 'procedure should also be possible for significant new indications, and not only new products'. Also, currently 'no priority review is granted for a neglected disease but it would be beneficial to accelerate regulatory decisions for these new drugs'. And a final example provided by respondents: 'EMA does not apply accelerated assessment for conditional marketing authorisation application although legislation would not exclude this'.

Timelines

According to respondents, 'there appears to be a high hurdle for EMA to retain the accelerated assessment timelines during review'. Respondents felt this is partly so because it is 'too easy for regulators to change from accelerated to standard approval timelines'. Another problem seems to be that the 'current regulation is not sufficiently flexible in terms of clock-stops, cancelling the benefit of accelerated assessment'. Respondents noted that for MAHs the 'workload is difficult to handle practically in a short timeframe. A "rolling review" would facilitate the process (taking part of the workload off the critical path)'. In practice, respondents 'see a good number of products revert back to a "normal timetable"' and wonder if 'more could be done to support applicants that at least gain an initial accelerated assessment?' There were also respondents who believed that the current legislation should be adapted and that 'the assessment timelines for an accelerated assessment application should be shortened, e.g. priority review in the US'.

11. Risk-management plans

General

Respondents thought that the balance of how the requirements for risk-management plans (RMPs) are currently implemented 'is not sufficiently focused on safety concerns vs. administrative burden'. More specifically, 'the definition of "important" should be revised as many risks classified as important are not important in terms of outcomes, e.g. injection site reactions'. Some respondents thought that 'the 60 days deadline to update RMP following an important milestone being reached should be removed. In addition, current developments mean that 'additional resources to put together the information are necessary and additional costs for the marketing authorisation holder'.

Well-established products

Respondents considered the requirements for risk-management plans 'disproportional, specifically if "routine pharmacovigilance" is the main measure'. Respondents believed that the requirements should be simplified for 'very well-established products', such as non-prescription medicines, 'generic and old products,' and that 'more flexibility would be welcome, so as to avoid cumbersome documents for products with very stable safety profiles, thus reducing the resources required both on regulators and MAH sides'. Respondents suggested that 'the US Risk Evaluation and Mitigation Strategies (REMS) system and related focus may be a more proportionate model'.

Variations

Respondents also worried that 'maintenance of risk-management plans could be very complex, especially taking into consideration the new (July 2013) Commission variations guideline and the EMA's interpretation of that guideline'. An example given by a respondent was that, the 'new variation classification category C.I.11 adds significant complexity as requiring that any non-agreed working change in the risk-management plan is supposed to be done via type II variation'. Respondents believed that 'variations due to updates are to be minimised unless there are significant updates'.

Templates

Respondents also experienced a high regulatory burden due to administrative inefficiencies. For example, respondents noted that 'there are redundant chapters in the template', e.g. 'table V.1 of the GVP Module V' and that 'there is a lot of repetition in the template'. Respondents thought that 'the template should be revised to improve collation of information': it should 'be short and crisp within one page and not around 15 pages'. It was suggested that this should especially be possible 'for well- established products like OTC'.

Guidance

Respondents believed that 'further guidance should be issued' as there are 'still some uncertainties regarding new legislation and PRAC input'. Examples are a 'lack of clarity over submission route e.g. Variation, PSUR'; the fact that 'measuring effectiveness of minimisation measures is an evolving science with no clear criteria set to-date, and yet they are required

in the RMP' (GVP Module XVI); and that 'the guidance that was promised on the publication of the public summaries is still not available: content guidance is required as a matter of urgency, along with expectations of when public summaries will be published'. Furthermore, with respect to the concerns mentioned in the above sections about well-established products and variations, respondents requested more guidance: there is a need for 'greater clarity for how to write RMPs for products with mixed legal status and generics'. Respondents believed that further guidance is also needed for variations: 'the revised Variation Regulations and the EMA clarification document issued over the summer require further clarity in particular which changes to the RMP should be submitted as variations for national/MRP/DCP licensed products'.

Assessments

Respondents noted that authorities do not always follow procedures, for example: 'individual authorities are not following the GVP module definitions with respect to potential and identified important risks, reflected in their requests for RMPs and in assessment reports; several authorities request to make a risk an identified risk when really only fulfilling definition of a potential risk'. Another area where respondents expressed concerns is that 'usually the assessment of the RMP is not provided to applicants in due time which doesn't allow applicants enough time to prepare responses to questions if any. In addition, some RMP revisions have not been assessed'.

12. Mutual recognition procedure

General

Respondents thought that 'the basis of the procedure is well understood and can function well'. However, respondents also stated that, timelines are often 'not reliable' and in practice 'true mutual recognition does not exist'.

Decentralised procedure

Many respondents experienced the same difficulties in the mutual recognition procedure (MRP) as in the decentralised procedure (DCP): the MRP 'suffers from similar drawbacks as for DCP'. However, some respondents maintained that 'DCP is more smooth than MRP'. In particular for OTC products 'DCP is the preferred route of registration but legislation can force applications into MRP if a national license already exists'.

Timelines

Respondents experienced that timelines of the assessment procedure are not adhered to by a number of national regulatory agencies: 'timelines are not well-respected, resulting in major delays and complex communications during the procedure', 'for instance the preparation of replies to questions'. Respondents emphasised that the 'CMS should rely more on the Reference Member State assessment report and should make their comments within the agreed timeline'. The duration of the timelines of the national phase, following an EU-wide approval, is experienced by respondents as a problem. In some countries, the 'national phase can be a lot longer than 30 days'. Respondents reported that in some cases the company 'still has to wait more than a year' 'for validation of

translations of packaging information'. This can lead 'to different safety information in different countries even if via the MRP there is an English version of a common approved product information'. Respondents suggested that the 'harmonised national phase duration' should be better enforced in reality and that 'maybe national translations could be reviewed independently from the approval phase'.

Harmonisation

Besides the variability between member states concerning adherence to timelines and the validation phase, respondents also experienced other points of divergence and noted that 'CMDh directions and guidelines are not followed by all CMSs'. An important problem for OTC companies is the fact that the 'Legal status can vary per country' (prescription and non-prescription), which is often directly conflicting with the legal requirement to have a harmonised product information as a deliverable of the MRP/DCP (i.e. harmonised SmPC, the patient information leaflet [PIL] and labelling) and hence 'preventing to include some countries in the procedure' or leading to parallel procedures being run. Respondents suspected that there is a 'continued over-use of "potential serious risk to public health" by national competent authorities in order to block OTC status'. While some respondents suggested that it 'should be possible to have flexibility in the SmPC or allow a harmonised' non-prescription and prescription SmPC, other respondents maintained that 'specific national requirements should no more exist'.

Annex 7 - List of respondents

Company	Membership
Arkopharma	AESGP
AbbVie	EFPIA
Almirall	EFPIA
Amgen	EFPIA
AstraZeneca	EFPIA
Baxter	EFPIA
Bayer	EFPIA
Bayer Consumer Care	AESGP
Biogen Idec	EFPIA
Boehringer Ingelheim	AESGP ‡
Boehringer Ingelheim	EFPIA ‡
Bristol-Myers-Squibb	EFPIA
Celgene	EFPIA
Chiesi Farmaceutici	EFPIA
Eisai	EFPIA
Eli Lilly	EFPIA
Esteve	EFPIA
GSK	AESGP
GSK	EFPIA
Johnson & Johnson	EFPIA
Johnson & Johnson	AESGP
Lundbeck	EFPIA
Menarini	EFPIA
Merck Serono	EFPIA
MSD	EFPIA ‡
MSD Consumer Care	AESGP ‡
Novartis	EFPIA
Novartis Consumer Health	AESGP
Novo Nordisk	EFPIA
Orion	EFPIA
Pfizer	EFPIA
Pfizer Consumer Healthcare	AESGP
PGT Healthcare	AESGP
Roche	EFPIA
Sanofi	AESGP ‡
Sanofi	EFPIA ‡
Sanofi Pasteur	EFPIA
Takeda	EFPIA
UCB	EFPIA

‡ Combined response for NCE and OTC division

Annex 8 - List of examples provided by respondents

1	Issues with the creation of national text following approval of harmonized text during the national phase of the decentralised procedure and following approval of Type II variation
2	Different approaches between Member State agencies concerning line extensions
3	Delay in CHMP Opinion due to poor dialogue between Rapporteurs/CHMP and European Commission
4	A lack of clarity regarding how National Competent Authorities will interpret and implement the new Pharmacovigilance legislation
5	Disharmonisation between central and national regulatory agencies, leading to a different Health Care Professional communications per country
6	Rigid interpretation of the EMA regarding new variation legislation results in increased costs for all small and minor changes to be submitted as type II variations
7	Lack of consistency in EMA decisions to release confidential information and lack of a robust internal process at the EMA
8	Overview of seven high priority topics
9	A lack of guidance regarding the new risk-based approach regarding risk-management plans
10	Lack of harmonisation between Member States regarding type IA variations resulting in rejection or reclassification as type IB variations.
11	Differences between Member States regarding timelines for type IB Variations
12	Different timelines and consistency in requirements for type II variations
13	Difference in classification of active substances versus excipients between Germany and Sweden
14	Lack of clarity about requirements for the submission of variations and slow validation process hamper quick authorisation of variations
15	Inconsistency of feedback and advice by national competent authorities in (pre-)registration phase
16	Issues with true-recognition between member states for mutual recognition procedure / decentralised procedure of OTC products
17	Disharmony between member states about exemption for products approved via mutual recognition procedure / decentralised procedure
18	Mutual recognition procedure and decentralised procedure fail because of missing flexibility of the system
19	Lack of guidelines on the evaluation of medicinal products in the paediatric population
20	Preparation of paediatric investigation plans requires excessive details
21	Lack of a standardised procedure for advanced therapy medicinal products market authorization requests
22	Lack of consistency and clarity of EMA guidelines for naming conventions and reporting levels
23	Lack of harmonisation of prescription to non-prescription switching criteria between different Member States
24	Issues with collection of global AE nutritional information
25	Problems with communication during validation of mutual recognition procedure variation leading to delays
26	Multiple changes in regulation and additional changes to Electronic Common Technical Document structure create software compliance issues

27	Lack of harmonisation between EU countries for starting compassionate use programs
28	Lack of communication between PRAC and industry impede required periodic safety update reports / summary of product characteristics changes
29	Lack of consistency relating to paediatric requirements and processes
30	Lack of transparency of CHMP procedures and outcome for approval of a new chemical entity via centralised procedure
31	Inconsistent timelines of the authorisation phase for decentralised procedure
32	Issues with the submission of herbal medicinal products due to lack of harmonisation between Member States
33	Concerns about variation regulation for marketing authorisation, especially with regards to implementation of the new ICH quality concepts
34	Increase of administrative burden and costs for companies due to new requirements for the submission of results for paediatric studies as type II variation application
35	PIP process requires unnecessary efforts because initial PIP submission is required too early in drug development and compliance check is a non-value added step in PIP process
36	Lack of flexibility of CHMP and national EU health authorities prevents combination of conditional approval and accelerated assessment process to enhance approval times in EU
37	Limited acceptance of innovation of drug development for approval in Europe
38	No clear communication on whether a CHMP Oral Explanation Meeting at Day 180 of the procedure is needed or not
39	Lack of harmonisation at the level of the Paediatric Committee about requirements of studies
40	Lack of harmonisation and flexibility of centralised procedure hampers switching from prescription to non-prescription status
41	Lack of harmonisation of OTC application between different EU member states
42	Lack of harmonisation and clarity of clinical trial authorisation document requirements and timelines in EU member states
43	Lack of consistency about requirements and timelines for market authorisation application results in delay of submissions
44	Lack of consistency in the timeline and requirements of post-authorization phases
45	Difficulties with the recruitment of patients in the age group 6 - 35 months requires changes of paediatric regulation
46	New medical device regulations may hamper innovation and fast approval of new medical devices
47	Complexity of the regulatory system and inconsistency of regulatory processes across EU Member States impedes single program for compassionate use
48	The extent of studies required by the Paediatric Committee in a PIP is increasingly demanding
49	The new pharmacovigilance legislation is introducing complexity to the individual case safety reports and increases the administrative burden for sponsors of non-EU non-interventional studies
50	Better implementation of the grouping of variations, the process and fee structure is needed
51	Issues with safety referrals and the implementation of the pharmacovigilance legislation
52	Lack of clarity of the new variation regulation concerning type II variations
53	Modified PIP being rejected even through agreements were reached
54	Need for more transparency and flexibility in CHMP opinion building to provide opportunities for interaction between applicant and CHMP

55	No adoption of a CHMP opinion possible in case the decision of the European Commission on a technically similar orphan drug is pending
56	Several issues with the variations legislation and its implementation
57	Lack of sufficient dialogue between HTA bodies, National Competent Authorities and EMA results in different advice about data requirements
58	Lack of efficiency in the submission of information to regulators across the EU
59	Rewards and incentives associated with the paediatric regulation were insufficiently provided
60	Need for harmonised product information for all markets in a decentralised procedure

Annex 9 - Scoring of reported reasons for CMDh referral

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

BE: bioequivalence; TE: therapeutic equivalence; CI: confidence interval; PL: package leaflet; GCP: good clinical practice.

Annex 10 - Survey / Paediatric investigation plans (PIPs)

Introduction

This survey is part of the Escher II: Regulatory Review Project that is cofunded by EFPIA and AESGP. The survey is part of the Paediatrics case study that will evaluate the timing and outcomes of Paediatric Investigation Plans (PIPs) submitted and agreed upon in 2007, 2008, 2009, and 2010.

We would like to ask you to provide us with some information regarding the PIPs and/or waivers that have been submitted to the Paediatrics Committee (PDCO) by your company in 2007, 2008, 2009, 2010. We would like to thank you in advance for filling out this questionaire, as the response of your company greatly contributes to the success of this Escher case study.

1. **Has your company submitted a PIP or waiver in 2007, 2008, 2009, or 2010 that has been agreed by the PDCO?**
   - ❒ Yes (Please continue to question 2)
   - ❒ No (Thank you for your response. You do not have to answer any additional questions.)

2. **How many PIPs and waivers of your company's products have been AGREED by the PDCO in 2007, 2008, 2009, and 2010? Please only count original PIP or waiver submissions and not modifications or duplicates.**
   PIPs for Article 7 products:
   PIPs for Article 8 products:
   Waivers:

3. **For how many of the agreed PIPs/waivers in 2007, 2008, 2009, and 2010 has the development program now been terminated?**
   PIPs for Article 7 products:
   PIPs for Article 8 products:
   Waivers:

4. **The remainder of the questions are about PIPs for Article 7 products ONLY. Could you indicate for all PIPs for Article 7 products that were agreed on in 2007, 2008, 2009, or 2010, whether or not a full deferral was granted?**

   A full deferral means all studies have been deferred until after market authorisation, a partial deferral means that some of the studies in the PIP have been deferred until after market authorisation and some studies in the PIP were not deferred, and no deferral means that none of the studies in the PIP were deferred until after market authorisation.
   Article 7 product PIPs with full deferral
   Article 7 product PIPs with partial deferral
   Article 7 product PIPs with no deferral

5. For all Article 7 products that did NOT receive a full deferral, could you provide the following information:

- PIP number (first PDCO decision: e.g. EMEA00100PIP0110)
- PIP or waiver submission
- Timing of application (Phase I/Phase II/Phase III/other)
- Current status of product: Marketed/Still under development/Development program terminated

6. This is the end of this questionnaire. Thank you very much for participating in this study. If you wish to leave any additional comments, please use the text box below.

Annex 11 - Survey / Impact of the new pharmacovigilance legislation on activities of companies

Introduction

This questionnaire is part of the Escher II: Regulatory review Project that is cofunded by EFPIA and AESGP. The aim of this survey is to measure the impact of the new Pharmacovigilance legislation on the postmarketing activities of pharmaceuticals companies. More specifically, we want to assess the costs of compliance with all pharmacovigilance activities that are performed by your company in order to comply with the European requirements.

We will ask you questions regarding the following pharmacovigilance activities of your company:

- Post Authorisation Safety Studies (PASS)
- ADR reporting (including article 57 database)
- PSUR/PBRER reporting
- Safety department operations (including QPPV, Master File)
- Safety surveillance activities (including EURMPs)
- Safety-related labeling changes (including variations)

The results of this study will be published in the Escher II Project Report and will be used for scientific publications. All data will be anonymized and only aggregate estimates will be presented. No company-specific estimates or activities will be reported in any publication that uses data from this survey. Data will not be shared with other parties.

Please note that your answers will only be saved when using a single computer. It is not possible to login later and continue with answering the questions from a different computer.

This study is performed by researchers from Utrecht University, Utrecht, the Netherlands. For any questions regarding this survey, you can contact Jacoline Bouvy, email: j.c.bouvy@uu.nl. For general questions regarding the Escher Project, you can contact the project manager Jean Philippe de Jong, email: j.ph.dejong@escherproject.org.

We thank you very much for your time in filling out this survey.

Part I: Respondent and company details

In this first part of the questionnaire, we will ask you to provide some general details regarding your company.

1. What is your company's name?

2. What is your current job title?

3. What type of medicinal products does your company market in the EEA region?
(multiple answers possible)

- ❒ New Chemical Entities
- ❒ Biotechnology Products
- ❒ Over The Counter Medicines
- ❒ Biosimilar Products
- ❒ Generics

The questions on this page are about PostAuthorisation Safety Studies (PASS).

We would like to assess the costs of different types of Post Authorisation Safety Studies (PASS). However, we only want to include the costs of those studies that are specifically requested by regulatory authorities and not all studies that are performed after market approval by your company.

We would like information for each PASS with the following characteristics:

- Started after January 1st, 2007
- Completed (results have been reported to regulatory authorities)
- The study was specifically requested by regulatory authorities as part of the marketing authorisation (and was not already planned by your company)

If possible, could you provide the following information for these studies:

- Type of study (e.g. PK study, utilization study, survey, registry, clinical trial, or any other type)
- length of study (if applicable: number of months between inclusion of first and last patient)
- start date (month + year of inclusion of first patient)
- Total costs (including insurance costs, study facility costs, CRO costs, total employee costs, and any other relevant costs)

4. Please use the field below for a brief description of all required PASS

The questions on this page are about the handling of individual adverse event cases (reported after approval, including collection, scientific analysis, data entry into computer databases (Article 57 database), medical review, followup, and reporting to regulatory agencies)
Please answer these questions for the year 2013, unless specified otherwise.

5. How many people (as measured in FTEs) are employed by your company (either inhouseor outsourced) in order to perform this task for all products that are licensed in at least one EEA country?

6. Could you provide an estimate of all nonemployee related costs for handling of adverse event case reports? These costs include the annual costs of computerized databases and annual EudraVigilance costs.

7. Could you indicate what the total costs have been of setting up the EudraVigilance database for your company?

8. How many expedited ADR reports have been submitted by your company during the last three years? (i.e. one ADR report submitted to at least one agency in the EEA region)

The questions on this page are about the summary report production of aggregate postapproval adverse event information, including PSURs/PBRERs.
Please answere these questions for the year 2013, unless specified otherwise.

9. How many people (measured in FTEs) are employed by your company (both inhouse and outsourced) in order to perform this task for all products that are licensed in at least one EEA country?

10. How many PSURs and PBRERs has your company submitted in at least one EEA country during the last three years?
2011 (PSURs):
2012 (PSURs):
2012 (PBRERs):
2013 (PBRERs):

11. For all PBRERs that your company has submitted in 2013, could you indicate for how many of these PBRERs your company has also prepared a PSUR in 2013 that was submitted in a nonEEA region?
(We need this information to assess the impact of the nonharmonisation across regions regarding the PBRER format)

12. Could you indicate how many employee hours are required on average for the preparation of a single PSUR, before the implementation of the pharmacovigilance legislation (i.e. in 2011)?
If possible, please provide an estimate of the hours spent preparing a PSUR for a product registered less than two years, and an estimate for the hours spent preparing a PSUR for a product registered more than two years.

13. Could you indicate how many employee hours are required on average for the preparation of a single PBRER, after the implementation of the pharmacovigilance legislation (i.e. in 2013)?

If possible, please provide an estimate of the hours spent preparing a PBRER for a product registered less than two years, and an estimate for the hours spent preparing a PBRER for a product registered more than two years.

This question is about Safety department operations, including quality assurance, QPPV, Master File, technology support, and training.
Please answer this question for the year 2013.

14. How many people (measured in FTEs) are employed by your company (either inhouse or outsourced) in order to perform this task for all products that are registered in at least one EEA country?

The questions on this page are about Safety surveillance activity, including those related to post approval risk-management, the EU risk-management plan, signal detection and evaluation, safetyrelated product quality complaints, including product recall for safety reasons, responses to safety questions from regulators, literature review for adverse event signals, and provision of safety information to healthcare professionals.
Please answer the questions for the year 2013 unless specified otherwise.

15. How many people (measured in FTEs) are employed by your company (either inhouse or outsourced) in order to perform this task for all products that are registered in at least one EEA country?

16. How many EU-RMPs has your company produced in the year 2011?

17. How many EU-RMPs has your company produced in the year 2013?

The questions on this page are about activities required for safetyrelated labeling changes, including Variations. Please answer the questions for the year 2013, unless specified otherwise.

18. How many people (measured in FTEs) are employed by your company (either inhouse or outsourced) in orde

19. Could you indicate how many Variations your company has submitted during 2011 in the EEA region?
Type IA:
Type IB:
Type II:

20. Could you indicate how many Variations your company has submitted during 2013 in the EEA region?
Type IA:
Type IB:
Type II:

Part II: Impact of the new pharmacovigilance legislation
The questions on this page are about the impact of the new pharmacovigilance legislation that was implemented in July 2012.

21. Has there been a change in workload within your company as a result of the new Pharmacovigilance Legislation?

- ❒ The workload did not change
- ❒ The workload increased
- ❒ The workload decreased
- ❒ Mixed change: workload increased for some activities and decreased for other activities
- ❒ Mixed change: please indicate what activities increased and descreased in workload

22. In case of an increase in workload, has your company hired additional people as a result?

- ❒ No
- ❒ Yes

If 'yes', how many FTEs were hired? If possible, please specify whether these FTEs were temporary, permanent, and inhouse or outsourced.

23. In case of a decrease in workload, has your company reduced the number of people employed?

- ❒ No
- ❒ Yes

If 'yes', how many FTEs were reduced?

24. Which areas of pharmacovogilance have seen the largest impact of the new Pharmacovigilance Legislation, based on the experience of your company?

This is the end of the survey. If you have any comments about this survey or about the impact of the new Pharmacovigilance Legislation, please use the comment section below. Thank you for your time and effort in completing this survey!

25. Comments: (optional)

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