MARKETING AUTHORISATION OF NEW MEDICINES IN THE EU:
towards evidence-based improvement

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MARKETING AUTHORISATION OF NEW MEDICINES IN THE EU: towards evidence-based improvement

Markttoelating van nieuwe geneesmiddelen in de EU:
naar wetenschappelijk onderbouwde verbeteringen
(met een samenvatting in het Nederlands)

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CONTENTS

1

GENERAL INTRODUCTION

MARKETING APPROVAL OF NEW MEDICINES

Marketing approvals of new medicinal products can count on large interests of both patients in need of new medicinal therapies and the pharmaceutical industry. Drug regulatory authorities, such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) act as independent governmental third parties that decide about marketing authorisation [1,2]. The EU regulation of marketing approval of new medicinal products aims on the one hand to protect public health by preventing that low-quality, unsafe, or inefficacious products enter the market. On the other hand the regulation aims to promote public health by ensuring that patients gain access to medicines without unnecessary delay [3,4]. Consequently, regulators have to find the appropriate balance between the need to ensure that decision making is based on scientifically valid data and the need for access to new medicines [4,5]. They have to balance efficacy and safety evidence (with its inherent uncertainties), while taking into consideration the need for (better) medicines to treat the disease [5,6]. This system has been very successful in bringing many valuable safe and efficacious medicines to the market and, thus, contributed to improving public health. There are also important challenges that this system has to face in the future, in order to continue to serve both (sometimes conflicting) objectives of protecting and promoting public health [7].

CHALLENGES FOR THE DRUG REGULATORY SYSTEM

One of the challenges for the marketing authorisation system is to keep it efficient to ensure that a continuous flow of innovative and needed medicines will enter the market without unnecessary delay [6,8]. Currently there is a trend of rising research and development (R&D) expenditures, but no increase in the number of newly developed medicines submitted to regulatory agencies [9]. Figure 1 demonstrates that the number of approved new active substances has remained relatively stable over the past decade [10]. In 2011, 23 new active substances entered the European market and 32 new active substances were made available in the United States (US) [10]. The non-approval rates of new active substances at EMA usually lies around 25%, but was 40% in 2009 [11,12].

One of the reasons for this decrease in efficiency of drug development according to pharmaceutical companies is regulators being overly cautious, resulting in rising R&D expenditures and long drug development timelines [13]. Over the years, the emphasis on protecting public health increased: an extensive regulatory system has been constructed that covers virtually all aspects of drug development. For example, safety and pharmacovigilance requirements were added, partly as a consequence of previous market withdrawals. However, these have not been able to completely prevent later market withdrawals driven by safety issues [14,15]. Even in an overly regulated marketing approval system there will always be some

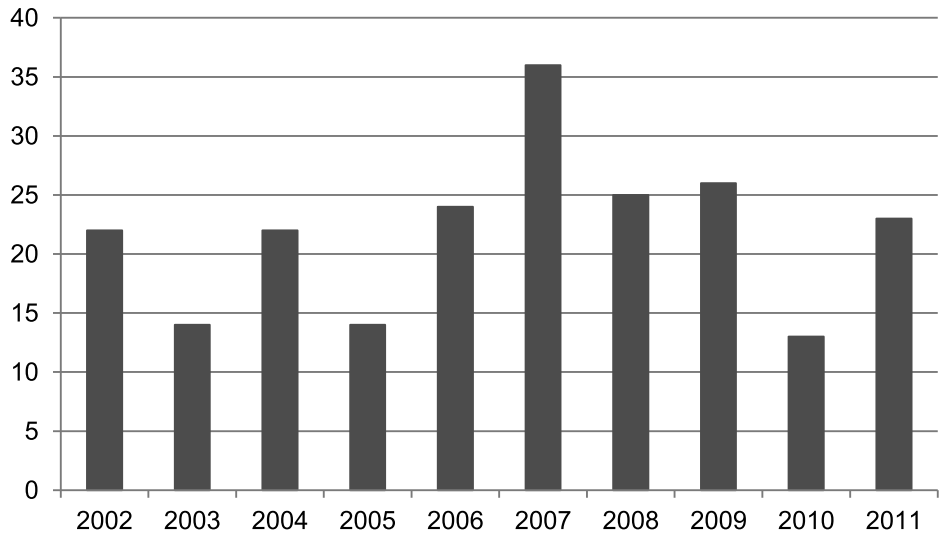

Figure 1. Number of new active substances approved in the EU 2002-2011. Adapted from [10]

uncertainty about the actual benefits and, especially, risks of a medicine at the time of initial approval, because of the limited information available [6,16].

Another main challenge for the regulatory system is to ensure that those medicinal products developed that are most needed by society [17]. The Priority Medicines Report demonstrated in 2004 that for certain highly prevalent disease areas such as some infectious and central nervous system diseases, as well as for many rare diseases, appropriate (better) treatments are needed [18]. Although regulatory agencies do not set the research agenda of pharmaceutical companies, they can stimulate drug development for such diseases, for example by facilitating the process of approval.

INITIATIVES FOR EFFICIENT MARKETING AUTHORISATION BY REGULATORY AGENCIES

Regulatory agencies acknowledged the need for improvement almost a decade ago and made incentives for efficient development of needed medicines part of their strategic priorities e.g. in the FDA Critical Path Initiative in 2004 and the EMA Roadmap to 2010 and 2015 [7,19,20]. Regulations have been introduced or revised to stimulate drug development for diseases for which treatments are highly needed, e.g. the orphan drug regulation [21] and the regulation for conditional [22] and exceptional approval [23] pathways, regulations for special patient populations such as the paediatric regulation [24] and for special products such as the regulation for advanced therapy medicinal products [25]. Moreover, regulations aimed at

increasing the efficiency of drug development and marketing authorisation rates of drugs were adopted. These include opportunities for better communications with stakeholders (e.g. through scientific advice from regulatory bodies) [26], allowing the use of adaptive clinical trials design [27] or surrogate markers of the clinically relevant outcome [28] and more emphasis on post-marketing surveillance [29].

DETERMINANTS FOR MARKETING AUTHORISATION

The many changes introduced in the regulatory system demonstrate that regulators in Europe understand their responsibility to facilitate and encourage innovations for needed medicines, while taking adequate measures not to jeopardise public health. There is a range of regulatory tools to achieve this, but it is still not clear what the determinants of successful marketing authorisation are. Eichler et al emphasized that, in order to lower non-approval rates of new active substances, it would be crucial to understand whether non-approval was due to failed drugs or due to failed drug development plans [12]. So far, only few studies focused on the application dossiers for new medicinal products to regulatory authorities to provide this crucial knowledge [30-34]. In 2002, Pignatti et al for example, already demonstrated that lack of randomized clinical trials was a major cause of non-approval [34]. Whether this still plays a role in the current regulatory decision process is unkown.

In order to further improve the marketing authorisation system there is a need for empirical studies to gain insight in the way benefits and risks are evaluated and approval decisions are made by regulatory authorities. It seems useful to study potential determinants for marketing approval in three stages of the drug development and regulatory approval cycle: (i) the *drug development plan* that the company has followed, further categorized in (pre)clinical learning studies in the exploratory development phase and confirmatory clinical phase III studies (ii) *clinical efficacy and safety outcomes* of the confirmatory studies and (iii) *medical need* which are input for the benefit-risk assessment of the regulatory authority to decide on marketing authorisation (Figure 2).

A special category of new medicines are medicines for rare diseases, so-called orphan medicinal products (OMPs) [21]. For most of the rare diseases no effective treatment exists, which makes orphan drug development an important public health issue. According to EMA the same regulatory standards exist for marketing approval of orphan and non-orphan medicinal products [35]. Given the complexities in clinical drug development, the question arises whether the clinical evidence supporting the licensing of OMPs can meet the same standards of scientific proof as compared to non-OMPs and which factors determine their marketing authorisation. It should also be recognized that marketing authorisation applications of OMPs are preceded by an orphan designation applications submitted to a regulatory agency. Heemstra et al. demonstrated the relevance

of disease-specific scientific output for translation of rare disease research into orphan drug discovery and development [36]. Such information may help drug developers to more efficiently bring orphan designated products to the market, in particular for those rare diseases for which no therapy exists.

Figure 2. Development and marketing approval of new medicines

SCIENTIFIC ADVICE

EMA's scientific advice regulation has been renewed and strengthened in 2006 to increase the opportunity of companies to discuss development plans with regulators [26]. Scientific advice can identify critical issues in drug development plans of the companies, and may contribute to successful marketing authorisation [37]. During scientific advice, issues related to all phases of medicine development can be discussed (see figure 2), e.g. quality (manufacturing, chemical, pharmaceutical and biological testing), preclinical (toxicological and pharmacological tests) or clinical issues (early and confirmatory clinical studies pre- and post-approval), as well as opportunities for conditional or exceptional approval [26]. Figure 3 demonstrates that there has been a considerable increase in regulatory scientific advice over the last decade [38]. An increasing proportion of applications for marketing authorisation has been preceded by scientific advice: in 2011 this was the case for 76% of marketing authorisation applications [11]. Scientific advice is generally considered an essential instrument of the regulatory system and it is increasingly being advocated [7]. Still, little is known, however, about the effects of scientific advice and the companies' opinions towards current scientific advice procedures.

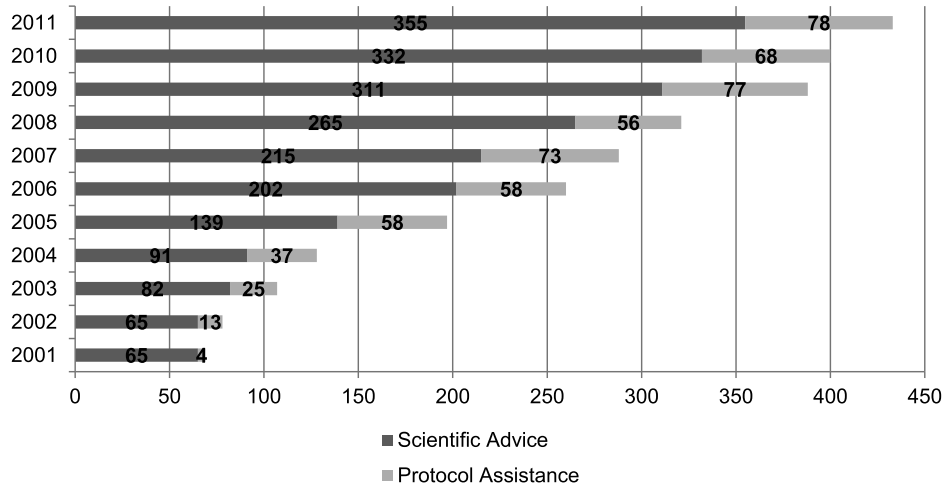

Figure 3. Numbers of scientific advice and protocol assistance provided by European Medicines Agency 2001-2011 [38]

REGULATORY SCIENCE AND THE AIM OF THIS THESIS

Recent years have seen an emergence of 'regulatory science'. Regulatory science aims to critically analyse the drug regulatory system and to fuel an evidence driven debate about how components of the regulatory system can be adjusted to improve the efficiency of the drug development chain. The Escher-project, part of TI Pharma, a public (academic) - private partnership, funds studies under the scope of 'Regulatory Science', aiming at improving the pharmaceutical R&D and the regulatory process by identifying and evaluating bottlenecks hampering marketing authorisation of medicinal products and by offering methodological solutions for efficient drug research.

This thesis, which is part of the Escher-project, offers empirical analyses of the drug regulatory system in the European Union to facilitate future evidence-based improvement and provides both a regulatory and industry perspective. First, we identify determinants of marketing approval of new medicines to show the crucial elements involved in drug licensing for new active substances. We focus on orphan drugs in particular, since drug development and benefit-risk assessment may even be more complex for rare diseases.

Secondly, we evaluate the role and content of current regulatory scientific advice, an important regulatory tool in drug development. Such analyses also allow to identify bottlenecks in drug development according to pharmaceutical companies. These bottlenecks and factors for success provide the evidence required for future improvement aimed at increased efficiency in licensing and patient access to medicines.

THESIS OUTLINE

In Chapter 2 we assess those factors that are associated with marketing authorisation of new medicines. In Chapter 2.1 we study all new active substances discussed by the Committee for Medicinal Products for Human Use (CHMP) in 2009 and 2010 and evaluate to what extent deficits in the drug development plan, disappointing clinical outcome (both efficacy and safety) or doubts about the clinical relevance of the data in the application dossier were associated with licensing failure. Previous studies raised the question whether differences exist in the issues raised by regulators in the assessment of regular (i.e. non-orphan) medicinal products versus orphan medicinal products. Regulators may more often raise developmental issues while assessing OMPs than for non-OMPs. Moreover these issues may less often result in non-approval since the need for newly available orphan drugs is high. In Chapter 2.2 we address these questions by comparing orphan and non-orphan marketing authorisation reviews.

Since OMPs are a challenging group of products from a developmental and public health perspective, factors for marketing approval of OMPs are further studied in Chapter 2.3. In this study also company and drug related characteristics are included, but emphasis lies on clinical drug development characteristics of confirmatory studies. Moreover, the role of medical need in regulatory approval decisions will be assessed. Chapter 2.4 focuses on the role of knowledge-related incentives for development of a special subgroup of OMPs, namely drugs to treat rare metabolic diseases.

In Chapter 3, we will evaluate regulatory scientific advice and report on the industry perspective towards challenges in drug development. In chapter 3.1 an overview of national scientific advice questions collected in all phases of drug development is provided and the differences between issues in drug development according to large and small companies are presented. In Chapter 3.2 we analyze European scientific advice about non-inferiority trials (a trial designed to assess whether a new drug is not worse than the currently available alternative drug) to determine where guidelines could be improved. In chapter 3.3 an interview study among regulatory strategy experts of small and medium-sized entreprises (SMEs) to learn about their views on scientific advice and the optimal dialogue with regulators is presented.

In chapter 4 the results of the several studies are put in context in a general discussion. Targets for improvement of the regulatory system for both regulators and pharmaceutical industry will be provided.

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2

DETERMINANTS FOR MARKETING AUTHORISATION OF NEW (ORPHAN) MEDICINAL PRODUCTS

2.1

FACTORS INFLUENCING NON-APPROVAL OF NEW DRUGS IN EUROPE

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ABSTRACT

2.1

The significant non-approval rate of marketing authorisation applications of innovative medicines in the current regulatory system is of serious concern for current and future drug development. In order to increase the approval rate it is necessary to understand the role of drug development and clinical outcomes in approval decisions of new active substances. Here we present a detailed analysis of all marketing applications for new active substances considered for approval at the European Medicines Agency (EMA) in 2009-2010 to assess to what extent the design of the development plan (specified in learning and confirming phase), the clinical outcome (efficacy and safety results) and clinical relevance according to the EMA Committee for Medicinal Products for Human use, were associated with licensing failure. We provide insights in concerns and major objections on main aspects of exploratory and confirmative drug development and the benefit-risk assessment and make some recommendations that should help improve the approval rate.

INTRODUCTION

The significant rate of non-approval of new medicines in the current regulatory system is of serious concern. In 2009 48 new active substances (NAS) received an outcome in the European marketing authorisation procedure; 29 (60%) were recommended for marketing authorisation and 19 (40%) received a negative opinion or were withdrawn shortly before an opinion was delivered [1]. This high non-approval rate threatens current and future innovative drug development and access to innovative medicines [1], in particular in the current situation of declining research and development (R&D) activity and pipelines containing less new products [2,3,4]. Increasing the approval rate, while safeguarding current regulatory standards, would be necessary from a public health and an entrepreneurial perspective [1].

In order to increase the approval rate it is important to assess and understand the role of critical steps in relation to non-approval of NAS. When marketing applications are submitted to EMA, a 210 day procedure starts leading to a recommendation by the EMA Committee for Medicinal Products of Human Use (CHMP) to the European Commission about marketing authorisation [5]. In order to decide on marketing authorisation of a new drug, CHMP defines and weighs benefits and risks by assessing i) the clinical outcome (efficacy and safety results) of the main studies and ii) the clinical relevance of the results. The design and conduct of the development plan iii) are taken into consideration to validate the clinical outcome. Each of these three elements of the benefit-risk assessment should be considered when explaining whether a NAS is approved or not for human use. In principle licensing failure beyond a companies' control only occurs in marketing authorisation applications with an appropriate development plan according to regulatory authorities, but with disappointing clinical efficacy and/or safety outcomes. In particular in studies with a first in class drug, new indication or new target, unexpected safety issues may occur. For such applications unfortunate findings or disagreements about benefits and risks between the EMA and the sponsor may lead to non-approval decisions. We argue that in the majority of cases deficits in the development plan play a role as well. Consequently, in this study we assessed to what extent the design of the development plan, the clinical outcome and clinical relevance are associated with licensing failure. Moreover, we paid particular regard as to what extent the different phases of the drug development plan (learning/exploratory and confirming) are associated with licensing failure.

METHODOLOGY

All marketing applications for NAS with an outcome in the centralised European marketing authorisation procedure between 1 January 2009 and 31 December 2010 were analyzed. NAS were defined as novel molecules that are either chemically synthesized or derived from a biological source that were not previously approved

for human use in the EU [6,7]. We excluded biosimilar applications as these were deemed not to be truly 'new' substances [6,7]. In case of applications for multiple indications for a new medicinal product, only one indication was randomly included.

The outcome used in this study was taken as the opinion of CHMP. Non-approved drugs were defined as NAS that received a negative opinion with regard to European marketing authorisation as well as NAS that were withdrawn from the marketing authorisation procedure before receiving an opinion from CHMP. Approved drugs were defined as NAS that received a positive opinion by CHMP in 2009 or 2010.

When analyzing the development plan of NAS, we differentiated between the learning (exploratory phase I and II studies) and confirming phases (phase III studies) of drug development. The assessment by CHMP of each of these two phases was captured in 5 key variables.

Drug development plan

The 5 determinants that classify a positive learning phase were: 1) understanding of the mode of action either preclinical or clinical, 2) clinical proof of concept: a pharmacodynamic response adequate to demonstrate a human pharmacological activity or clinical effect according to predefined criteria in the target population in exploratory studies, 3) an appropriate dose finding study to select the doses for testing in phase III studies and 4) a PK program that addressed absorption, metabolism, distribution and elimination of the studied drug, sufficient interaction studies and studies in special populations and 5) whether potential safety issues had been adequately addressed in preclinical and phase I and II clinical studies.

The following 5 characteristics of the confirmatory pivotal trial design were considered: 1) adequacy of the design of the pivotal clinical studies (study arms, randomization, blinding and type of comparator), 2) the selection of clinically relevant endpoints, 3) identification of the representative target population (inclusion and exclusion criteria representative for the indication), 4) adequate statistical analysis plan and 5) sufficient trial duration.

Clinical outcome and clinical relevance

Clinical outcome of the drug was described by two key variables 1) a statistically significant effect on the primary endpoint of the pivotal studies and 2) the safety profile, as identified in the confirmatory pivotal trials. Clinical relevance was described by specific remarks by CHMP about three key variables: 1) a large effect size, 2) a high medical need for the indication with no alternative therapies available and/or 3) clinical relevance of the results in general.

Data collection and analysis

Subsequent to independent assessments of the dossier by two member countries (called rapporteur and co-rapporteur), CHMP deliberates about the submitted

dossier on days 120 and 180 of the marketing authorisation procedure and compiles a list of issues and major objections about the development plan, clinical outcomes and/or the clinical relevance if deemed necessary. Major objections are those issues that are considered by CHMP to be incompatible with a favourable outcome of the marketing authorisation procedure, unless resolved. In a final and decisive benefit-risk assessment at day 210 a recommendation about marketing authorisation is given [5].

For each of the 10 key variables of both the learning and the confirmatory drug development plans we examined whether any major objection had been raised by CHMP on day 120 of the marketing authorisation procedure or whether concerns were expressed by CHMP during the 210 days of the marketing authorisation procedure. Major objections on day 120 were studied, because these are considered to provide a complete overview of development problems encountered and were available for both non-approved and approved drugs. Although some new items for discussion may arise later in the authorisation procedure or concerns may become major objections in a later stage, we assume these to be a minority. Concerns were considered smaller issues than major objections, but still present in the final EPARs and WEPARs. Data about the key variables of clinical outcome and clinical relevance as expressed in the benefit-risk assessment at day 210 were collected from European public assessment reports and withdrawal assessment reports.

Relative risks and 95% confidence intervals (CI) were calculated for the risk of a negative outcome in the approval process associated with exposure to the various determinants, see Table 1 and 2. Summary scores were given to the three categories — development plan, clinical outcome and clinical relevance- according to the following definitions: An inappropriate development plan (-) was defined as having at least 1 major objection on any of the determinants of the learning or confirmatory phase on day 120 of the marketing authorisation procedure. Clinical outcome was not positive (-) if no convincing statistical significant effect on primary endpoints was reached and/or when serious safety concerns were raised. Clinical relevance of the results was defined as lacking (-) when none of the 3 clinical relevance variables were positive. In a summary scorecard the combinations of these three scores were demonstrated (Table 3). Univariate and multivariate logistic regression analyses were conducted that addressed the associations between the scores in the three assessment categories and the way the CHMP expressed its views on the dossier (Table 4).

Concerns and major objections were collected by author MP who considered all NAS assessments in the review period. Scoring concerns is complex because of the lengthy assessment reports and opportunities for differences in interpretation. In contrast, the major objections at day 120 could be retrieved from well-structured documents and leave hardly any room for subjectivity. In order to verify

the method of data collection employed in review of the assessments, in addition to the primary reviewer (MP), a second reviewer collected concerns and major objections of a subset of nine of these according to the protocol with variable definitions in a blinded way. Comparison resulted in a kappa of 0.69, which indicates that no major differences between the two researchers existed in terms of data scoring [8]. In addition, all aggregated analyses (Tables 3, 4, 5 and 6) were based on major objections only.

EMA data were collected and analyzed in a confidential way in accord with a Memorandum of Understanding between the Dutch Medicines Evaluation Board and the EMA.

RESULTS

In 2009 and 2010 in total 68 marketing applications had an outcome in the marketing authorisation procedure. Of these, 45 (66%) were approved, whereas 23 (34%) where not, of which 6 received a negative opinion and 17 were withdrawn before receiving an opinion. Two NAS were withdrawn before day 120 of the procedure. For these drugs day 80 major objections were taken as an assumption for day 120, since both assessment reports of the rapporteur and co-rapporteur were very similar. Seven applications for NAS had multiple indications, of which one was randomly included. In Table 1 general drug related characteristics are provided of these 68 NAS. No significant differences were found in non-approval rates between new chemical entities (NCEs, 36%) or biologicals (31%). Moreover no differences were found between orphan drugs (29%) and non-orphan drugs (35%). Table 1 also demonstrates that non-approval rates were highest for products to be used in oncology (62%), haematology (50%) and central nervous system (50%) indications.

The summary scores in the three categories development plan, clinical outcome and clinical relevance — are shown in Table 3, stratified for approved and non-approved applications. All eight drugs with a positive rating for the development plan, a positive clinical outcome and convincing clinical relevance were approved, whereas 12 out of 14 applications for which all three scores were negative were not approved.

Univariate and multivariate logistic regression analyses demonstrated that a disappointing assessment of the clinical outcome was a major driver for non-approval (odds ratio: 21.7; 95% confidence interval: 5.0–94.0) (Table 4). Negative scores on clinical relevance contributed less to the likelihood of non-approval (odds ratio: 4.6; 95% confidence interval: 1.1–20.0) than negative scores on clinical outcome. Moreover, the data in Table 4 indicate how important the underlying development plan is for increasing the likelihood that a medicinal product is approved (odds ratio: 6.1; 95% confidence interval: 0.9–42.7).

Table 1. General characteristics of non-approved and approved new active substances in 2009 and 2010 and their univariate relative risks of non-approval

	Total N=68	Non-approved N=23	Approved N=45	Univariate RR (95% CI)
Year of outcome				
2009	48	19 (40%)	29 (60%)	NA
2010	20	4 (20%)	16 (80%)	NA
Type of drug				
NCE	36	13 (36%)	23 (64%)	Ref.
Biological	32	10 (31%)	22 (69%)	0.9 (0.4-3.0)
Orphan Drug (OD) status				
Non OD	51	18 (35%)	33 (65%)	Ref.
OD	17	5 (29%)	12 (71%)	0.8 (0.3-2.2)
Indication				
Cardiovascular & respiratory	12	1 (8%)	11 (92%)	0.3 (0.4-3.2)
Oncology	13	8 (62%)	5 (38%)	2.5 (0.7-9.3)
Haematology	4	2 (50%)	2 (50%)	2.0 (0.3-11.7)
Infections	15	6 (40%)	9 (60%)	1.6 (0.4-6.4)
CNS	6	3 (50%)	3 (50%)	2.0 (0.4-9.9)
Bone & Muscle system	6	0 (0%)	6 (100%)	NA
Other	12	3 (25%)	9 (75%)	Ref.
Previous approval elsewhere				
Yes	29	7 (24%)	22 (76%)	Ref.
No	39	16 (41%)	23 (59%)	1.7 (0.7-4.1)
Company size				
Non-SME	56	17 (30%)	39 (70%)	Ref.
SME	12	6 (50%)	6 (50%)	1.6 (0.6-4.2)
Scientific advice received				
Yes	45	14 (31%)	31 (69%)	Ref.
No	23	9 (39%)	14 (61%)	1.3 (0.5-2.9)

NA: Not applicable

Table 2. Key variables of Development plan, Clinical outcome and Clinical relevance and univariate relative risks of non-approval

	Total N=68	Non-approved N=23	Approved N=45	Univariate RR (95% CI)
Development plan *Learning phase*				
1. Mode of action well explained?				
Satisfactory	52	15 (29%)	37 (71%)	Ref.
Concerns	12	4 (33%)	8 (67%)	1.2 (0.4-3.5)
Major objections	4	4 (100%)	0 (0%)	3.5 (1.2-10.4)
2. Clinical proof of concept given?				
Satisfactory	42	8 (19%)	34 (81%)	Ref.
Concerns	18	10 (56%)	8 (44%)	2.9 (1.2- 7.4)
Major objections	8	5 (63%)	3 (37%)	3.3 (1.1-10.0)
3. Dose finding for confirmatory studies?				
Satisfactory	39	6 (15%)	33 (85%)	Ref.
Concerns	16	7 (44%)	9 (56%)	2.8 (1.0-8.5)
Major objections	13	10 (77%)	3 (23%)	5.0 (1.8-13.8)
4. Clinical PK program conducted?				
Satisfactory	38	10 (26%)	28 (74%)	Ref.
Concerns	19	5 (26%)	14 (74%)	1.0 (0.3-2.9)
Major objections	11	8 (73%)	3 (27%)	2.8 (1.1-7.0)
5. Safety pharmacology studies?				
Satisfactory	40	12 (30%)	28 (70%)	Ref.
Concerns	15	6 (40%)	9 (60%)	1.3 (0.5-3.6)
Major objections	13	5 (38%)	8 (62%)	1.3 (0.5-3.6)
Confirmatory phase				
1. Appropriate study design applied?				
Satisfactory	45	13 (29%)	32 (71%)	Ref.
Concerns	4	1 (25%)	3 (75%)	0.9 (0.1-6.6)
Major objections	19	9 (47 %)	10 (53%)	1.6 (0.7-3.8)
2. Clinically relevant primary endpoint used?				
Satisfactory	55	17 (31%)	38 (69%)	Ref.
Concerns	2	0 (0%)	2 (100%)	NA
Major objections	11	6 (55%)	5 (45%)	1.8 (0.7-4.5)
3. Representative target population studied?				
Satisfactory	41	9 (22%)	32 (78%)	Ref.
Concerns	11	5 (45%)	6 (55%)	2.1 (0.7-6.2)
Major objections	16	9 (56%)	7 (44%)	2.6 (1.0-6.5)

Table 2. continued

	Total N=68	Non-approved N=23	Approved N=45	Univariate RR (95% CI)
4. Trial duration according to guidelines?				
Satisfactory	49	17 (35%)	32 (65%)	Ref.
Concerns	9	2 (22%)	7 (78%)	0.6 (0.2-2.8)
Major objections	10	4 (40%)	6 (60%)	1.2 (0.4-3.4)
5. Appropriate statistical analysis?				
Satisfactory	41	9 (22%)	32 (78%)	Ref.
Concerns	5	2 (40%)	3 (60%)	1.8 (0.4-8.4)
Major objections	22	12 (55%)	10 (45%)	2.5 (1.1-5.9)
Clinical outcome				
1. Statistical significance of effect on primary endpoint				
Clearly confirmed	47	8 (17%)	39 (83%)	Ref.
Uncertainties still remain	11	5 (45%)	6 (55%)	2.7 (0.9- 8.2)
Not confirmed	10	10 (100%)	0 (0%)	5.9 (2.3-14.9)
2. Safety profile				
Satisfactory	32	6 (19%)	26 (81%)	Ref.
Doubts, uncertain issues	22	5 (23%)	17 (77%)	1.2 (0.4-4.0)
Serious concerns	14	12 (86%)	2 (14%)	4.6 (1.7-12.2)
Clinical relevance				
1. Effect size				
Large	19	1 (5%)	18 (95%)	Ref.
As expected	28	4 (14%)	24 (86%)	2.7 (0.3-24.3)
Modest/Small	21	18 (86%)	3 (14%)	16.3 (2.2-122.0)
2. Medical need				
Important	22	7 (32%)	15 (68%)	Ref.
Moderate	45	15 (33%)	30 (67%)	1.1 (0.4-2.6)
Minor	1	1 (100%)	0 (0%)	3.1 (0.4-25.5)
3. Clinical benefit convincingly shown?				
Compelling	28	1 (4%)	27 (96%)	Ref.
As expected	27	10 (37%)	17 (63%)	10.4 (1.3-81.0)
Doubtful	13	12 (92%)	1 (8%)	25.8 (3.4-198.7)

Table 3. Summary scorecard of EMA assessment of 68 Marketing Authorisation Applications*

Development plan	Clinical outcome	Clinical relevance	Frequency N=68	Non-approved N=23	Approved N=45
+	+	+	8	0	8
+	+	–	6	0	6
+	–	+	2	0	2
+	–	–	2	2	0
–	+	+	20	2	18
–	+	–	8	2	6
–	–	+	8	5	3
–	–	–	14	12	2

* Definitions of positive (+) and negative (–) scores are given in the Methodology section

Table 4. Univariate and multivariate analysis of EMA assessments of 68 Marketing Authorisation Applications*

	Total N=68	Non-approved N=23	Approved N=45	Univariate OR (95%CI)	Multivariate OR (95%CI)
Development plan					
Appropriate	18	2 (11%)	16 (89%)	Ref.	Ref.
Not *"Appropriate"*	50	21 (42%)	29 (58%)	5.8 (1.2-27.9)	6.1 (0.9-42.7)
Clinical outcome					
Positive	42	4 (9%)	38 (91%)	Ref.	Ref.
Not *"Positive"*	26	19 (73%)	7 (7%)	25.8 (6.7-99.1)	21.7 (5.0-94.0)
Summary Clinical relevance					
Clinical relevance	38	7 (18%)	31 (82%)	Ref.	Ref.
No *"Clinical relevance"*	30	16 (53%)	14 (47%)	5.1 (1.7-15.1)	4.6 (1.1-20.0)

* Definitions of positive (+) and negative (–) scores are given in the Methodology section

Clinical outcome: Efficacy and safety results

When considering the unadjusted associations, unconfirmed statistical significance on primary endpoints and serious safety issues, were both associated with non-approval, see Table 2.

Table 5 shows the different scenarios for clinical outcome of the NAS. At least 42 of these demonstrated a positive clinical outcome. Having either unconvincing results on the primary endpoint or serious safety concerns is strongly associated with non-approval. Four NAS failed despite a positive clinical outcome on efficacy and safety. One drug was withdrawn by the company due to worldwide safety

issues, not yet identified in this marketing application procedure, whereas another drug showed some positive results but not in the intended general indication. The results of the remaining two drugs were difficult to interpret due to GCP and/or bioequivalence issues (combination product).

Despite the strong association between disappointing clinical outcome and non-approval, some exceptions exist. An example that got approved despite safety concerns is Ruconest (conestat alfa), a novel drug for the treatment of hereditary angioedema. It is a recombinant analogue of human C1INH that is purified from the milk of rabbits. Ruconest could cause serious adverse events in patients allergic to rabbits, which was dealt with by a warning in the summary of product characteristics [9]. Otherwise six NAS got approved to the market with unconvincing statistical results on the primary endpoints. In some cases uncertainties about the results in the target population existed, but sufficient evidence was presented to approve the drug for a subpopulation e.g. Iressa (gefitinib) for the treatment of adults with locally advanced or metastatic Non Small Cell Lung Cancer. The results for overall survival were not convincing for the whole population, but the drug was finally approved with a restricted indication for patients with tumours harbouring activating EGFR mutations, after the company committed to do a prospective study in this subgroup [10]. Similarly uncertainties about the beneficial effects of Fluenz (influenza vaccine (live attenuated, nasal) in adults were present, but the drug got approved for the prophylaxis of influenza in individuals 24 months to less than 18 years of age [11]. Mozobil (plerixafor) showed clinical efficacy in patients that undergo mobilisation for autologous HSC transplantation and who have shown to be poor mobilisers after initial mobilisation with G-CSF alone. For this subgroup Mozobil was considered approvable as second line treatment [12]. Additionally, some NAS were approved because of high medical need e.g. Daxas (roflumilast) for the treatment of COPD patients [13] and Esbriet (pirfenidone) for the treatment of Idiopathic Pulmonary Fibrosis (IPF) [14]. Although data may have left some uncertainties with regard to efficacy due to lack of statistical significance on primary efficacy endpoints, overall data was deemed sufficient for licensing.

Development Plan: Learning and Confirming

Similarly, four scenarios were distinguished depending on the quality of the learning and confirming phases of drug development; and their association with non-approval were assessed, see Table 6. First, in cases where the clinical learning phase was positive and the confirmatory studies were adequately designed, a positive benefit-risk assessment would be expected (Scenario A in Table 6; reference group). Only 18 of 68 drugs fell within this category. Almost all NAS (n=16) fulfilling this scenario received marketing approval. The two exceptions were drugs that failed due to a disappointing clinical outcome only. Second, when the clinical learning phase was positive, but was followed by an inappropriate design of the confirmatory pivotal

Table 5. Combinations of (in)significant efficacy results and serious safety risks and their relative risks of non-approval*

Clinical Outcome		Total N=68	Non-approved N=23	Approved N=45	Relative Risk (95%CI)
A. Statistically significant effect on primary endpoints Safety profile	+ +	42	4 (9%)	38 (91%)	Ref.
B. Statistically significant effect on primary endpoints Safety profile	+ –	5	4 (80%)	1 (20%)	8.4 (2.1-33.6)
C. Statistically significant effect on primary endpoints Safety profile	– +	12	7 (58%)	5 (42%)	6.1 (1.8-20.9)
D. Statistically significant effect on primary endpoints Safety profile	– –	9	8 (89%)	1 (11%)	9.3 (2.8- 31.0)

* Definitions of positive (+) and negative (–) scores are given in the Methodology section

Table 6. Summary table of EMA assessment of the development plan and relative risks of non-approval*

Development Plan		Total N=68	Non-approved N=23	Approved N=45	Relative Risk (95%CI)
A. Learning phase Confirmatory phase	+ +	18	2 (11%)	16 (89%)	Ref.
B. Learning phase Confirmatory phase	+ –	20	5 (25%)	15 (75%)	2.3 (0.4-11.6)
C. Learning phase Confirmatory phase	– +	8	3 (37%)	5 (63%)	3.4 (0.6-20.2)
D. Learning phase Confirmatory phase	– –	22	13 (59%)	9 (41%)	5.3 (1.2-23.6)

* Definitions of positive (+) and negative (–) scores are given in the Methodology section

studies, a drug was more likely to receive a negative opinion by CHMP (Scenario B in Table 6; RR 2.3 (95%CI 0.4-11.6) for non-approval as compared to scenario A). Third are cases where the clinical learning phase was negative, and early efficacy or safety evidence was lacking. As expected non-approval rates were higher in this situation (Scenario C in Table 6; RR 3.4 (95%CI 0.6-20.2) versus scenario A). Finally, in cases where the learning phase was negative and the design of the confirmatory clinical trial(s) was inappropriate, the lack of appropriate evidence for a beneficial therapeutic effect in early and confirmatory studies was associated with a negative opinion in the marketing authorisation procedure (Scenario D in Table 6; RR 5.3 (95% CI 1.2-23.6) versus scenario A).

Viewing these results collectively demonstrate that having major objections in both phases of drug development is strongly associated with non-approval. Moreover they show that a significant proportion of non-approved marketing authorisation applications of NAS had an inappropriate drug development plan. Our analysis showed that 13 of the 23 non-approved NAS (57%) had major objections on day 120 for characteristics of both the learning and the confirmatory phases, whereas 22% (N=5) had at least 1 major objection in the confirmatory phase and 13% (N=3) had at least 1 major objection for any of the aspects of the learning phase.

Interestingly, Table 6 shows that of the 22 NAS with major objections in both the learning and the confirmatory phases; 9 were still approved to the market. For these drugs the deficits found at day 120 had been resolved in the subsequent 90 days of the procedure either by providing necessary data or by justification of the submitted data.

Table 2 lists the frequency of underlying concerns and major objections according to regulators of all variables that describe the development plan, consisting of the learning and confirmatory phase. Major deficits with regard to learning phase variables (mode of action, proof of concept, dose finding and pharmacokinetics) existed for both approved and non-approved NAS, but (still) were significantly associated with licensing failure. Related to the confirmatory phase, most major objections concerned study design, which included issues about the number and type of study arms, the type of comparator, blinding, and randomization, see Table 2. Examination of this table shows that only major objections about the selection of a representative target population (OR 2.6 95% CI 1.0-6.5) and about statistical analyses conducted (OR 2.5 95% CI 1.1-5.9) were significantly associated with non-approval.

DISCUSSION

The high non-approval rate of NAS is part of the current trend of declining R&D productivity. Although this trend may be the result of a combination of various scientific, technological and managerial factors [15], we focused here on relevant

deficits in drug development, clinical outcomes and their relevance to regulatory decision making. The 68 products intended for varying indications in our analysis were all unique, having a past of years of drug development and *unique* assessment procedures. The examples described show how complex regulatory decision making can be and that exceptions are needed in some cases. Despite these differences between drugs, their approval decision is based on similar requirements of efficacy, safety and quality. Indeed our analysis of 68 NAS at EMA in the study period identified disappointing efficacy and safety concerns as major factors influencing non-approval. Moreover deficits in drug development were identified as major contributing factors to regulatory decision making which could be improved in future drug development.

Benefit-Risk assessment

The assessment of efficacy and safety results and their implications in practice currently is accomplished by grounded views of CHMP members with expertise in the field [5]. Since efficacy and safety are explicit elements of the benefit-risk assessment, which directly lead to marketing authorisation opinions, a strong association with clinical outcome meets our expectations. Decisions about marketing authorisation are attended with varying uncertainty about efficacy and safety results from pivotal clinical trials [16]. Uncertainty can be of statistical nature due to the size of the study population or missing data or it can origin from contradictive study results in case of multiple studies. Higher uncertainty around efficacy and safety outcomes is associated with non-approval. The role of clinical relevance in the benefit-risk assessment could best be described as complementary when positive. Positive scores on clinical relevance can help overcome doubts with regard to clinical outcome, particularly when good alternative treatment options are lacking for the disease, such as in the case of pirfenidone (Esbriet) for the treatment of idiopathic pulmonary fibrosis [14]. In addition an inappropriate development plan decreases the internal and external validity of data. Obviously, a benefit-risk assessment is a complex procedure in which many uncertainties have to be dealt with appropriately, in order to explain the outcome to the interest groups involved. Formal scientific methods for decision-making have gained attention in the last few years. Different approaches are being studied to standardize benefit-risk assessment and therefore enhance transparency and consistency of the decision process [17,18].

Drug development - Role of learning and confirming

Our results represent those NAS developed in a way that was deemed sufficient to submit the product in the centralised procedure of EMA. Our data show that according to European regulators 74% (50 of 68) of development plans submitted to EMA have deficits, leading to one or more major objections and a lower likelihood of a positive approval result. Apparently discrepancies exist between what applicants think is acceptable and relevant and what is deemed appropriate

by regulators. Although applicants may consider pivotal trials and their outcomes most relevant in marketing authorisation applications, this study shows that the learning phase should not be underestimated in regulatory decision making.

Learning in early drug development

In theory, sponsors base their decision about proceeding or not into phase III drug development, on proof of concept results delivered from phase II studies. In an in depth analysis on data from phase II decisions from a large number of development programs, three fundamental PK/PD principles were associated with the likelihood of candidate survival with improved chance of succession to phase III development: understanding the drug target exposure, target binding and functional pharmacological activity at the target site of action [19]. It was previously emphasized that reducing phase II and III attrition rates is one of the major ways of enhancing R&D productivity. Redirecting resources to invest in proof of concept studies and better target validation could increase the success rate of phase II studies and R&D productivity in general [2,15,20]. Another relevant reason to learn is that confirmation sometimes fails: the more that is known about the pharmacodynamics and pharmacokinetics of a drug, the greater the understanding as to what to measure on the causal path from drug intake to effect, which is expected to lead to more efficient and predictable drug development [21].

The relevance of appropriate dose finding has been emphasized for quite some years. Adequate pre-market determination of dosage could ensure continued safe and effective product use post-marketing. Intensified efforts to achieve an adequate understanding of dose–response relationships prior to final testing and regulatory approval of the dosage and target population have been recommended [20,22,23].

Our data further underline the relevance of e.g. mode of action, proof of concept studies, and dose finding studies to decreasing attrition rates, increasing marketing authorisation and with that improve R&D productivity. In 4 out of 5 non-approved NAS with major objections on proof of concept, additionally no statistical significant effect on the primary efficacy endpoints in phase III was found. Still, the number of NAS with unconvincing proof of concept among the submitted NAS was high (30 of 68 NAS). In the current need for replenishing pipelines, decisions about progressing into phase III may be made on marginal statistically significant efficacy in phase II, with a higher chance of disappointing results in phase III [20,24-26].

In addition, currently, differences between therapeutic groups exist in the conduct of learning studies aimed at mode of action, proof of concept and dose finding for Phase III. For some of those indications of which the underlying biological mechanism is well-known, biomarkers can be identified and proof of concept demonstrated in the target population, e.g. for diabetes products, osteoporosis and increasingly for oncology products [27]. An example of a drug with positive scores on all aspects of exploratory studies is Prolia (denosumab), a fully human

IgG2 mAb targeting the ligand for receptor activator for nuclear factor kappa-B (RANKL), approved to the market for the treatment of osteoporosis. The mode of action of Prolia was well elucidated by studies showing the high binding affinity of the mAb to the ligand, preventing its binding to the RANK receptor. Moreover, thanks to the availability of a clear biomarker, proof of concept could be shown on bone mineral density [28]. In contrast, for some indications like psychiatric disorders current knowledge is limited to the mode of action and the type of receptor binding. Limited opportunities therefore exist to demonstrate proof of concept, however new biomarkers are now being studied for some areas such as schizophrenia [29].

Future fundamental research is needed to facilitate exploratory research for both currently known and highly innovative therapies. Examples of applied sciences that have contributed to efficient innovative drug development are PK/PD modeling and clinical trial simulation. In particular studying dose response relations in various clinical situations has been facilitated by PK/PD modeling. In general modeling and trial simulation can be used to drive decision making in drug development [30].

Confirmatory drug development

The confirmatory phase is designed to provide evidence for convincing efficacy of the drug and acceptable risks in a large and representative target patient population. A well designed confirmatory phase yields accurate and valid (efficacy and safety) data for the benefit-risk assessment. When considering the confirmatory phase III studies it becomes clear that as many as 42 (62%) of 68 NAS had deficits in either study design, choice of primary endpoint, selection of the target population, statistical analysis or trial duration or a combination of these. Moreover, still 24 of these 42 drugs received marketing authorisation. Although increased relative risks for the confirmatory phase variables with non-approval were shown, confidence intervals were wide. Only target population and statistical analysis demonstrated a statistically significant association with licensing failure. CHMP may find some deficits in the development plan acceptable in the light of a positive clinical outcome and recognition of the clinical relevance. However, these associations need some more explanation. In particular *study design* is an essential element of the drug development plan that was previously found to be associated with marketing authorisation [31,32]. In our study for all drugs that were approved despite major objections about the *study design* at day 120, objections were solved by the submission of either an active compared trial or the results of an ongoing trial in the final phase of the marketing authorisation procedure, the commitment of the company to perform such a study in the near future, the justification of the chosen design and/or comparator or the adoption of the indication. Moreover, studies provided in the dossier offered promising and clinically relevant efficacy and safety results. For non-approved NAS these solutions were absent and results provided were doubtful or negative.

In previous studies of marketing authorisation of orphan drugs at FDA and EMA, clinical trial characteristics, such as target population [33] use of an active comparator and an appropriate primary endpoint [34] were measured at day 210 of the marketing authorisation procedure and found to be associated with failure or success of marketing authorisation. These studies support an association between an inappropriate confirmatory development program and non-approval in the marketing authorisation procedure.

The EMA and national drug regulatory authorities provide scientific advice, an opportunity to discuss difficulties in drug development. Companies who may lack experience on how to develop a NAS according to existing guidelines, face ethical or practical issues that prevent the company from complying with guidelines, or have different interpretation of these guidelines can ask for scientific advice. Such a dialogue between the pharmaceutical companies and regulators could solve issues in (early and confirmative) drug development. In our study, no association was found between receiving scientific advice and non-approval. In a previous study Regnstrom also showed that only compliance to scientific advice was associated with marketing authorisation rather than receiving scientific advice itself [35]. Pharmaceutical companies should be encouraged to use their early clinical studies as a positive clinical learning phase and to discuss the confirmatory drug development plan with regulators beforehand.

Limitations

Remarkably, no differences were shown in non-approval rate between new chemical entities and biologicals, in contrast to that previously shown by Regnstrom [35]. Our dataset was smaller, which may explain part of these differences. This relatively small size of the dataset may be a point of consideration in our study, although we have included all NAS submitted to the EMA in 2009 and 2010. We would argue that similar patterns of results would arise in a larger dataset because there were no major changes in the regulatory process or requirements.

Another complicated issue is the evidence for clinical relevance, which was based on statements by the CHMP with regard to 'clinical relevance', 'medical need and the availability of alternative therapies' and 'effect size' in the assessment report. Although the absence of such a statement cannot be deemed as absence of evidence of clinical relevance, any compelling or outstanding results can be expected to be included in the report.

CONCLUDING REMARKS

We dichotomized the assessment of recent European registration dossiers into positive or negative scores, thereby reducing the huge amount of data and the subtle regulatory weighting of all the information possibly relevant for patients into simple

binary terms. This is also what happens when regulators determine the benefit–risk profile of a dossier for a new medicinal product: the system requires a 'yes' or a 'no'. Overall, negative clinical outcome results seem to contribute most significantly to current non-approval rates. Our study also indicates that relevant learning-phase studies are valuable in reducing the number of failed dossiers and speeding up pharmaceutical innovation. Drug developers are encouraged to increase investments in such studies before moving to large and more costly Phase III trials.

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2.2

EU MARKETING AUTHORISATION REVIEWS OF ORPHAN AND NON-ORPHAN DRUGS DO NOT DIFFER

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ABSTRACT

Marketing authorisation application dossiers of 17 orphan drugs (ODs) and 51 non-ODs evaluated by the European Medicines Agency (EMA) in the period 2009-2010 were compared. We identified whether any differences existed between ODs and non-ODs in number and type of deficits brought forward during the EMA review, regarding the clinical development plan, clinical outcome and medical need and studied whether these deficits were similarly associated with marketing approval in the EU. In 71% of the ODs dossiers and 65% of the non-ODs dossiers marketing approval was granted. Differences in deficits were found, but similarities in the way ODs and non-ODs were reviewed and marketing approval decisions were taken, underline that regulatory standards are equally high.

INTRODUCTION

Over the last decades major progress has been made on bringing therapies for rare diseases to the clinic [1-3]. Despite all the challenges that go along with orphan drug (OD) development, many pharmaceutical companies have gained interest in strategies for developing rare disease treatments. This increasing interest has several antecedents, including a surge in new scientific knowledge about the molecular mechanisms and etiology of rare diseases, awareness of public health gain by treating rare diseases timely and effectively, and previously unnoticed market opportunities by the industry [4,5]. For many reasons, however, the development of ODs remains complex, also due to limited availability of patients for clinical testing and the scarce translational knowledge about diagnosing and evaluating treatment efficacy in rare diseases in general [2,6].

Given all these complexities, the question arises whether the evidence supporting the licensing of ODs can meet the same standards of scientific proof as compared to non-ODs. In general drug regulators are expected to secure similar scientific and regulatory standards when reviewing and assessing the benefits and risks of OD applications compared to non-ODs [7]. Though several authors have expressed concerns about whether reality meets such expectations. Kesselheim et al have compared the design of Phase III studies of approved ODs and non-ODs for oncology diseases by the US Food and Drug Administration (FDA). Their study showed that ODs were authorized to the market with a less rigorous study design, less hard endpoints and more serious safety concerns than non-ODs [8]. Also Joppi et al stated recently that study design and outcomes of EU marketing authorisations of ODs have often been inadequate [5]. In a previous study of our team on ODs approved to the market since the launch of the Orphan Regulation in the EU in 2000, we found that in three out of four licensed ODs, approval was based on robust randomized clinical trials and endpoints that were considered clinically relevant [9]. Thus, there is not a clear picture whether ODs are reviewed and assessed according to lower standards as one would expect compared to non-ODs.

In order to address this question further, we looked in this study at all new active substances with an orphan designation evaluated by the European Medicines Agency (EMA) in 2009-2010 and compared these with all non-ODs evaluated in the same period regarding the number and nature of deficits (i.e. objections against approval, concerns or serious doubts) identified by the EMA during the review process in three areas: (1) clinical development plan, (2) clinical outcome and (3) medical need. In addition we compared the regulatory decision making process of ODs and non-ODs by analyzing whether deficits in the three areas were similarly associated with marketing approval.

Box 1. Methodology

All marketing applications and their EMA assessment reports related to new active substances (NAS) with an outcome in the EU Centralized Procedure between 1 January 2009 and 31 December 2010 were included in this study (N=68). NAS were defined as novel molecules that are either chemically synthesized or derived from a biological source that were not previously approved for human use in the EU. ODs were those new active substances that had obtained an orphan designation by the EMA. In case of applications for multiple indications for a new medicinal product, only one indication was randomly included in the analysis. The outcome used in this study was taken as the opinion of the EMA Committee for Medicinal products of Human Use (CHMP). Approved applications were defined as NAS that received a positive opinion by CHMP. EMA data were collected and analyzed in a confidential way in accord with a Memorandum of Understanding between the Dutch Medicines Evaluation Board and the EMA. Lead author MP analyzed and scored all the assessment reports.

The assessment of the *clinical development plan* was based on five clinical drug development-related characteristics including 1] adequate design of the pivotal clinical studies (randomization, blinding, control group) 2] the selection of appropriate clinical endpoints, 3] a representative target population (inclusion and exclusion criteria representative for the indication), 4] trial duration and 5] adequate statistical analysis plan. We examined whether any major objection has been raised by CHMP on day 120 of the marketing authorisation procedure or whether concerns remained at the end of the procedure as expressed by CHMP in European Public Assessment Reports (EPARs) and withdrawal assessment reports (WEPARs). Major objections on day 120 were studied, because these provide a complete overview of development problems encountered and were available for both non-approved and approved drugs. The assessment of the *clinical outcome* was scored on statistical significant results and meeting predefined criteria on the primary efficacy endpoints and the safety profile (2 key variables). *Medical need* included explicit remarks by the CHMP about the medical need of the product and the lack of alternative therapies. The *Development Plan* as a whole was classified as negative when more than one concern or major objection on day 120 of the procedure was expressed on any of the five variables; otherwise positive. *Clinical Outcome* was scored negative if no convincing statistical significant effect on primary endpoints was reached and/or when serious safety concerns were raised during the 210 days of the procedure; otherwise positive. *Medical need* was classified as negative when an alternative therapy for the disease was available.

Stratified analyses were performed for ODs and non-ODs to assess any association between deficits in the dossiers and the likelihood of marketing approval in the groups, ODs and non-ODs. In order to assess whether OD's associations with marketing approval showed similarity with those of non-ODs, interaction was measured on an additive scale and expressed by the Relative excess risk due to interaction (RERI) [10].

MAIN RESULTS

All marketing authorisation applications for new active substances evaluated by the EMA between 1 January 2009 and 31 December 2010 were included in the study (see Box 1 for Methodology). In the study period, 17 ODs and 51 non-ODs were reviewed by the EMA. The diseases (according to the approved indications) of the ODs and non-ODs are given in Annex 1. Of these 17 ODs 12 (71%) were approved, compared with 33 (65%) of the 51 non-ODs, showing similar proportions with a positive result.

Figure 1 depicts the number of deficits regarding the selected 5 main variables of the clinical development plan, as identified during the EMA review for both ODs and non-ODs dossiers, demonstrating strong similarity between the two drug classes. Table 1 shows the total numbers of deficits identified during the EMA review regarding selected parts of the applicant's dossier on clinical development plan, clinical outcome and medical need. In the next sections we will discuss for ODs and non-ODs the identified deficits during the EMA review in more detail, focusing on some of the observed differences between the two drug classes.

In order to demonstrate the frequency- of identified deficits on any of the aspects of the clinical development plan, clinical outcome or medical need for ODs and non-ODs and their association with marketing approval, an aggregated univariate and multivariate analysis was conducted (Table 2). Table 2 shows clearly that clinical outcome deficits were strongly associated with a negative result of the authorisation procedure. A significant association was also found for any deficits in the clinical development plan, but less convincing. Whether the new product would fill a medical need could not be identified as a strong driver of the EMA's approval decision.

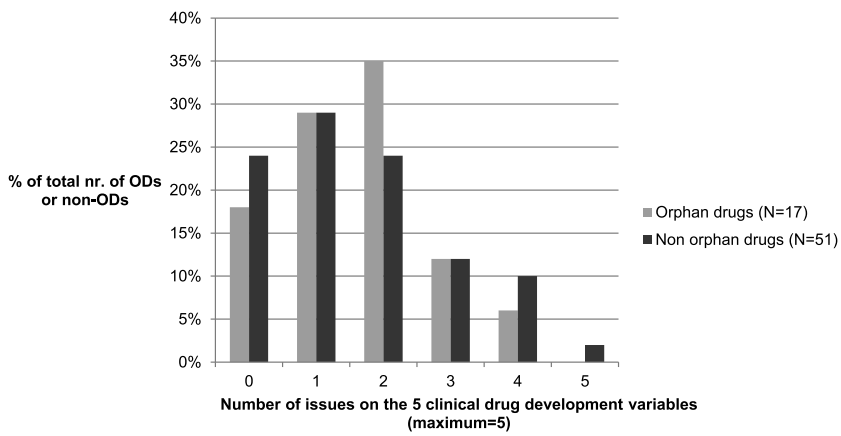

Figure 1. Differences in the *number* of deficits on any of the 5 variables of the clinical development plan (study design, clinically relevant primary endpoint, study population, trial duration, statistical analysis) according to EU regulators were small for orphan (N=17) and non-orphan drugs (N=51)

Table 1. Deficits in EU regulatory dossiers and approval outcome of orphan and non-orphan medicinal products in 2009-2010

	Orphan drugs		Non-orphan drugs	
	Total (N=17)	Approved (N=12)	Total (N=51)	Approved (N=33)
Clinical development plan				
1. Appropriate study design applied?				
Satisfactory	11 (65%)	8 (73%)	34 (67%)	24 (71%)
Problems identified	6 (35%)	4 (67%)	17 (33%)	9 (53%)
2. Clinically relevant primary endpoint used?				
Satisfactory	10 (59%)	8 (80%)	45 (88%)	30 (67%)
Problems identified	7 (41%)	4 (57%)	6 (12%)	3 (50%)
3. Representative target population studied?				
Satisfactory	14 (82%)	11 (79%)	27 (53%)	21 (78%)
Problems identified	3 (18%)	1 (33%)	24 (47%)	12 (50%)
4. Trial duration according to guidelines?				
Satisfactory	11 (65%)	6 (55%)	38 (74%)	26 (68%)
Problems identified	6 (35%)	6 (100%)	13 (26%)	7 (54%)
5. Appropriate statistical analysis?				
Satisfactory	12 (71%)	11 (92%)	29 (57%)	21 (72%)
Problems identified	5 (29%)	1 (20%)	22 (43%)	12 (55%)
Clinical outcome				
1. Statistical significance on primary endpoint				
Clearly confirmed	11 (65%)	10 (91%)	35 (69%)	29 (83%)
Not confirmed	6 (35%)	2 (33%)	16 (31%)	4 (25%)
2. Safety profile				
Satisfactory	5 (29%)	4 (80%)	27 (53%)	22 (82%)
(Uncertain) serious concerns	12 (71%)	8 (67%)	24 (47%)	11 (46%)
Medical need				
1. Alternative therapies available				
No	11 (65%)	8 (73%)	11 (22%)	7 (64%)
Yes	6 (35%)	4 (67%)	40 (78%)	26 (65%)

In addition, to test whether the associations of clinical development plan, clinical outcome and medical need with marketing authorisation showed similarity for ODs and non-ODs, the relative excess risk due to interaction (RERI) values were calculated. All the three RERI intervals include the value of 0.0 supporting statistically the conclusion of strong overall similarity of regulatory decision making in the study period.

Table 2. Univariate and Multivariate Relative risks for the quality of the development plan, clinical outcome and clinical relevance and marketing authorisation for orphan and non-orphan drugs

	Orphan drugs				Non-orphan drugs				
	Total N=17	**Approved N=12**	**Univ. RR**	**Multiv. RR**	**Total N=51**	**Approved N=33**	**Univ. RR**	**Multiv. RR**	**RERI**
Development plan									
Appropriate [a]	8	7 (88%)	Ref	Ref	27	21 (78%)	Ref	Ref	-0.2
Not "*appropriate*"	9	5 (56%)	0.64 (0.2-2.0)	0.85 (0.3-2.8)	24	12 (50%)	0.64 (0.3-1.3)	0.74 (0.4-1.5)	(-0.8-0.4)
Clinical outcome									
Positive [b]	10	10 (100%)	Ref	Ref	32	28 (88%)	Ref	Ref	-0.09
Not "*Positive*"	7	2 (29%)	0.29 (0.1-0.8)	0.3 (0.06-1.3)	19	5 (26%)	0.29 (0.1-1.3)	0.32 (0.1-0.8)	(-0.8-0.6)
Medical need									
High [c]	11	8 (73%)	Ref	Ref	11	7 (64%)	Ref	Ref	-0.08
Low	6	4 (67%)	0.9 (0.3-3.0)	1.1 (0.3-3.5)	40	26 (65%)	1.0 (0.4-2.4)	1.1 (0.5-2.5)	(-0.5-0.4)

[a] Development plan was defined ´Appropriate´ when no more than 1 concern or objection were raised by regulators
[b] Clinical outcome was defined ´Positive´ when efficacy results were convincing and no serious safety issues were raised
[c] Medical need was high when alternative pharmacological therapies for the disease were lacking

Clinical development plan

2.2

In about one out of three dossiers for ODs *and* non-ODs deficits regarding study design were observed (Table 1). However, there were some differences seen in the type of deficits. For ODs the use of single arm trial designs, lack of blinding and the use of bibliographical data instead of conducting a new trial were identified most frequently, while for non-ODs deficits related to study design were most often about the choice of comparator. Three ODs were approved with evidence only based on single arm studies, one after reexamination and two as conditional approvals with follow-up obligations.

We referred already to the study of Kesselheim et al on ODs for oncological diseases pointing out lower methodological standards for these products [8]. Our study demonstrates that for ODs the main concern of regulators was not having a comparative arm at all, thus clinical evidence solely based on a comparison with historical controls, which is in line with the results by Kesselheim. On the other hand, less robust study designs such as single arm studies were only accepted in two OD cases based on compelling evidence (e.g. large effect size, strong proof of principle) on a conditional basis, with an obligation for the company to collect additional evidence post-approval.

In 41% of all OD marketing applications deficits were identified regarding the clinical endpoint chosen in phase III studies, which was in contrast with only 12% for non-ODs applications. The approval rates of 57% for ODs and 50% for non-ODs in case of doubts about or objections against the clinical endpoint, demonstrates similarity between the two drug classes in this regard. Two of the three ODs that where not approved were oncology applications with no robust data on clinical endpoint (e.g. survival, end-organ involvement). Otherwise, two hematological products were approved albeit the absence of survival data, i.e. Mozobil based on clinically relevant effects on haematopoietic stem cell mobilization [11] and Arzerra showing a relatively high response rate in those patients that suffered from a disease with a high medical need and was conditionally approved [12].

Finding the right target population was less often a critical issue in ODs applications compared to non-ODs (18% versus 47%), possibly a reflection of the inherited nature of many of the rare diseases where a genetic defect is closely linked to the diagnosis and the sought indication for the OD. For genetic diseases that can be well diagnosed and identified, the study population may represent a relatively high percentage of the total study population [13]. On the other hand, the presence of very heterogeneous study populations in many OD trials, also given the small numbers, underdiagnosis, and selection bias at subject inclusion, remains a challenge in developing treatments for many rare diseases [14,15]. For non-ODs most issues raised were about the representativeness of the study population for the proposed indication. In order to receive marketing authorisation additional studies

in the lacking study population were submitted, the indication was restricted or a warning was included in the Summary of Product Characteristics.

Clinical outcome

Overall our data showed that deficits in the evidence needed to show efficacy did not occur more often for ODs than for non-ODs. The EMA concluded as often for ODs as for non-ODs that Phase III outcomes were uncertain or not convincing. Four of the six ODs that did not reach the primary endpoints or had unconvincing results were not approved to the market. For the other two drugs that were approved, a statistical effect on primary endpoints was demonstrated for a subgroup only (Mozobil) or uncertainty about long-term efficacy was high (Esbriet) [11,16]. Similarly, among the non-ODs four drugs with uncertainty about the statistical effect, (e.g. contradictive study results or results in a subpopulation) were approved, whereas all drugs with unconfirmed effect on the primary endpoint failed to receive marketing authorisation.

The safety profiles of ODs more often lead to regulators' concerns compared to those of non-ODs (71% and 47%, respectively). For the ODs particularly often doubts were raised about *potential* risks rather than concerns about *identified* risks in Phase III studies (9 out of 12 ODs, 13 out of 24 non-ODs). Regulatory decisions always go together with uncertainty [17], but apparently, the safety profiles of ODs are accompanied with more uncertainty about risks of adverse events at time of marketing authorisation, most likely also due to a lower number of patients included in the safety database. Despite this difference, an equal majority of both ODs as well as non-ODs with *potential* serious safety issues were approved with additional obligations such as follow-up studies and/or an update of the Risk Management Plan e.g. to initiate monitoring (7 out of 9 ODs and 10 out of 13 non-ODs). Similarly, all but one of the ODs and non-ODs with *identified* serious safety issues did not reach the market for that reason. Still, Mozobil, an OD for mobilization of haematopoietic stem cells was approved to the market under condition of strict monitoring of thrombocytopenia [11]. However, a previous study has demonstrated that ODs as such have limited serious safety events post-approval in a follow-up period of at longest eight years after initial approval [18].

Medical need

In ODs dossiers a claimed high medical need (defined as no alternative therapy available for the disease or the subpopulation of the indication) was more frequently acknowledged than in non-ODs dossiers (65% and 22%, respectively). These numbers follow our expectations since ODs per definition are indicated for severely disabilitating or life threatening diseases without a treatment available. In addition, more ODs were approved to the market under conditional or exceptional approval than non-ODs (35% and 6%, respectively). However, overall

being classified as a product with 'high medical need' resulted statistically not more often in a positive approval decision (Table 2).

Examples of ODs with 'lower medical need', according to our definition, are the so-called 'follow-on' ODs for rare diseases for which one or more ODs were already on the market at the time of the procedure. These drugs received orphan status because of a 'significant benefit', a clinically relevant advantage (e.g. evidence of potential greater efficacy, an improved safety profile or more patient convenience due to new pharmacokinetic characteristics compared to existing ODs [19]. The chance of having a follow-on OD for a rare disease submitted to EMA is associated with the disease prevalence, turnover of the first OD, disease class (in particular oncology) and specific scientific output [20].

GENERAL DISCUSSION

In this study we focused on whether any differences existed between ODs and non-ODs in number and type of deficits brought forward during the EMA review and whether these deficits were similarly associated with a positive or negative result of the procedure. ODs and non-ODs dossiers were compared on deficits in eight areas regarding clinical development plan (N=5), clinical outcome (N=2) and medical need (N=1). At the end, in 71% of the ODs dossiers and 65% of the non-ODs dossiers a positive opinion was given. We found some differences in deficits, but strong similarities in the way ODs and non-ODs were reviewed and assessed.

There were differences between ODs and non-ODs in the area of study design (i.e. use of single arm studies), clinically relevant endpoint (i.e. more challenging for ODs), finding the appropriate target population (i.e. for ODs less a challenge than for non-ODs), safety profile (i.e. for most ODs less favorable), acknowledged high medical need (i.e. in two third of ODs dossiers, one fifth of the non-ODs dossiers). But overall these differences did not result in differential weighing of the benefit-risk of the products under review, both ODs and non-ODs. Previous work by Kesselheim showed that ODs were approved based on less robust data than non-ODs [8]. Indeed, due to the limitations inherent to studying rare diseases, original OD submissions will be based on smaller studies. However, our analysis demonstrated that apparently the EMA did not accept lower levels of evidence (development and outcome) for ODs and non-ODs, unless (i) this could be well justified by the applicant, or (ii) when limited opportunities for further research allowed exceptional approval [21] or (iii) when the company committed to add additional data to meet the standards of drug development that EMA requires, and the OD was conditionally approved e.g. because of medical need. The EU regulation for conditional approval applies to both ODs *and* non-ODs to be used in emergency situations, or for severely disabilitating or life threatening diseases, in particular when no other therapies exist when, the balance of risks and benefits is positive, based on the evidence available [22].

We measured in this study EMA's identified and weighted deficits (i.e. concerns, doubts and objections) rather than the study design characteristics e.g. (type of endpoint) and outcomes themselves on which the products, both ODs and non-ODs, were evaluated, and approved or rejected in the end. We assume for the purpose of this study that the number and nature of these deficits reflect in a valid way any real deficits with the dossiers. Because all the experts and committees of the EMA evaluate these dossiers in an unblinded fashion (for OD/non-OD), one may expect bias in the ODs and non-ODs dossiers review, in the way any deficits were identified, recorded and worded in the assessment reports and other communications. Our finding of essential similarity between the way ODs and non-ODs dossiers were reviewed therefore could be biased because possible real differences may be hidden or underestimated because of selective identification or wording. We doubt whether that is the case in our study due to strong consistency in comments in our study (e.g. lack of overall survival was a deficit mentioned for orphan and non-orphan oncological products and active compared trials were recommended where possible for ODs as well).

Deficits in the development plan of ODs at the time of marketing approval were just as strongly associated with marketing approval as those of non-ODs. Our results therefore encourage future OD developers to search for opportunities for a comparative study design or alternative innovative designs and clinically relevant endpoints or validated bio-markers. In order to do so, both OD developers could have substantial benefit of appropriate learning studies to identify the biology underlying a disease, to explain a dose response relation and a logic order of events [7,23,24].

To solve developmental complexities within future ODs development clear communication about the level of evidence required is needed e.g. in scientific advice. This may help companies to develop drugs according to high standards and have their ODs approved to the market [7,25]. Progress is made by harmonizing EMA and FDA guidelines for ODs development [26,27]. Moreover joint scientific advice is offered for ODs development [28].

In conclusion, we found strong similarity in the way ODs and non-ODs were reviewed and marketing approval decisions were taken. Some differences between deficits in ODs and non-ODs dossiers were found, but deficits in the clinical development plan and clinical outcomes were both drivers of regulatory decision making, not differentially between ODs and non-ODs. Our findings indicate that, in contrast to common belief, regulatory standards are equally high for ODs as for non-ODs.

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Annex 1. Orphan and non-orphan drugs, conditions and approval status

Orphan drugs Brand name	INN	Orphan conditions	Approval status
Vorinostat	suberoylanilide hydroxamic acid	Cutaneous T-cell lymphoma	Withdrawn in 2009
Bosatria	mepolizumab	Hypereosinophillic syndrome	Withdrawn in 2009
Oncophage	vitespen	Renal cell carcinoma	Negative opinion in 2009
Cerepro	sitimagene ceradenovec	Glioma	Negative opinion in 2010
Ethyl eicosapent soft gelatin capsules	ethyl eicosapent	Huntingtons disease	Withdrawn in 2009
Cayston	aztreonam lysine	Lung infections in cystic fibrosis	Approved in 2009
Mozobil	plerixafor	Mobilization of haematopoietic stem cells	Approved in 2009
ChondroCelect	characterized autologous chondrocytes in suspension	Repair treatment of symptomatic cartilaginous defects	Approved in 2009
Rilonacept regeneron	rilonacept	Cryopyrin-associated periodic syndromes	Approved in 2009
Ilaris	canakinumab	Cryopyrin-associated periodic syndromes	Approved in 2009
Firdapse	amifampridine	Lambert–Eaton myasthenic syndrome	Approved in 2009
Revolade	eltrombopag	Idiopathic thrombocytopaenic Purpura	Approved in 2009
Arzerra	ofatumumab	Chronic lymphocytic leukemia	Approved in 2010
Esbriet	pirfenidone	Idiopathic pulmonary fibrosis	Approved in 2010
Votrient[a]	pazopanib	Renal cell carcinoma	Approved in 2010
Vpriv	velaglucerase alfa	Gaucher disease	Approved in 2010
Xiapex	collagenase clostridium histiolyticum	Dupuytren's contracture	Approved in 2010

[a]Since April 2010 Votrient has no longer orphan status, but it has been evaluated and approved to the market by the EMA while having the orphan status

Non-orphan drugs Brand name	INN	Non-orphan conditions	Approval status
Ixempra	ixabepilone	Breast Cancer	Negative opinion in 2009
Biferonex	IFN beta-la	Relapsing remitting multiple sclerosis	Negative opinion in 2009
Emerflu	A/ Vietnam/1194/2004 (H5N1) like strain	Protecting from pandemic flu	Negative opinion in 2009
Cylatron	peginterferon alfa 2b	Stage III melanoma	Withdrawn in 2009
Factive	gemifloxacine	Mild or moderate community-acquired pneumonia	Withdrawn in 2009
Gemesis	bercaplermin	Treatment of periodontally related defects	Negative opinion in 2009
Contusugene ladenovec	contusugene ladenovec	Recurrent or refractory squamous cell carcinoma of the head and neck	Withdrawn in 2009
Ramvocid	orativancin	Complicated skin and soft tissue infections	Withdrawn in 2009
Opaxio	paclitaxel poliglumex	Non-small cell lung cancer	Withdrawn in 2009
Zunrisa	casopitant mesylate	Postoperative nausea and vomiting (PONV)	Withdrawn in 2009
Mersarex	iclaprim mesylate	Complicated skin and soft tissue infections	Withdrawn in 2009
Zactima	vandetanib	Non-small cell lung cancer	Withdrawn in 2009
Recothrom	thrombin alfa	Haemostasis	Withdrawn in 2009
Sliwens	eplivanserin hemifumarate	Chronic insomnia	Withdrawn in 2009
Comfyde	carisbamate	Epilepsy	Withdrawn in 2010
Joulferon	albinterferon alpha 2b	Chronic hepatitis C	Withdrawn in 2010
Zeftera	ceftobiprole medocardil	Complicated skin and soft tissue infections	Negative opinion in 2010
Zenhale	mometasone furoate anhydrus + formoterol fumarate dihydrate	Asthma	Withdrawn in 2010

Synflorix	pneumococcal polysaccharide conjugate vaccin	Invasive pneumococcal disease	Approved in 2009
Conbriza	bazedoxifene	Osteoporosis	Approved in 2009
Exalief	eslicarbazepine acetate	Epilepsy	Approved in 2009
Removab	catumaxomab	Malignant ascites	Approved in 2009
Ellaone	ulipristal	Emergency contraception	Approved in 2009
Iressa	gefitinib	Non-small cell lung cancer	Approved in 2009
Victoza	liraglutide	Diabetes mellitus	Approved in 2009
Samsca	tolvaptan	Hyponatraemia	Approved in 2009
Cimzia	certolizumab pegol	Rheumatoid arthritis	Approved in 2009
Javlor	vinflunine ditartrate	Transitional cell arcinoma of urothelial tract	Approved in 2009
Onglyza	saxagliptin	Diabetes mellitus	Approved in 2009
Simponi	golimumab	Rheumatoid arthritis	Approved in 2009
Eporatio	epoetin theta	Anaemia	Approved in 2009
Resolor	prucalopride	Chronic constipation	Approved in 2009
Multaq	dronedarone hydrochloride	Rhythm control in patients with atrial fibrillation	Approved in 2009
Prevenar 13	pneumococcal saccharide conjugated vaccine adsorbed	Vaccination against diseases caused by *Streptococcus pneumoniae*	Approved in 2009
Onbrez breezhaler	indacaterol maleate	Chronic obstructive pulmonary disease	Approved in 2009
Scintimun	besilesomab	Investigation of sites of inflammation and / or infection	Approved in 2009
Elonva	corifollitropin alfa	Controlled ovarian stimulation	Approved in 2009
Urorec	silodosin	Prostate hyperplasia	Approved in 2009
Menveo	MenACWY	Meningococcal disease	Approved in 2009
Prolia	denosumab	Osteoporosis	Approved in 2009
Aflunov	prepandemic Influenza vaccin (H5N1)	Active immunisation against H5N1 subtype of Influenza A virus	Approved in 2010
Arepanrix	split spirion inactivated AS03 Pandemic influenza vaccin	Prophylaxis of influenza	Approved in 2010

Brilique	ticagrelor	Acute coronary syndrome	Approved in 2010
Brinavess	vernakalant hydrochlorid	Atrial fibrillation	Approved in 2010
Daxas	roflumilast	Chronic obstructive pulmonary disease	Approved in 2010
Fluenz	influenza vaccine (live attenuated, nasal)	Prophylaxis of seasonal Influenza	Approved in 2010
Humenza[b]	pandemic influenza vaccine (H1N1)	Pandemic influenza	Approved in 2010
Pumarix	pandemic influenza vaccine (H5N1) split virion, inactivated adjuvanted	Pandemic influenza	Approved in 2010
Rapiscan	regadenoson	Radionuclide myocardial perfusion imaging (MPI)	Approved in 2010
Ruconest	conestat alfa	Hereditary angioedema (HAE)	Approved in 2010
Sycrest	asenapine	Bipolar disorder	Approved in 2010

[b] No longer authorized, voluntarily withdrawn the marketing authorisation for commercial reasons

2.3

DETERMINANTS OF SUCCESSFUL MARKETING AUTHORISATION OF ORPHAN MEDICINAL PRODUCTS IN THE EU

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ABSTRACT

In 2010, the European Regulation for Orphan Medicinal Products (OMPs) was in force for ten years. In this study we assessed possible determinants of applications for OMPs in the EU since 2000 that are associated with a successful marketing authorisation. Our analysis shows that clinical trial characteristics such as demonstrating convincing evidence of a beneficial effect on the primary endpoint, the selection of a clinically relevant endpoint, providing RCT data as pivotal study evidence and the submission of sound dose finding data are critical success factors. In addition, high medical need seems to counterweigh uncertainties about the scientific evidence in the benefit–risk assessment of OMPs.

INTRODUCTION

The European regulation of orphan medicinal products (OMPs) sets rules and provides specific incentives for sponsors of medicinal products intended for the diagnosis, prevention and/or treatment of rare diseases. In the European Union a disease is defined as rare if it occurs in five people or less per 10 000 of the population in the European Union (EU) member states and the disease is life-threatening or chronically debilitating. In addition, the regulation states that no alternative treatment should be available or that any new treatment is expected to deliver a significant additional benefit [1–3]. The number of rare diseases is estimated to be between 5000 and 8000, affecting ~30 million people in the EU [3]. For most of the rare diseases no effective treatment exists, which makes orphan drug development an important public health issue [2]. The European regulation aims to create and enhance opportunities for developing drugs for patients with rare diseases. Sponsors that develop such a medicinal product could request an orphan designation for their product in order to benefit from incentives such as direct access to the centralised marketing authorisation procedure and 10-year market exclusivity, protocol assistance during the product-development phase, financial incentives (i.e. fee reductions or exemptions) and national incentives [1].

By May 2011, a total of 855 orphan designations had been granted, whereas just 64 OMPs had been authorised for marketing in the EU since the introduction of the regulation on OMPs in 2000 (http://ec.europa.eu/health/documents/community-register/ html/orphreg.htm) [4]. Since 2000 the number of submissions for marketing authorisation of OMPs has increased [5]. Arriving at a positive or negative opinion about a marketing authorisation for an OMP is subject to comprehensive evaluation of the available scientific evidence for quality, efficacy and safety of the product. The final and decisive benefit–risk assessment, the task of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), is based on the results and appropriate implementation of an extensive quality, preclinical and clinical development programme. However, other aspects including drug substance-, indication- or company-related factors such as previous experience with the drug substance or the availability of alternative pharmaceutical treatments for the disease could shape the context of the benefit–risk assessment for the new orphan treatments. Owing to the exceptional characteristics of orphan diseases and the patients, orphan drug development is a complex, challenging and risky enterprise, which might explain the relatively high attrition rates in the marketing authorisation procedure [6–8].

Several studies have been undertaken to learn from the successes and failures of previous marketing applications for OMPs. In previous studies by Joppi et al. the methodological quality of marketing application dossiers of OMPs that received marketing authorisation in the EU in the periods 2000–2004 [9] and 2000–

2007 [10] has been assessed. Methodological limitations of the clinical dossiers were found during both periods. In an earlier study by our group, marketing applications for OMPs in the EU that gained marketing approval up to October 2006 were compared with a sample of designated, but not yet approved, OMPs. Substance-, indication- and company-related predictors for orphan drug approval in the EU were assessed. Previous company experience in obtaining approval for another OMP was also identified to be associated with marketing approval. Besides, existing small molecules were more likely to gain marketing approval than biotechnology products [11]. Recently, we also studied a broad range of characteristics related to failure to achieve marketing authorisation by the US Food and Drug Administration (FDA). Characteristics of the clinical trial programme, the substance, the company and interaction with the FDA were studied for non-approved and approved marketing applications for orphan drugs at the FDA, and several of them were found to be associated with marketing approval [12].

The present study aims to assess determinants of successful marketing applications for OMPs in the EU, but now with a more comprehensive and methodologically advanced approach, comparing all approved and non-approved marketing applications for OMPs in the EU since the orphan drug regulation was established in 2000.

Data of OMP dossiers from the period 2000–2006 were confidentially collected and analysed in an aggregated fashion. Data for all approved and non-approved OMPs post-2006 were collected from European Public Assessment Reports (EPARs), which are available on the EMA website (http://www.ema.europa.eu). These documents provide a summary of the complete drug development plan as submitted by the sponsor and the scientific discussion and final benefit–risk evaluation by the CHMP of the EMA.

INDICATION-RELATED CHARACTERISTICS

From 2000 to the end of 2009, a total of 114 marketing applications for OMPs received an opinion about marketing authorisation by the CHMP or were withdrawn by the sponsor during the authorisation procedure. Of these, 97 were applications for new OMPs (including four double applications for the same indication), whereas 13 applications were for extensions of indications of previously approved drugs by the EMA. Four applications were submitted for multiple indications on the same date. Applications for multiple indications for one OMP were analysed as separate marketing applications (n = 114). Table 1 provides key characteristics related to the drug substance, indication, development plan, sponsor and dialogue with the EMA for the studied OMPs.

These 114 marketing applications have led to a successful authorisation of 59 OMPs for 73 indications (64%). Of those 73 approved applications, 27 (37%) were

approved under exceptional circumstances and three (4.1%) were conditionally approved. Thus, 41 applications failed in the authorisation procedure. The number of approved and non-approved marketing applications for OMPs per year increased over the years. After an initial increase over the first eight years, the number of approved marketing applications has decreased during the past two years (Fig. 1). Univariate and multivariate analyses were performed to evaluate crucial determinants for success, as described in Box 1.

Most of the marketing applications for OMPs were for oncological products (35.1%; Table 1). When comparing the number of non-approved and approved marketing applications for each indication category, 28 out of 40 (70%) oncological applications and 15 out of 17 (88%) applications for metabolic diseases received marketing authorisation. By contrast, for immunological diseases or anti-infectious diseases only three out of eight (37.5%) and one out of five (20%) received marketing authorisation (Fig. 2).

Balancing uncertainties in the evidence for efficacy and safety of OMPs versus a high medical need characterises regulator dilemmas in the assessments of OMPs [13,14]. Our results suggest that European benefit–risk assessment seems to be driven by the context of medical need, as shown by the clear association between lack of an alternative therapy for the disease and a positive marketing authorisation (Adjusted odds ratio (ORadj.) 4.6, 95% CI 1.1–20.4; Table 2). Although marketing applications for orphan indications should comply with existing regulatory guidelines just as they do for other drugs, a higher degree of uncertainty about safety issues and/or efficacy results could be considered acceptable for orphan indications for which no treatment exists. Regulator responsibility to provide access to efficacious and safe products for the population is reflected by the fact that 41% of all approved marketing applications was approved under exceptional circumstances or as conditional approval. These approvals partly represent those orphan indications for which medical need was highest owing to lack of an alternative pharmacotherapeutic option.

CLINICAL DRUG DEVELOPMENT CHARACTERISTICS

The core of the benefit–risk assessment is the scientific discussion of the clinical drug development programme. In our case study, several characteristics of the clinical development plan were shown to influence a marketing authorisation decision.

Study endpoints: effect and clinical relevance

The strongest determinants of marketing approval were data showing a beneficial effect on the primary endpoint (when present 83.1% were approved, when absent this figure was just 24.3%) and clinically relevant endpoint used according to EMA review (when present approval was 75%, when absent it was 26.9%). Nine OMPs

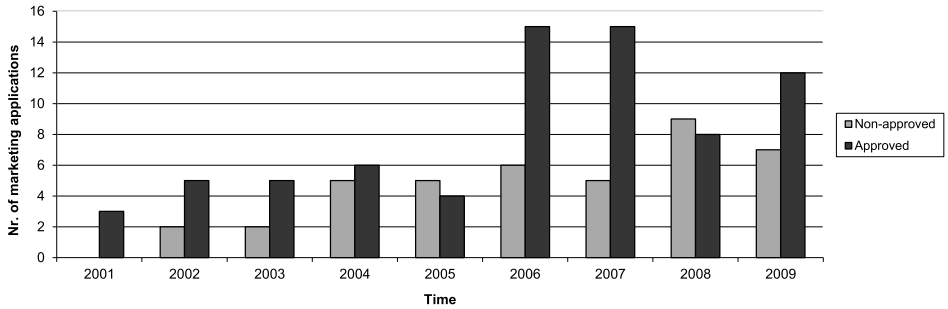

Figure 1. Number of approved and non-approved marketing applications for orphan medicinal products per year in the EU (2001-2009, N=114)

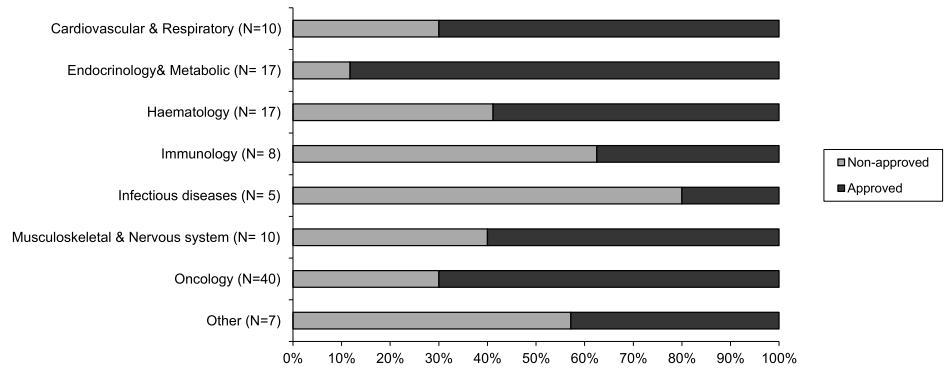

Figure 2. Proportion of non-approved and approved marketing applications for orphan medicinal products in the EU indication category

were approved without convincing results on the primary endpoint defined in the protocol (Table 2). This occurred when (i) survival data were requested but could not be provided or statistical significance could not be reached [e.g. Nexavar®, sorafenib tosylate for renal cell carcinoma, based on progression-free survival (PFS) it was concluded that a favourable and clinically meaningful effect had been demonstrated], (ii) when a clinical beneficial effect could not be demonstrated for the whole study population, whereas benefits were shown for a specific subgroup [e.g. Ceplene®, histamine dihydrochloride for the treatment of acute myeloid leukaemia (AML), approved as maintenance therapy for adult patients with AML in first remission concomitantly treated with interleukin (IL)-2 only] or (iii) when data were shown in a small study with limited patient numbers (e.g. Increlex®, mecasermine for the treatment of growth factor-1 deficiency, exceptionally approved). From all of the studied dossiers of OMPs, 13 were withdrawn or received a negative opinion despite a beneficial effect on the primary endpoint

Box 1. Methodology

Potential determinants for marketing authorisation that were studied were related to drug substance, indication, clinical development plan, company and dialogue with the EMA. Drug-related determinants included previous approval of the drug in any country irrespective of indication and whether the drug was a small molecule product or a biological or advanced therapy medicinal product. Previous approval could either mean that exactly the same product with a similar indication and formulation made by the same company was previously approved by another regulatory agency or that the same molecular substance was previously approved, but for a different indication and/or formulation and/or developed by another company. Biologicals were defined as vaccines, blood and blood components and recombinant proteins. Advanced therapy medicinal products (ATMP) were defined as tissue engineered products, cell somatic cell therapy products and gene therapy medicinal products [30]. Indication-related determinants were the prevalence of the disease in the EU according to EMA data and availability of alternative pharmaceutical therapies for the orphan disease, assessed at the time of marketing application. Determinants used to characterise the drug development plan were the conduct of dose-finding studies, the rigor of the pivotal clinical study design [randomized clinical trial (RCT) yes or no] and the evidence of a beneficial effect on the primary endpoint. This was defined as reaching statistical significance in controlled studies or meeting predefined criteria in uncontrolled studies. In case more pivotal trials were conducted for the indication under review, the trial with the most robust study design (as defined by randomization and controlled design of the trial) and the largest number of patients was included in the analysis. We also evaluated assessment reports of the EMA looking at the suitability in terms of the clinical relevance of the studied primary endpoints and concerns or objections made related to the identification of an appropriate target population according to EMA review. Sponsor-related determinants were company size, defined as small and medium-sized enterprise (SME) status of the company according to the SME definition of EMA [31], and company experience in OMP development. A company was considered experienced when a marketing application for an OMP had previously been submitted at EMA. The dialogue with EMA was defined as protocol assistance obtained from the EMA. The study outcome of interest was a positive opinion of the CHMP on the recommendation for marketing authorisation for European patients. Non-approved marketing applications were defined as applications that received a negative opinion by the CHMP or that were withdrawn from the marketing authorisation procedure between day 120 and the end of the procedure. Data analysis Univariate odds ratios (OR) and 95% confidence intervals (95% CI) of marketing authorisation were calculated applying logistic regression analyses. All variables with a univariate OR with a P value <0.20 were included in a multivariate logistic regression model to calculate adjusted odds ratios (ORadj.) (95% CI). All statistical analyses were conducted by using the statistical software package SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Table 1. Baseline characteristics of marketing applications for orphan medicinal products in the EU

	Total no. of marketing applications N=114
Characteristics of the drug substance	
Previous approval in any country	
No	25 (21.9%)
Yes	89 (78.1%)
Small molecule	
No	29 (25.4%)[a]
Yes	85 (74.6%)
Indication characteristics	
Disease class	
Cardiovascular & Respiratory	10 (8.8%)
Endocrinology & Metabolic	17 (14.9%)
Haematology	17 (14.9%)
Immunology	8 (7.0%)
Infectious diseases	5 (4.4%)
Musculoskeletal & Nervous system	10 (8.8%)
Oncology	40 (35.1%)
Other	7 (6.1%)
Lack of alternative therapy for the disease	
No	73 (64.0%)
Yes	41 (36.0%)
Prevalence in the EU	
<5 per 100.000	30 (26.3%)
5-10 per 100.000	42 (36.8%)
> 10 per 100.000	42 (36.8%)
Clinical development plan characteristics	
Dose Finding studies performed?	
No	66 (57.9%)
Yes	48 (42.1%)
RCT conducted as pivotal trial	
No	48 (42.1%)
Yes	66 (57.9%)
Beneficial effect on primary endpoint according to EMA review	
No	37 (32.5%)
Yes	77 (67.5%)
Regulators' concerns on the clinical development plan	
Clinically relevant endpoint used according to EMA review	
No	26 (22.8%)
Yes	88 (77.2%)

Table 1. continued

	Total no. of marketing applications N=114
Representative target population identified according to EMA review	
No	31 (27.2%)
Yes	83 (72.8%)
Company characteristics	
Company size	
SME	27 (23.7%)
Large	87 (76.3%)
Company experience in orphan drug development	
No	72 (63.2%)
Yes	42 (36.8%)
Regulatory dialogue with EMA	
Protocol assistance obtained from the EMA	
No	59 (51.8%)
Yes	55 (48.2%)

[a] This group consists of 28 biologicals and 1 advanced therapy medicinal product

(Table 2). In nine of these cases, the endpoint was considered not to be clinically relevant according to regulatory review by the EMA.

The multivariate analysis confirmed that a beneficial effect on the primary endpoint (ORadj. 53.9, 95% CI 8.4–345.2) and the clinical relevance of the endpoint (ORadj. 15.0, 95% CI 2.9–77.8) according to EMA review were strongly associated with a positive marketing authorisation outcome (Table 2). A similar result was found when we assessed FDA data, where failure of the primary endpoint was related to a negative outcome of marketing authorisation (Odds ratio (OR) 25.7, 95% CI 5.3–125.1) [12]. Because the primary endpoint provides the main evidence for efficacy these results were as expected. However, the clinical relevance of the primary endpoint was not part of the FDA review process [12]. By contrast, in the EU clinical relevance of the selected endpoint according to guidelines or previous advice from regulators was strongly associated with success in the marketing authorisation procedure, next to the effect size of the efficacy results. Drug companies seem to make a trade-off between selecting a robust endpoint such as survival which demands high numbers of patients and long-term studies to demonstrate a statistical significant effect and surrogate endpoints usually requiring smaller and shorter studies, but for which translation of the findings into clinical relevance is more problematic [12–14]. Although previous studies criticised the authorised EU marketing applications for demonstrating efficacy based on surrogate endpoints [9,10], the availability of valid

biomarkers and surrogate endpoints with demonstrated clinical relevance seems to contribute significantly to the surge in numbers of approved OMPs [15].

Rigor of the clinical trial data

Our results show that all meaningful clinical effects of OMPs should preferably be shown in an Randomized clinical trial (RCT) (ORadj. 6.9, 95% CI 1.3–36.1; Table 2). According to the CHMP, in general an application based upon one single pivotal study can suffice for a marketing authorisation if the data are compelling, the study is well designed, the outcome is positive and the data are robust in terms of efficacy and safety [16,17]. If an active comparator is available, the conduct of non-inferiority studies can be challenging because a large sample size of patients is needed. Consequently, single-arm studies are frequently performed for OMPs (n = 48, 42.1%; Table 1). However, examples demonstrate that when an RCT is considered feasible it is the most preferable way to gain successful marketing authorisation. This is also described in the EMA guideline on clinical trials in small populations [17], and could be illustrated by the assessment of Vidaza®(INN-azacitidine) for the treatment of myelodysplastic syndromes. Although no authorised treatment for myelodysplastic syndromes exists yet, the CHMP requested a comparative trial with chemotherapy that had become standard of care in off-label use to demonstrate prolonged survival [18].

Dose finding

As for regular drug development, relevant dose-finding data are requested for OMPs and in this study were shown to be an independent determinant of success (ORadj. 8.1, 95% CI 1.6– 41.2; Table 2). The relevance of exploratory dose-finding studies to learn about the appropriate dose regimen in confirmatory clinical studies was also previously emphasized [19]. A dose-finding study leads to an understanding of the dose–response relationship and enables selection of the optimal dose of the drug in representative patients, which might prevent unnecessary failure of confirmatory studies [19].

DRUG SUBSTANCE AND SPONSOR-RELATED CHARACTERISTICS

Previous studies showed that experience in orphan drug development is an important predictor for subsequent marketing authorisation in the EU and the USA [11,12]. Many complexities exist in orphan drug development that make it plausible that experience in developing and marketing an OMP increases the likelihood of subsequent marketing approval. Orphan drug development by inexperienced companies can be hampered by a limited geographical outreach with poor access to patients and a lack of regulatory knowledge and experience in RCT design [11]. In the present study, experience with the molecular substance

(defined as previous approval of the drug) and company experience were also associated with a positive outcome of an application, but these associations did not reach statistical significance (Table 2).

UNCERTAINTIES IN BENEFIT–RISK ASSESSMENT

Balancing benefits and risks of OMPs in the context of medical need is subject to an extensive scientific discussion at the level of the CHMP. This is inherent to specific issues in orphan drug development, such as lack of active comparator drugs and sufficient power to show an effect on clinically relevant endpoints, although clear cases can exist: those OMPs for diseases without alternative options, for which a clinical beneficial effect has been demonstrated in a controlled trial, are likely to receive a positive opinion by the CHMP. Similarly, OMPs for which hardly any clinical benefit was demonstrated in poorly designed studies are more likely to receive a negative opinion by the CHMP. In most cases, however, existing uncertainties are assessed in the context of available data, especially in applications without convincing evidence for clinical benefit. As described before, for some OMPs a beneficial effect, that met predefined criteria, could not be demonstrated for the whole study population. A non-prespecified positive finding in a subgroup would normally be considered to be hypothesis-generating only [20,21], but for some OMPs the CHMP has found such results sufficient for approval. A high level of uncertainty regarding benefits and, in particular, risks also applies particularly to biological products owing to their safety issues and complex manufacturing processes of which experience is more limited compared with that for other drugs. The strong association between biological products and failure of marketing authorisation (ORadj. 17.1, 95% CI 2.1–138.9; Table 2) was driven by manufacturing, quality and safety issues, which seem to have contributed to a negative CHMP opinion. These biological products might not necessarily have deficits in the clinical development programme, which could explain some of the differences in the univariate and multivariate results.

REGULATORY DIALOGUE

The number of applications for orphan designation has increased during the past few years. This could result in more OMPs being authorised for marketing in the EU during the following ten years [5,22]. Drug developers and regulators could face new challenges in (innovative) orphan drug development that goes beyond guidelines. Increasing knowledge about disease progress, prevalence data and how to conduct a clinical trial is needed [2,23–25]. Such complex drug-development challenges need frequent and strong scientific discussions between industry and the regulatory community. Regulatory dialogue can, and should, have an essential

Table 2. Association between determinants and approval of marketing applications for orphan medicinal products in the EU (univariate and multivariate logistic regression)

	Total (N=114)	Marketing authorisation (N=73)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Characteristics of the drug substance				
Previous approval in any country				
No	25	11 (44.0%)	1 (Ref)	1 (Ref)
Yes	89	62 (69.6%)	2.9 (1.2-7.3)	1.7 (0.4-7.4)
Small molecule				
No	29 [a]	14 (48.2%)	1 (Ref)	1 (Ref)
Yes	85	59 (69.4%)	2.4 (1.0-5.8)	17.1 (2.1-138.9)
Indication characteristics				
Lack of alternative therapy for the disease				
No	73	42 (57.5%)	1 (Ref)	1 (Ref)
Yes	41	31 (75.6%)	2.3 (0.98-5.4)	4.6 (1.1- 20.4)
Prevalence in the EU				
> 10 per 100.000	42	26 (61.9%)	1 (Ref)	
5-10 per 100.000	42	25 (59.5%)	0.9 (0.4-2.2)	N.A.[b]
<5 per 100.000	30	22 (73.3%)	1.7 (0.6-4.7)	
Clinical development plan characteristics				
Dose Finding studies performed				
No	66	38 (57.6%)	1 (Ref)	1 (Ref)
Yes	48	35 (72.9%)	2.0 (0.9-4.4)	8.1 (1.6-41.2)
RCT as pivotal trial				
No	48	26 (54.2%)	1 (Ref)	1 (Ref)
Yes	66	47 (71.2%)	2.1 (1.0-4.6)	6.9 (1.3-36.1)

Table 2. continued

	Total (N=114)	Marketing authorisation (N=73)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Beneficial effect on primary endpoint				
No	37	9 (24.3%)	1 (Ref)	1 (Ref)
Yes	77	64 (83.1%)	15.3 (5.9-40.0)	53.9 (8.4-345.2)
Regulators' concerns on the clinical development plan				
Clinically relevant endpoint used according to EMA review				
No	26	7 (26.9%)	1 (Ref)	1 (Ref)
Yes	88	66 (75.0%)	8.1 (3.0-22.9)	15.0 (2.9-77.8)
Representative target population identified according to EMA review				
No	31	16 (51.6%)	1 (Ref)	1 (Ref)
Yes	83	57 (68.7%)	2.1 (1.0-4.8)	0.55 (0.12-2.5)
Company characteristics				
Company size				
SME	27	13 (48.1%)	1 (Ref)	1 (Ref)
Large	87	60 (69.0%)	2.4 (1.0-5.8)	2.1 (0.5-9.4)
Company experience in OMP development				
No	72	39 (54.2%)	1 (Ref)	1 (Ref)
Yes	42	34 (80.9%)	3.6 (1.5-8.8)	1.9 (0.4-8.3)
Regulatory dialogue with EMA				
Protocol assistance obtained from the EMA				
No	59	38 (64.4%)	1 (Ref)	N.A.[b]
Yes	55	35 (63.4%)	1.0 (0.5-2.1)	

a This group consists of 28 biologicals and 1 advanced therapy medicinal product
b N.A. = Not Applicable (p-value in univariate analysis > 0.20)

role in safeguarding sustained knowledge exchange and increasing successful marketing authorisation. Protocol assistance is provided for OMP developers either for free (for small and medium-sized enterprises; SMEs) or with a 90% fee reduction (for non-SMEs). In previous studies with EMA and FDA dossier data it has been shown that compliance with scientific advice is associated with marketing approval [12,26]. In our study having protocol assistance or scientific advice was not associated with a successful marketing application (Table 2). Unfortunately, compliance with scientific advice could not be studied, because non-compliance was not documented in a standardized way in the study data. To increase the dialogue, the EMA and FDA have announced parallel scientific advice programmes for all products with a possible clinical significance for both agencies [27,28].

Some limitations of our case study should be reported. First, the total number (114) of non-approved and approved marketing applications has limited opportunities for analysis. Obviously, the confidence intervals of the association estimates are wide. The strength of this study reflects the fact that we included all marketing applications for OMPs in the EU since the advent of the orphan drug regulation in 2000. Second, some of the variables are correlated with each other. Specific indications might be related to the availability of an alternative therapy and therefore the availability of an active comparator, disease prevalence and difficulties with selecting appropriate endpoints. Owing to the low numbers per indication, category interaction could not be tested. Third, regulator concerns were extracted from conclusions in EPARs. Despite the fact that these are standardized documents in terms of structure and subheadings, EPARs can differ in length, completeness and amount of detail in the benefit–risk discussion. Heterogeneity in the content of EPARs might have introduced some misclassification.

CONCLUDING REMARKS

In the space of ten years the marketing authorisation procedure of OMPs in Europe has evolved through trial and error, but with a clear vision on improving the health of patients with a rare disease. Our analysis of all marketing applications for OMPs in the EU aimed toward learning from ten years of regulation on OMPs has shown that demonstrating convincing evidence on the primary endpoint and the selection of a clinically relevant endpoint are crucial for success. However, other characteristics of the development plan such as an RCT as the pivotal study and sufficient learning (i.e. appropriate dose finding) have a significant role. Medical need, defined as lack of an alternative therapy for the disease, was also shown to be a relevant factor that colours the outcome of a benefit– risk assessment. These findings have a clear message to drug developers and regulators. Although orphan drugs have their inherent challenges in terms of development and assessment of benefit–risk, robust data on the real clinical benefit for the patients with a rare disease remain pivotal.

Certainly, measuring with different standards as recently suggested by Kesselheim et al. [29] is not in the long-term interest of these patients. By contrast, taking the high medical need for drugs that target rare diseases into account remains an important factor when building and evaluating OMP dossiers.

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2.4

LEVEL OF SCIENTIFIC KNOWLEDGE DRIVES DRUG DEVELOPMENT FOR EXCEPTIONALLY RARE METABOLIC DISEASES

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ABSTRACT

Background: Both FDA and EMA have systems in place for allocating so-called orphan designations for possibly promising medicinal products for treating rare diseases. We studied to what extent the level of scientific knowledge on exceptionally rare metabolic inherited diseases and their potential orphan medicinal products is associated with enterprises deciding to apply for an orphan designation**.**

Methods: All metabolic diseases with a genetic cause and prevalence of 9 patients per 1 million of the population or less were selected from the 'Orphanet database of Rare diseases'. The outcome of interest was the first application for an orphan designation for one of these rare diseases at FDA or EMA. The level of *publicly available* knowledge of the disease and drug candidate before a first orphan designation application was defined as whether a protein function corresponding with the pathologic gene was known, whether an appropriate animal study was identified for the disease, whether preclinical proof of principle was ascertained and the availability of data in men. Other determinants included in the study were metabolic disease class, the prevalence of the disease, prognosis and time of first description of the disease in the literature. Univariate relative risks (RRs) and 95% confidence intervals (CIs) of an orphan designation application were calculated for each of these determinants. In addition, a multivariate Cox regression analysis was conducted (Forward LR).

Results: In total, 166 rare metabolic genetic diseases were identified and included in the analysis. For only 42 (25%) of the diseases at least one orphan designation was applied for at either FDA or EMA before January 2012. The multivariate results identified preclinical proof of concept of a potential medicinal product as major knowledge related determinant associated with an orphan designation application (RRadj 5.0, 95% CI 2.3-11.1) and confirmed that prevalence of the disease is also associated with filing an application for an orphan designation (RRadj 2.5, 95%CI 1.3-4.9).

Conclusion: In only one out of four known exceptionally rare metabolic inherited diseases sponsors applied for an orphan designation at FDA or EMA. These applications seem to be associated with the prevalence of the rare disease and the level of available scientific knowledge on the proof of concept linking possible drug candidates to the disease of interest.

INTRODUCTION

Rare diseases are a complex and heterogeneous mosaic of an estimated 6000-8000 conditions. Several jurisdictions, including the US and the EU, recognized the need to stimulate the development of products for this group of diseases and have introduced specific legislation with a number of (economic) incentives (see Box 1) [1,2]. In the first 25 years of the Orphan Drug Act in the US 1892 products have been designated as orphan, and 326 products have been approved [5]. These 326 products target more than 200 rare diseases and represent a difference in the lives of millions of rare disease patients. In the EU, more than 850 orphan drug designations have been granted by the European Commission and more than 60 orphan medicinal products have received marketing authorisation [6].

The majority of the estimated 6000-8000 rare diseases has a prevalence of less than 10 patients per 1 million inhabitants (less than 5000 patients in the EU) [7]. The small number of patients and consequently small market size makes it even less attractive for the pharmaceutical industry to invest in the development of therapies for low prevalence rare diseases. Heemstra et al. showed that translation of rare disease research into an orphan drug discovery and development programme is more likely for a more prevalent rare disease than a less prevalent rare disease [8]. The latter was confirmed by Yin who reported that "the US Orphan Drug Act has led to a significant and sustained increase in new trials among more prevalent rare diseases, but not for less prevalent rare diseases"[9]. However, a recent overview by the FDA revealed that orphan medicinal products approved for low prevalence rare diseases are not uncommon [5]. An example of an authorised product to treat a low prevalence rare metabolic disease is idursulfase (Elaprase®), an enzyme replacement therapy to treat Hunter syndrome also known as mucopolysaccharidosis Type II [10]. Hunter syndrome is a rare genetic lysosomal storage disease characterized by the accumulation of glycosaminoglycans due to the deficiency of the enzyme iduronate-2-sulfatase. Life expectancy is extremely low with death occurring before adolescence due to serious cardiovascular and respiratory complications [11]. Idursulfase improves lung function and the walking ability of Hunter syndrome patients [10]. Apart from Elaprase®, other products on the market for low prevalence rare metabolic diseases are for example Orfadin® (Tyrosinemia type I) and Carbaglu® (N -acetylglutamate synthetase (NAGS) deficiency). Apparently, creating the right circumstances for orphan drug development of low prevalence rare disorders is feasible.

The question arises what drives the translation of rare disease research into orphan drug development in the area of low prevalence rare diseases. A sponsor of a potential orphan medicinal product has to submit to the regulatory authorities scientific evidence that confirms the rationale for the use of its medicinal product in the proposed orphan indication [1,12]. To establish the mechanism of action of

the medicinal product preclinical and/or clinical data 'are generally required' (see box 1) [1,3,4]. Heemstra et al. showed that disease-specific scientific output was a predictive factor for successful translation of rare disease research into an orphan drug development programme [8]. However, the authors did not differentiate between different research areas such as disease etiology and pathophysiology, availability of suitable animal models and/or (pre-)clinical proof of concept studies. Therefore, we studied to what extent disease characteristics as well as the level of publically available scientific knowledge on low prevalence rare metabolic diseases and its potential medicinal products is associated with a sponsor's decision to apply for an orphan designation at FDA or EMA. Considering that the majority of low prevalence rare diseases remain without therapy, increased knowledge of the underlying translational process will provide better input for novel approaches to improve orphan drug development.

METHODS

All metabolic diseases with a genetic cause and prevalence of less than 10 patients per 1 million of the population were extracted from the 'Orphanet database of Rare diseases' on 17 January 2012 [13]. The outcome of interest for this study was the first application for an orphan designation at the FDA or EMA. In case of multiple applications for an orphan designation for the same rare disease indication at either FDA and/or EMA, we selected the first application as a proxy for the intention to initiate the development of a drug for the rare disease leading to marketing authorisation [14,15].

Determinants that described the level of available scientific knowledge of the disease before the first orphan designation application were: (1) whether the protein function corresponding with the pathologic gene was identified (yes, no), (2) whether an appropriate animal model was available for the disease (yes, no). Scientific knowledge related to drug candidates was (3) preclinical proof of principle of any drug candidate either in vitro or in an animal model of the disease and (4) the availability of data in men. The availability of data in men was defined as any clinical testing of a drug candidate in patients with the rare disease, irrespective of the type of treatment (symptomatic or curative), the underlying study (a case report or a comparative study), whether the treatment was successful or not, and - in case of the diseases for which an orphan designation was available- irrespective whether the drug described was the drug of the orphan designation application.

Data about the protein involved in initiating the pathophysiological pathway and the availability of an appropriate animal model were identified from the OMIM database of genetic diseases [16]. Pubmed publications were the data source for the animal model (additional to OMIM), preclinical proof of concept and the availability of clinical data. All Pubmed publications for each disease were identified by Pubmed

Box 1. Orphan designation criteria and incentives at EMA and FDA

Regulatory agencies worldwide have recognized the need for the development of drugs for rare diseases and introduced incentives for the development of orphan medicinal products, such as free scientific advice, ten years of market exclusivity and financial advantages [1,2]. These benefits only apply to those medicinal products that receive an orphan designation by the regulatory authorities.

EMA orphan designation criteria define that a medicine should be (i) intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating disease, affecting a maximum of 500 in 1 million people in the EU. Besides, (ii) it must be unlikely that the revenue after marketing authorisation will cover the investments in its development. The designation is granted when (iii) no satisfactory treatment for the disease exists or when the new medicinal product is of significant benefit to the patients. In addition, (iv) an application for an orphan designation should explain the medical rationale of the medicinal product by means of the mechanism of action as far as it's known, and some preclinical or clinical date 'are generally' required by the EMA [3].

Similarly FDA regulation states that a request for orphan designation of a drug for a specified rare disease or condition should include that (i) The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year, and (ii) that for such a drug there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States and a statement as to whether the sponsor submitting the request is the real party in interest of the development and the intended or actual production and sales of the product, and (iii) a description of the rare disease or condition for which the drug is being or will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed, accompanied by a description of the drug and a discussion of the scientific rationale for the use of the drug for the rare disease, including all data from nonclinical laboratory studies, clinical investigations, and other relevant data that are available to the sponsor, whether positive, negative, or inconclusive. Copies of pertinent unpublished and published papers are also required [4].

search strings, taking into account all available synonyms for the disease and the date of the orphan designation application (for diseases with an orphan designation) or the cut-off date 01-01-2012 (for the diseases without orphan designation) [17]. The availability of clinical studies was verified at clinicaltrial.gov [18].

Other determinants that were studied were the metabolic disease class according to the Orphanet classification, the prevalence of the disease (<1 per 1 million of population or 1-9 per 1 million of population) and the prognosis of the disease (fatal or non-fatal). Besides, the period in which the disease was first described (before 1977 or starting from 1977) was assessed to study the association with time. The disease class, prognosis and prevalence were all collected from Orphanet, as indicated in July 2012 [19]. In case of multiple prognoses depending on disease severity, the worst prognosis was included. The year in which the disease was first described in the scientific literature was derived from OMIM [16]. For ten diseases OMIM did not mention the year the disease was first described, and consequently another public source of information (Pubmed and other public references) was used to retrieve the data.

Univariate relative risks (RRs) of applying for an orphan designation and 95% confidence intervals (CIs) were calculated for each of these determinants. In addition, a multivariate Cox regression analysis was conducted (Forward LR) to obtain adjusted relative risks (RRadj). The most recent year that a rare inherited metabolic disease with an orphan designation was first described was 1997. Absence of an orphan designation for diseases first described after 1997 may be due to insufficient time to translate fundamental disease knowledge into sufficient (pre-)clinical data required for the application of an orphan designation. Therefore, a sensitivity analysis was performed in which all diseases that were first described after 1997 were excluded.

RESULTS

In total 166 metabolic genetic diseases with a prevalence of 9 per 1 million patients or less were identified from the Orphanet database of Rare diseases. Table 1 provides the Orphanet classification of these diseases [19]. This table shows that three metabolic disease subclasses, i.e. lysosomal diseases (subclass of Metabolic diseases involving complex molecules), protein metabolism disorders (subclass of Metabolic Intoxication diseases) and mitochondrial disorders (subclass of Energy metabolism disorders) represented more than half of the study diseases (N=91). The other inherited metabolic diseases were a heterogenous group of disorders.

For 42 (25%) of the diseases at least one orphan designation was applied for at either FDA or EMA, whereas for the remaining 124 (75%) diseases such an orphan designation application was not submitted before January 2012. Figure 1 depicts the applications for the 42 orphan designations over time. After 2000 there was

Table 1. Classification of exceptionally rare diseases included in the present study according to Orphanet

General classification	Total (N=166)	Disease group classification	Total
Metabolic disease involving complex molecules	62	Lysosomal diseases	31 (50%)
		Purine or pyrimidine metabolism disorder	10 (16%)
		Sterol metabolism disorder	8 (13%)
		Metabolic neurotransmission anomaly	5 (8%)
		Peroxisomal disease	4 (6%)
		Metal transport or utilisation disorder	3 (5%)
		Protein glycosylation disorder	1 (2%)
Metabolic intoxication disease	36	Amino or protein metabolism disorder	34 (94%)
		Hyperoxaluria	1 (3%)
		Methylmalonic aciduria - microcephaly - cataract	1 (3%)
Energy metabolism disorder	45	Mitochondrial disorder	26 (58%)
		Fatty acid oxidation or ketogenesis disorder	7 (9%)
		Creatine biosynthesis disorder	2 (4%)
		Ketolysis disorder	2 (4%)
		Enolase deficiency	1 (2%)
		Gluconeogenesis disorder	1 (2%)
		Hemolytic anemia due to glucophosphate isomerase deficiency	1 (2%)
		Phosphoglycerate kinase 1 deficiency	1 (2%)
		Pyruvate metabolism disorder	1 (2%)
		Thiamine-responsive megaloblastic anemia syndrome	1 (2%)
		Tricarboxylic acid cycle disorder	1 (2%)
		Triose phosphate-isomerase deficiency	1 (2%)
Carbohydrate metabolism disorder	12	Glycogen storage disease	7 (58%)
		Glucose transport disorder	4 (33%)
		Familial hyperinsulinism	1 (8%)
Other metabolic disease	11	Metabolic disease associated with a progressive neurological disorder	6 (55%)
		Miscellanous metabolic disease with mostly hepatic presentation	4 (36%)
		Hereditary hypercarotenemia and vitamin A deficiency	1 (9%)

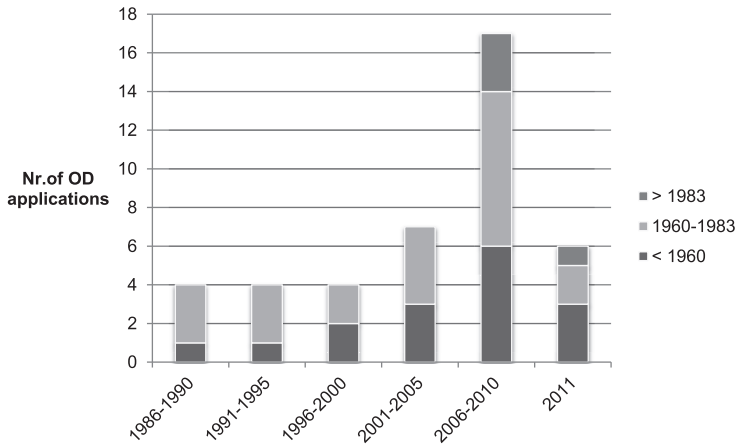

Figure 1. Number of first applications for an orphan designation at FDA or EMA over time and according to the period in which the exceptionally rare metabolic inherited diseases were first described

an increase in the number of orphan designation applications which became even larger from 2006 onwards. The figure also shows when low prevalence-rare metabolic diseases with an orphan designation were first described in the scientific literature. Diseases with a long history, first described in the scientific literature before 1960, were still well represented among the orphan designation applications in 2011. First orphan designation applications for relatively new diseases, described after 1983, were submitted from 2006 onwards.

Table 2 demonstrates the univariate relative risks (RR) for submitting an application for an orphan designation at FDA or EMA for different disease characteristics and type of publically available scientific knowledge. Considering the level of scientific knowledge preclinical proof of concept of drug candidates had the largest univariate RR for an orphan designation application (RR 6.0 (95%CI 3.0-12.0)). The availability of data in men (RR 3.3 (95%CI 1.7-6.6)) and the availability of an animal model (RR 3.0 (95%CI 1.5-6.0)) also demonstrated a positive association with the likelihood that a sponsor had filed an orphan designation application. A similar, but not significant, association was found for the identification of the protein(s) linked to the gene suspected to be the underlying cause of the disease (RR 26.1 (95%CI 0.7-966)). For none of the 26 diseases for which the protein function was not yet fully identified an orphan designation application was submitted. Ten out of these 26 diseases were mitochondrial diseases (subclass of energy metabolism disorders), which suggests that for this disease group the pathophysiological pathway requires further elucidation.

The metabolic diseases involving complex molecules and the metabolic intoxication diseases were similarly associated with orphan designation

applications, whereas the energy and carbohydrate metabolism disorders were less likely to be included in an orphan designation application (RR=0.2 (95%CI 0.1-0.6) as compared to metabolic diseases involving complex molecules). The positive associations with an orphan designation application for metabolic diseases involving complex molecules and metabolic intoxication diseases were mainly driven by lysosomal (storage) diseases and amino or protein metabolism

Table 2. Univariate relative risks of an orphan designation application at EMA or FDA for different disease characteristics and for publicly available scientific knowledge

Disease characteristics	Total N=166	OD application N=42	No OD application N=124	Univariate RR (95%CI)
1. Metabolic disease class				
Metabolic disease involving complex molecules	62	23 (37%)	39 (63%)	Ref
Metabolic intoxication disease	36	14 (38%)	22 (61%)	1.1 (0.5-2.0)
Energy metabolism disorder	45	3 (7%)	42 (93%)	0.2 (0.1-0.6)
Carbohydrate metabolism disorder	12	1 (8%)	11 (92%)	0.2 (0.03-1.7)
Other metabolic disease	11	1 (9%)	10 (91%)	0.3 (0.03-1.8)
2. First description of the disease				
≤ 1977	98	36 (37%)	62 (63%)	4.2 (1.8-9.9)
> 1977	68	6 (9%)	62 (91%)	Ref
3. Prevalence				
1-9/1.000.000	38	25 (66%)	13 (34%)	5.0 (2.7-9.2)
<1/1.000.000	128	17 (13%)	111 (87%)	Ref
4. Prognosis				
Fatal despite treatment	96	34 (35%)	62 (65%)	2.7 (1.3-5.8)
Non fatal	61	8 (13%)	53 (87%)	Ref
Unknown	9	0 (0%)	9 (100%)	NA
Scientific knowledge related variables				
5. Protein function identified?				
Yes	140	42 (30%)	98 (70%)	26.1 (0.7-966)
No	26	0 (0%)	26 (100%)	Ref
6. Animal model available?				
Yes	87	33 (38%)	54 (62%)	3.0 (1.5-6.0)
No	79	9 (11%)	70 (89%)	Ref
7. Preclinical proof of concept?				
Yes	53	31 (58%)	22 (42%)	6.0 (3.0-12.0)
No	113	11 (10%)	102 (90%)	Ref
8. In men data available?				
Yes	76	31 (40%)	45 (59%)	3.3 (1.7-6.6)
No	90	11 (12%	79 (88%)	Ref

disorders, respectively. For 17 of 31 (55%) lysosomal diseases and for 13 of 34 (38%) of amino or protein metabolism disorders an orphan designation application was submitted. Finally, a relatively high prevalence (1-9 per 1 million), poor disease prognosis and first description of the disease ≤1977 were all positively associated with the application for an orphan designation (Table 2).

The multivariate analysis (Table 3) confirmed a strong association between the preclinical proof of concept of potential medicinal products and applying for an orphan designation (RRadj 3.9 95%CI 1.9-8.3) and also proved that prevalence of the disease is associated with an orphan designation application (RRadj2.8 95%CI 1.4-5.4). An additional sensitivity analysis that excluded all diseases that were first described after 1997 demonstrated only small differences in (adjusted) RRs (data not shown).

Table 3. Multivariate relative risks of an application for an orphan designation at EMA and/or FDA for level of available knowledge and different disease characteristics (Forward LR)

Variable	Univariate RR (95%CI)	Multivariate RR (95%CI)
Prevalence		
1-9/1.000.000	5.0 (2.7-9.2)	2.8 (1.4-5.4)
<1/1.000.000	Ref	Ref
Preclinical proof of concept?		
Yes	7.4 (3.5-15.5)	3.9 (1.9-8.3)
No	Ref	Ref

DISCUSSION

The majority of low prevalence rare diseases remain without therapy, the development of medicines for such diseases is considered an unmet medical need. This study demonstrates the importance of mature scientific knowledge in the public domain for orphan drug development. The preclinical proof of concept of a drug candidate and disease prevalence were identified as important factors driving sponsors to apply for an orphan designation for a drug candidate. The orphan designation application rather than the approval was taken as study outcome, since we were interested in the level of disease knowledge and disease characteristics around the start of the development of a drug for low prevalence rare metabolic diseases. In practice all but one designation applications were approved. Thus, our study also demonstrates the association between the level of knowledge of the disease and/or drug and granting orphan designations.

Knowledge of the disease

Our results demonstrate that for the majority of low prevalence rare metabolic diseases included in the study the causative gene and function of the relating protein

was known and that the diseases for which this knowledge was lacking belonged to similar metabolic disease subclasses (e.g. mitochondrial diseases). Although basic knowledge of the disease is generally considered a prerequisite for further (pre)clinical drug development in general [20,21], the elucidation of the protein function was not identified as an independent driver for sponsors to apply for an orphan designation. A total of 98 (70%) low prevalence rare genetic metabolic diseases with an elucidated protein function did not have an orphan designation. Apparently, additional and more important reasons exist that explain the observed lack of orphan drug development for low prevalence rare metabolic diseases. First, elucidation of the protein function is only one component of the elucidation of the complete pathophysiological pathway from gene (translation) to clinical symptoms and the identification of drugable targets. Secondly, even if extensive disease knowledge is available this does not guarantee the successful development of an orphan drug. For example, cystic fibrosis, an inherited chronic disease that affects 70,000 people worldwide, has been studied extensively and the pathophysiology is well known. However, the first medicine (ivacaftor; Kalydeco®) to treat the underlying cause of cystic fibrosis was only approved recently [22]. Still, pathophysiological knowledge of one disease within a disease subclass may stimulate or act as catalyst for disease research for other diseases within the same subclass. For the mucopolysaccharidosis diseases (5 out of 7 with an orphan designation) the underlying pathophysiology is relatively well understood: a lack of specific lysosomal enzymes leads to the degradation of glycosaminoglycans or mucopolysaccharides. The accumulation of partially degraded glycosaminoglycans causes interference with cell, tissue, and organ function causing severe clinical symptoms [11]. Just like in the example of idursulfase to treat Hunter syndrome or mucopolysaccharidosis Type II, enzyme replacement therapies have been developed as a response to enzyme deficiencies in several other mucopolysaccharidosis diseases. Similarly we found for the amino or protein metabolism disorders that all five urea cycle disorders, leading to ammonia detoxification, received an orphan designation. The urea cycle is well studied and several treatment strategies have been developed such as drug suppletion therapies (arginine therapy) or a drugable target such as circulating nitrogen (designated product glyceryl tri-(4-phenylbutyrate). Rare diseases may also share (parts of) the same biochemical pathway, and consequently an orphan drug may be beneficial for more than one disease. Nitisinone, a product approved for tyrosinemia type I (Orfadin®) may also potentially have a beneficial clinical effect for patients suffering from alkaptonuria (AKU). The AKU society, a patient association, is currently collaborating with academia and industry to study the potential clinical effect of nitisinone for AKU [23].

Knowledge of the drug

Preclinical proof of concept of drug candidates was identified as the major type of knowledge needed for an orphan designation. According to our definition,

preclinical proof of concept was considered achieved in case of a promising result in an *in vitro* or animal study with *any* drug candidate studied in the target population, irrespective of which drug was included in the orphan designation application. To obtain an orphan designation a sponsor has to provide (pre-) clinical data that confirms the medical plausibility of the intended drug candidate [3.4]. Yet, for 40% of the metabolic diseases for which proof of concept was demonstrated in a preclinical study, an orphan designation was not applied for. A possible explanation related to low prevalence is the difficulties a sponsor may face during the subsequent clinical development because of the extremely small patient populations available for clinical research. Kakkis et al. recently identified 15 inherited exceptionally rare metabolic diseases with a relevant corresponding animal model, a treatment with a known mode of action and a clinically relevant treatment effect in animals but that had stalled in clinical development. They demonstrated the substantial potential benefit that surrogate endpoints could offer to clinical drug development. The acceptance of surrogate endpoints in clinical development of these promising treatments would reduce the number of patients needed for approval and may also persuade sponsors to apply for an orphan designation [24].

In contrast to preclinical proof of concept, clinical testing (data in men) was only associated with an application for an orphan designation in the univariate analysis. This may be because of the way 'data in men' were defined: as *any* treatment described in the scientific literature, (i) either successful or not, (ii) either a case report or a small trial and (iii) either a symptomatic or a curative treatment. The thought behind this definition was that (ad i) any drug developer could learn from published data about any drug treatment for the disease, (ad ii) that requiring a clinical trial was not realistic for low prevalence-rare diseases, and (ad iii) that orphan designations can be applied for symptomatic treatments as well as curative treatments.

Other drivers for an orphan designation application

The dataset consisted of low prevalence rare metabolic diseases (<10/million), the majority (N=128; 77%) of the diseases had a prevalence of less than 1 patient per million inhabitants. Our study showed that diseases with a prevalence of 1-9 per million had a higher chance of an orphan designation application than diseases with a prevalence of less than 1 per million. Our finding that prevalence is an important factor that drives sponsors to apply for an orphan designation is in line with previous results by Heemstra et al [8]. For some diseases less than 20 cases have been described worldwide. Therefore, a likely explanation for this finding is that a disease prevalence of less than 1 per million is considered too small for the pharmaceutical industry to invest in the development of a therapy, despite the availability of considerable disease knowledge, incentives offered by

the Orphan Regulation and opportunities for conditional marketing approval and approval under exceptional circumstances in the EU [25,26]. The latter is best illustrated by the group of gamma-glutamyl cycle disorders (N=4, subclass of protein metabolism disorders), involved with the synthesis and degradation of glutathione. At the time of our analysis only about ten patients were described. Despite elucidation of the gamma-glutamyl cycle, the genes and proteins involved and knock-out mouse models being available no orphan designations have been applied for by sponsors at the time of our analysis.

Another explanation may be that for some diseases pharmacological treatment may not be necessary, because either the symptoms are not severe (e.g. hereditary hypercarotenemia and vitamin A deficiency) or because other non-pharmacological treatments or life style changes are sufficient, such as diet or exercise restrictions (e.g. for glucose-galactose malabsorption) [27]. Third, medicinal products that are already approved to the market can be prescribed off-label to treat symptoms, e.g. anti-epileptics to treat convulsions as a consequence of progressive neuronal damage of McLeod neuroacanthocytosis syndrome [28] or vitamin B12 injections for cobalamine deficiency disorders such as Gräsbeck-Imerslund disease [29]. For these congenital disorders the focus may be on care rather than on cure. Finally, some metabolic diseases may be well treated by suppletion of amino acids such as arginine or carnitine (for some types of organic aciduria) or carbohydrates such as glucose (for ketolysis disorders) [19].

Limitations and further research

The methodology of our study has some limitations, mainly related to potential discrepancies between the availability of knowledge in scientific literature and the knowledge referred to in the applications for orphan designation. We studied whether the knowledge as *available in scientific literature* was an incentive to initiate further research to the disease and drug candidates. However, an orphan designation application can also be based on unpublished studies, e.g. a preclinical proof of concept study of the drug candidate only known to the company or institution filing the application, but this information is not available in the public domain and could therefore not be included in the present study.

A limitation of this study is that the results do not identify whether the drug described in a publication of preclinical proof of concept or in a case report was similar to the drug included in the orphan designation application. This approach was needed to study both rare diseases with and without an application for an orphan designation in a similar way. This limitation could be considered acceptable, with the assumption that drug developers can learn from any experience with drug candidates targeting low prevalence rare diseases. Finally, the amount and quality of the scientific output about a disease was not taken into account. Our study demonstrated that for diseases first described before 1977 more orphan

designations have been requested than for diseases that were first described after 1977. Both the amount and quality of the scientific output as well as the repetition of results may play a role here and could be the subject of a follow-up study.

Overall conclusion and policy implications

The majority of low prevalence rare diseases remain without therapy. This study shows that for low prevalence rare metabolic diseases preclinical proof of concept of drug candidates and disease prevalence play an important role in the translation of disease knowledge into an orphan drug development programme. To expand drug development for low prevalence rare diseases we recommend that future incentives should be aimed at stimulating fundamental research to elucidate the pathophysiology of the disease as well as the identification of drugable targets. Although not exclusively, the latter represents an important incentive for public or private parties to test potential drug candidates in a suitable preclinical model. If found promising, another important hurdle has been taken towards the ultimate goal: a therapy for a patient suffering from a (low prevalence) rare disease.

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3

EVALUATING SCIENTIFIC ADVICE

3.1

REGULATORY SCIENTIFIC ADVICE IN DRUG DEVELOPMENT: DOES COMPANY SIZE MAKE A DIFFERENCE?

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ABSTRACT

Purpose: To assess whether the content of Scientific Advice (SA) questions addressed to a national drug regulatory agency is associated with company size. This may help to increase understanding about the knowledge, strategic, and regulatory gaps companies face during drug development.

Methodology: A cross-sectional analysis was performed of SA provided by the Dutch Medicines Evaluation Board (MEB) in 2006–2008. Definition of company size was based on ranking by total revenues (Scrip's Pharmaceutical Company League Tables 2008). The content of each SA question was scored according to predefined domains (quality, nonclinical, clinical, regulatory, and product information), their subdomains (e.g., efficacy), and a selection of additional content variables (e.g., endpoints, choice of active comparator).

Results: In total, 201 SA documents including 1,087 questions could be identified. Small, medium-sized, and large companies asked for SA 110 (54.7%), 40 (19.9%), and 51 (25.4%) times, respectively. Clinical questions were asked most often (65.9%), mainly including efficacy (33.2%) and safety questions (24.0%). The most frequent topics were overall efficacy and safety strategy. Small companies asked quality and nonclinical questions more often ($P<0.001$) and clinical questions less frequently than large companies ($P=0.004$). Small companies asked significantly more clinical questions about pharmacokinetics, including bioequivalence, than medium-sized and large companies ($P<0.001$).

Conclusion: The array of topics addressed in SA provides an interesting outlook on what industry considers to be still unresolved in drug development and worthwhile to discuss with regulators. Company size is associated with the content of SA questions. MEB advice accommodates both innovative and non-innovative drug development.

INTRODUCTION

Marketing authorisation of a new medicinal product is a critical step in giving the public access to innovative therapies that are needed to fill current pharmaceutical gaps and unmet medical needs. Despite the increasing number of applications for marketing authorisation in Europe, the proportion of applications with a negative decision remains relatively high, around 25–30%, and was even 40% for new active substances with a resolved outcome in 2009 [1,2]. There is increasing concern about the obvious gap between the output of drug development and registration strategies applied by companies, and EU regulatory expectations [3,4]. Industry response to this development indicates that improved communication with regulatory authorities during drug development is needed [5]. Additional regulatory requirements in recent years have complicated the authorisation procedure and have made innovative drug development more costly. Furthermore, with complex biologicals, advanced therapies, and personalized medicines becoming more important, the need for more specific guidance in drug development has increased [6,7].

Before and during the marketing authorisation procedure for a medicinal product, pharmaceutical companies have various opportunities to discuss critical issues in the drug development process with regulators. A continuous and ongoing regulatory dialogue between pharmaceutical industry and regulatory authorities has often been recommended as a strategy to support innovative drug development in an efficient and tailored way [3,5,8–10]. A relevant part of scientific regulatory dialogue is so-called Scientific Advice (SA), the opportunity for (early) communication between a company and a regulatory authority of quality, nonclinical, and various clinical aspects (e.g., study design, choice of endpoint, indication) of drug development. In Europe an increasing proportion of market application authorisations are preceded by SA; 47% of all applications in 2007 received SA and in 2008 this percentage was 56% [1].

An applicant for SA can be a pharmaceutical company or scientists developing a product. Applicants are encouraged to seek regulatory SA as many times as necessary, but industry and authorities are not obliged to adhere to the advice received or committed to accept any result of a SA procedure [11]. In Europe, SA can either be sought from the European Medicines Agency (EMA) or from one or more of the national regulatory agencies. National regulatory agencies provide SA either as a response to national SA requests or as an answer to European SA requests, outsourced by the EMA Scientific Advice Working Party (SAWP) to one or two of its member countries according to expertise. A recent study looking at SA provided by EMA demonstrated that the level of industry adherence to SA and company size were both predictors of a positive outcome in a marketing authorisation procedure. The study also showed that among companies submitting a marketing application to EMA, large companies requested SA most frequently and were more adherent to the advice than medium-sized and small companies [9].

Considering that adherence to SA is associated with a positive outcome in a marketing authorisation procedure and that variability in adherence to SA exists among companies, the question arises whether company size matters when looking at the type of SA that pharmaceutical companies are seeking. Answering this question may help to learn more about the knowledge, strategic and regulatory gaps companies face during drug development and how these differ among the various types of enterprises.

3.1

METHODS

Study design and scientific advice characteristics

A cross-sectional analysis was performed of national SA provided by the Dutch Medicines Evaluation Board (MEB) in the years 2006–2008. SA documents were retrieved from the MEB SA Database. Requests for SA that were rejected by the MEB for reasons of lack of expertise or previously received EMA advice were excluded. In this study, individual requests for SA were considered, so follow-up SAs for a similar medicinal product were included.

Products for which SA was given in the study period were categorized according to anatomical main group of the ATC classification [12]. In case an ATC classification was missing, the anatomical main group was assessed based on the intended indication of the product. Products were also categorized as new chemical substance (NCS; chemical substance not previously approved), generic (a product with identical qualitative and quantitative composition and similar pharmaceutical form as original product), biologicals (defined as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant proteins), and new application of existing drugs (previously approved chemical substances for which a new indication, dosage form, or other variation was being developed, in such a way that there was a need for additional efficacy and safety studies).

Company size was defined as small, medium-sized, and large, based on ranking by total revenue as reported in Scrip's Pharmaceutical Company League Tables 2008 [13]. Companies were defined as large if ranked 1–20, mediumsized if ranked 21–150, and small if the company was not on the ranking list. This definition was in line with a previous study on SA [9]. For each SA, we evaluated whether previous advice for the same product had been requested at the MEB, whether parallel advice had been sought at another national regulatory agency, or both.

Data collection: characteristics of questions

Each SA submission consisted of a variable number of questions asked by companies. All questions in 2006, 2007, and 2008 were collected and analyzed in a standardized fashion. Each question, being the unit of analysis, was scored separately according to variables at three different levels: domains, subdomains,

and content variables (Figure 1). At the first level, the question content was analyzed according to the following domains: quality, nonclinical, clinical, regulatory, and product information. Scoring more than one domain was allowed, for example, when a clinical issue and a product information issue were discussed in the same question.

Secondly, subdomains were formulated and scored for questions in the nonclinical and clinical domains. The subdomains of the nonclinical domain were pharmacodynamics, pharmacokinetics, and toxicology. For the clinical domain, subdivisions were pharmacodynamics (including dose finding studies), pharmacokinetics (including bioequivalence studies), efficacy, or safety. Again, scoring more than one subdomain was allowed.

Additionally, at the third and most detailed level, each question was scored by a selection of content variables, e.g., primary endpoint, choice of active comparator, trial duration, and overall efficacy program. The content variables were selected based on general regulatory requirements of the drug development process and existing EMA regulatory guidelines. In this third step, a distinction was made between specific and strategic questions. Strategic questions were defined as questions in which general feedback was asked about, e.g. the overall quality program or the clinical efficacy program. An example of a strategic question was: "Does the MEB agree that the results of the clinical efficacy program will be sufficient to achieve market approval of the product for the specific indication?". Specific questions were defined as being related to specific topics of the

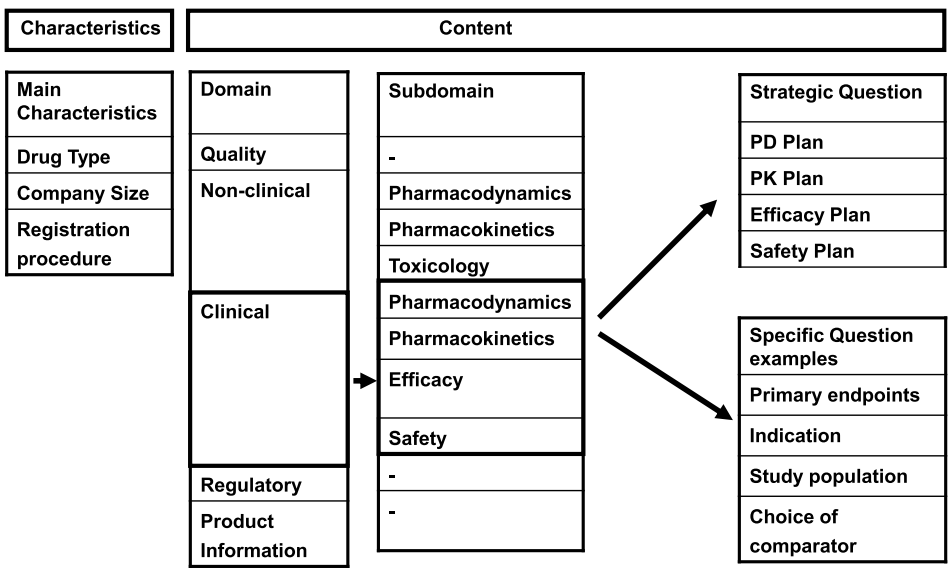

Figure 1. Scoring method for SA questions

development plan for a particular study. An example of a specific question was: "Does the MEB agree with the chosen primary endpoints for this indication?".

Data analysis

Associations between the type of SA questions and company size were assessed by Pearson's chi-squared analysis. P-values were calculated for each variable. Differences in average number of questions were assessed by a one way ANOVA test.

RESULTS

During the study period, the MEB provided SA 214 times. Thirteen advice documents were missing (four and nine documents in 2006 and 2007, respectively). In total, 201 SA documents, including 1,087 questions, could be identified. SA was provided for 187 products, with 117 companies (80 small, 21 medium-sized, and 16 large companies) receiving SA in the study period. The general SA characteristics are given in Table 1.

SA was most frequently given for nervous system drugs (24.9%), but for a variety of other therapeutic areas SA was provided as well. More than 60% of SA was given for generics and new applications of existing drugs. Small, medium-sized, and large companies requested SA 110 (54.7%), 40 (19.9%), and 51 (25.4%) times respectively. More than 40% of the companies seeking SA had previously received advice for the same drug at the MEB or another national agency.

On average five questions per SA submission were asked (Table 2). Clinical questions were asked most frequently [716 times (65.9%)]. Within the clinical subdomain, efficacy and safety questions were most frequently asked [361 (33.2%) and 261 (24.0%) times, respectively].

Small companies asked significantly fewer questions per SA compared to medium-sized and large companies ($P < 0.001$). Large and medium-sized companies asked significantly more SA questions about new chemical entities than small companies did ($P<0.001$). Small companies asked 70% of SA questions about drug development of generics and new applications of existing drugs. These small companies were a diverse representation of companies, including generic companies (20%), innovative pharmaceutical or biotech companies (40%), and other companies mainly consisting of medical technology companies, those working on new applications of drugs, and consultants. Medium-sized companies, about 85% of which were innovative pharmaceutical or biotechnology companies, most frequently asked SA questions related to the development of biologicals ($P<0.001$).

With regard to domain, the majority of questions asked by companies were about clinical development issues, while for small companies quality and nonclinical questions were more common. One out of five SA questions was

Table 1. Baseline Characteristics of scientific advice

Variables	Advice (N=201) (%)
Year	
2006	77 (38.3%)
2007	47 (23.4%)
2008	77 (38.3%)
ATC-Code	
A/Alimentary tract & Metabolism	12 (6.0%)
B/ Blood& Blood forming organs	16 (8.0%)
C/ Cardiovascular system	34 (16.9%)
G/ Genito-Urinary system & sex hormones	15 (7.5%)
J/ Antiinfectives	13 (6.5%)
L/ Antineoplastic & Immunomodulating prod.	29 (14.4%)
N/ Nervous system	50 (24.9%)
Other	32 (15.9%)
Product Type EMEA	
NCE	43 (21.4%)
Generic	59 (29.4%)
New application of existing drug	64 (31.8%)
Biological (including biosimilars)	34 (16.9%)
Other (General advice)	1 (0.5%)
Orphan drugs	
Orphan drug	3 (1.5%)
Non-orphan drug	198 (98.5%)
Company Size	
Small	110 (54.7%)
Medium-sized	40 (19.9%)
Large	51 (25.4%)
Type of Registration Procedure	
Central	48 (23.9%)
Decentral	42 (20.9%)
Mutual Recognition Procedure	19 (9.5%)
National	11 (5.5%)
To be decided	75 (37.3%)
Missing	6 (3.0%)
Previous/ Parallel advice	
No previous	102 (50.7%)
At MEB	17 (8.5%)
At Other agencies	62 (30.8%)
At MEB & other agencies	9 (4.5%)
Missing	11 (5.5%)

on regulatory issues, with no difference among types of companies. Within the clinical domain, small companies asked significantly more often about pharmacokinetics,including bioequivalence, than medium-sized and large companies. These companies posed efficacy questions less often than large

Table 2. Company size in relation to characteristics and content of SA questions

Questions N=1087	Small Pharma	Medium Pharma	Large Pharma	Total	P-values
Total No. of Questions	431 (39.7%)	310 (28.5%)	346 (31.8%)	1087(100%)	<0.001
Average No. of Questions	3.9 (1-18)	7.8 (1-27)	6.8 (1-17)	5.4 (1-27)	<0.001
Sd	3.2	5.7	3.9	4.3	
ATC-Code					
A/Alimentary tract & Metabolism	29 (6.7%)	0 (0.0%)	41 (11.8%)	70 (6.4%)	<0.001
B/ Blood & Blood form. organs	26 (6.0%)	66 (21.3%)	7 (2.0%)	99 (9.1%)	<0.001
C/ Cardiovascular system	39 (9.0%)	63 (20.3%)	69 (19.9%)	171 (15.7%)	<0.001
G/ Genito-Urinary system & sex hormones	6 (1.4%)	48 (15.5%)	60 (17.3%)	114 (10.5%)	<0.001
J/ Antiinfectives	40 (9.3%)	15 (4.8%)	8 (2.3%)	63 (5.8%)	<0.001
L/ Antineoplastic & Immunomodulating products	58 (13.5%)	30 (9.7%)	75 (21.7%)	163 (15.0%)	<0.001
N/ Nervous system	114 (26.5%)	80 (25.9%)	58 (16.8%)	252 (23.2%)	0.003
Other	119 (27.6%)	8 (2.6%)	28 (8.1%)	155 (14.2%)	<0.001
Product Type EMEA					
NCE	47 (10.9%)	89 (28.7%)	173 (50.0%)	309 (28.4%)	<0.001
Generic	125 (29.0%)	17 (5.5%)	31 (9.0%)	173 (15.9%)	<0.001
New application	178 (41.2%)	106 (34.2%)	101 (29.2%)	385 (35.4%)	0.002
Biological (incl.biosimilars)	80 (18.6%)	98 (31.6%)	41 (11.8%)	219 (20.1%)	<0.001
Other (General advice)	1 (0.2%)	0	0	1 (0.1%)	0.46
Previous/parallel advice					
No previous	233 (54.1%)	90 (29.0%)	98 (28.3%)	421 (38.7%)	<0.001
At MEB	9 (2.1%)	38 (12.3%)	64 (18.5%)	111 (10.2%)	<0.001
At other agencies	161 (37.4%)	154 (49.7%)	134 (38.7%)	449 (41.3%)	0.002
At MEB & other agencies	6 (1.4%)	11 (3.5%)	32 (9.2%)	49 (4.5%)	<0.001
Missing	22 (5.1%)	17 (5.5%)	18 (5.2%)	57 (5.2%)	0.973
Domain					
Quality	43 (10.0%)	26 (8.4%)	5 (1.4%)	74 (6.8%)	<0.001
Non-Clinical	69 (16.0%)	22 (7.1%)	19 (5.5%)	110 (10.1%)	<0.001
Clinical	272 (63.1%)	192 (61.9%)	252 (72.8%)	716 (65.9%)	0.004
Regulatory	86 (20.0%)	59 (19.0%)	60 (17.3%)	205 (18.9%)	0.649
Product Information	11 (2.6%)	22 (7.1%)	22 (6.4%)	55 (5.1%)	0.009
Clinical Subdomain					
Pharmacodynamics	26 (6.0%)	13 (4.2%)	27 (7.8%)	66 (6.1%)	0.154
Pharmacokinetics (incl.BE)	123 (28.5%)	30 (9.7%)	41 (11.9%)	194 (17.8%)	<0.001
Efficacy	105 (24.4%)	101 (32.6%)	155 (44.8%)	361 (33.2%)	<0.001
Safety	97 (22.5%)	78 (25.2%)	86 (24.9%)	261 (24.0%)	0.639
Type of Questions					
Strategic Questions	93 (21.6%)	64 (20.6%)	65 (18.8%)	222 (20.4%)	0.627

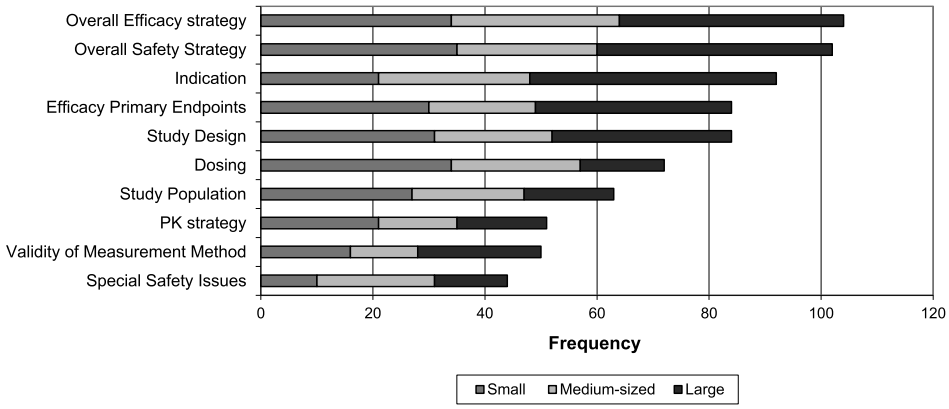

Figure 2. Top ten Most frequently asked topics according to size of firm

companies (24.4 vs. 44.8%, P<0.001). The proportion of safety and strategic questions was not associated with company size.

In Figure 2, the overall top ten of most frequently addressed topics on the most detailed third level of variables is given, showing a strong preference for clinical topics. Overall, the most frequently asked questions were about overall efficacy strategy (9.6%) and safety strategy (9.1%). In addition, strategy questions about the clinical pharmacokinetic program were in the top ten. Indication, primary endpoints, dosing, and study population were examples of popular specific topics. More details of the ten most frequently asked topics are given in Table 3.

DISCUSSION

One of the main findings in this study was that SA provided by a national authority is indeed different, both quantitatively and in terms of kind of questions, when looking at company size. Our content analysis of SA demonstrates that the majority of questions raised by companies, particularly the large ones, were about clinical drug development. Small companies gave more attention to quality and nonclinical issues than large companies.

The array of topics addressed in SA provides an interesting outlook, given all the limitations caused by strategic behavior of companies and selective acceptance of SA by regulators, on what industry considers to be still unresolved in drug development and worthwhile to discuss with regulators.

Regnstrom et al. emphasized the importance of adherence to SA for a successful marketing approval [9]. The question arises whether our findings of companies' priorities in drug development are in line with the most often occurring major objections or factors for approval failure. A 2002 study with EMA data found that major objections

Table 3. The top ten most frequently asked topics and example questions

Topic	Definition	Question example
Overall Efficacy Strategy	Questions related to the overall clinical study program in order to prove efficacy of a drug.	*Does the MEB think the proposed efficacy program is appropriate for a marketing authorisation?*
Overall Safety Strategy	Questions related to the overall clinical study program in order to prove safety of a drug.	*Does the MEB think the proposed safety program is appropriate for a marketing authorisation?*
Indication	Questions related to the definition/wording of indication and the appropriateness of the suggested indication.	*Does the Agency agree that "Treatment of symptoms associated with interstitial cystitis / painful bladder syndrome including bladder pain, urinary urgency and frequency" is a registrable indication?*
Primary efficacy endpoints	Questions related to the appropriateness of the primary endpoint selected to prove efficacy of a drug.	*Does MEB agree that the primary endpoint of overall survival supported by the secondary endpoints of PFS, tumour response rate and duration of response is appropriate to support registration of drug X in first line in advanced non-small cell lung cancer?*
Study design	Questions related to the multiple methodological issues of one specific randomized clinical study.	*The recently initiated Phase II-III clinical trial has the following characteristics:"……" Is this trial design acceptable for definitive confirmation of the clinical benefit and of an acceptable safety profile of drug X?*
Dosing	Questions related to the appropriateness of the doses chosen for a clinical study.	*The scheme for the individual dosing is an 10 mg/kg loading dose followed by a 5 mg/kg maintenance dose. The company considers increasing the maintenance dose if no adverse effects are seen. Does the MEB agree to the proposed dosing regimen?*
Study population	Questions related to the appropriateness of the inclusion and exclusion criteria used for patient selection in a study.	*Does the Agency concur with the definition of the patient population to be studied in the phase 3 randomized trial to support regular approval in their respective proposed indications?*
Pharmacokinetic strategy	Questions related to the appropriateness of the complete clinical pharmacokinetics study program	*Does the MEB agree with the proposed clinical pharmacokinetic program?*
Validity of measurement method	Questions related to the application of specific measurement methods (e.g. symptom scores) to assess clinical endpoints.	*The MD Anderson Symptom Inventory (MDASI) will be used in the randomised phase 3 study to measure the patient reported outcomes of symptom severity and interference (SSI). Does the Agency concur with the use of the MDASI instrument?*
Special safety issues	Questions related to the investigation of specific safety issues at the organ-system level.	*Are there any specific aspects on safety you would like us to pay special attention to? Does the agency concur with the company's proposal to perform only ECGs in the proposed pivotal studies, given the absence of a QTc prolongation effect in a thorough QT study?*

raised by regulators in the marketing authorisation procedure were lack of adequate randomized controlled trials to prove clinical efficacy and the occurrence of unresolved safety issues [3]. The EMA reported in 2008 that critical issues related to study design (39%), patient population (35%), endpoint (35%), and the magnitude of an effect (48%) were important drivers of a negative application [1]. In a 2010 study with FDA data on orphan drugs, Heemstra et al. found that failing to achieve primary endpoints and failing to describe the target population were related to non-approval [10]. Our study also showed that topics such as study design, endpoints, study population, and special safety issues were all among the top ten most frequently addressed issues in SA.

Quality documentation is a particular bottleneck for small and medium-sized enterprises (SMEs). The EMA SME office reported that quality documentation caused 41% of the major objections in application procedures of SMEs in 2008 [14]. Our results demonstrated that SMEs asked significantly more often about quality issues than large companies did, with the latter hardly discussing any quality issues. This implies that SMEs lack knowledge regarding quality documentation or lack capacity to comply with the requirements.

Some limitations of this study need to be discussed. Firstly, the scoring method of the SA, although highly standardized, may be susceptible to some subjectivity. In order to minimize this, we scored the questions according to strict definitions of content variables. These variables were derived from scientific regulatory documents and guidelines. Secondly, our definition of company size differs from the official EU definition of SMEs. According to the official SME definition, only 15 of 201 SA requests would have been classified as an SME request. This would create a group of "large companies" that was too heterogeneous to draw any conclusions about. Therefore, we based the SME definition on ranking by total revenue as reported in Scrip's Pharmaceutical Company League Tables 2008, which was in line with a previous study on SA with EMA data [9]. Another limitation of our study is that we did not investigate the companies' reasons for seeking SA. These reasons may range from a real interest in the answers to expected positive effects on the regulatory process (and outcome) by the applicants owing to dialogue and alignment with regulators in general.

It should be noted that company budgets may drive the decision to ask SA. However, during a significant part of the research period, the MEB provided SA free of charge. In addition, the costs that were introduced later were very limited, ranging from 3500 to 8000 euro per SA. Therefore we believe it is unlikely that the costs of SA have influenced our results, and we do not consider this a limitation of our study.

The fact that some SA requests at the MEB were rejected may raise the question whether results of this study are representative for national SA provided by other regulatory agencies. Advice requests were rejected when advice had been obtained from EMA, in cases where the complexity was expected to be better dealt with at the EMA level, or when the product indication was outside the scope of the expertise of the MEB. Therefore the array of clinical areas represented in this study is also

a reflection of national MEB expertise. Despite national expertise in, for example, central nervous system and cardiovascular products, the MEB gave SA about drug development in a broad range of therapeutic areas (Table 1). Similar broad ranges are expected for SA at other national regulatory agencies in the EU as well. In addition, when comparing the Dutch national SA with other national SA, the top ten most frequently addressed topics will probably not be influenced by differences in expertise because the topics are related to drug development in general. Therefore, we think our results give a well-balanced overview of issues in drug development.

Regulatory dialogue about challenging issues at the critical edge of drug development is seen as a key success factor for bringing new medicinal products with a positive benefit-risk to the patient. An EMA brainstorm session held with regulators and pharmaceutical industry representatives in 2007 made clear that a special need exists for dialogue about new high-risk advanced therapies and technologies and for new scientific approaches in targeted drug development, such as validation of biomarkers, choice of study endpoints, or better methods to identify treatment responders. In addition, the use of more flexible and adaptive study designs was raised as a key issue to be discussed in a dialogue with regulators [5]. According to the EMA, many SMEs in particular are active in the development of the highly innovative advanced therapy medicinal products (ATMPs) [14]. SA related to such high-risk advanced therapies and technologies are channeled to the EMA. In contrast, other small companies asked MEB advice most frequently about generic applications, bioequivalence, and new application of existing drugs. One may argue that answers to these SA questions could also be found in regulatory guidelines. The need for such advice may be partly attributable to lack of experience in drug development or lack of clarity in existing guidelines.

The role of scientific advice also has bearing on the way companies formulate their questions. For all types of companies about 20% of all questions asked were "strategic." Further research should assess whether companies benefit more from asking specific or strategic questions. Also, in further research national SA could be compared to European SA to assess whether strategic questions are asked on both levels and to evaluate commonalities and differences in the roles of European and national SA. Moreover, a better understanding of the level of complexity of SA questions would give deeper insight into the issues addressed. This would also enable further research on how complexity drives market authorisation holders' behavior when it comes to SA.

In conclusion, SA as provided by a regulatory authority provides a detailed outlook of unresolved issues in drug development. This picture is a function of industry presence in a certain country, of the expertise at the national regulatory authority, but also of critical issues at the edge of regulatory decision making. Indeed, there is variability in how different companies deal with this. The results of this study show that company size is associated with the content of SA questions and that national

SA accommodates both innovative and non-innovative drug development. Clinical pharmacology topics are at the top of issues discussed in SA, a finding that asks for more analysis on how industry, regulatory, and academic clinical pharmacologists can fruitfully interact and align in order to stimulate drug innovation.

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3.2

REGULATORY SCIENTIFIC ADVICE ON NON-INFERIORITY TRIALS

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ABSTRACT

The active-controlled trial with a non-inferiority (NI) design has gained popularity in recent years. NI trials have methodological challenges, especially in determining the NI margin. Regulatory guidelines provide some general statements on how an NI trial should be conducted. Apart from the guidelines, regulators provide opportunities for companies to discuss critical trial issues prior to the trial's conduct; so-called Scientific Advice (SA). In our current study, we identified questions on NI trials that were posed by applicants of European SA in 2008 and 2009, and the responses given by the European medicines agency (EMA) to identify potential issues that may benefit from a more explicit guidance.

We included in our analysis 156 final-advice letters given to 94 different applicants. Our analysis of final advice letters in 2008 and 2009 yielded two major findings: (1) questions 'whether' and 'how' to conduct an NI trial were frequently asked by applicants, but 'how' questions were more frequent than 'whether' questions. (74% vs. 26%); (2) the choice of the NI margin seems to be EMA's main concern in NI trials (36% of total regulatory answers). In 40% of the EMA answers, they recommended the use of a stricter margin; and in 10% of the EMA answers on NI margin, they questioned the justification of proposed NI margin.

We conclude that difficulties still exist in selecting the appropriate methodology of NI trials. Straightforward and harmonized guidance on NI trials is needed, such as when to conduct NI trials and how to determine the NI margin. Regulatory guidelines (either as one general guideline or special sections on NI trials in disease-specific guidelines) may not be feasible to cover all therapeutic areas; in that case regulatory scientific advice may be used as an opportunity for tailored advice.

INTRODUCTION

Randomized *placebo*-controlled trials (RCT) are considered the gold standard to confirm a drug's efficacy. Nowadays, *active*-controlled trials are often performed instead of or in addition to placebo-controlled trials as the basis for marketing authorisation and reimbursement decisions. A previous study showed that for 48% of new medicines approved between 1999 and 2005 at least one active-controlled trial was conducted during the development phase [1].

An active-controlled trial may have a non-inferiority (NI) design. An NI trial intends to demonstrate that the new drug is not worse than its comparator (an active drug previously shown to be more effective than placebo) to a certain limit (NI margin), while, thus, indirectly showing that the new treatment is effective (i.e. more effective than placebo). However, NI trials pose several methodological challenges, especially in determining the NI margin. Previously we found that in 22% of the NI-trials the choice of NI margin was merely based on assumptions made by the investigators [2].

The ICH E9 [3], the ICH E10 [4], the European Medicines Agency (EMA) guidelines [5,6] and US Food Drug Administration (FDA) draft guideline on NI trials [7] are the currently available guidelines that advice on the appropriate conduct of NI trials in general. Most of the guidelines only have general statements on how a NI trial should be conducted. Nevertheless, the FDA and EMA provide more explicit guidance in guidelines for trials in certain therapeutic areas (such as diabetes mellitus and infectious diseases) on how to use NI trial methodology [8,9]. Interestingly, in those guidelines where a specific NI margin is given, discrepancies exist between FDA and EMA. For example, in the 2008 draft FDA guidance for diabetes mellitus, an NI margin of 0.3% *or* 0.4% HbA1C reduction is suggested, while the 2011 EMA guideline suggests an NI margin of 0.3% [8].

Apart from guidelines, regulators nowadays provide opportunities for companies to discuss critical trial issues prior to the trial's conduct, to improve the quality of pre-registration trials. An important part of such dialogue is formed by so-called Scientific Advice (SA). In Europe, SA can be sought either from the EMA or from one or more of the national regulatory agencies [10]. Regulatory SA can be asked as often as deemed necessary by an applicant, who is not obliged to adhere to the advice received or committed to accept any result of an SA procedure. In a previous study, we found that one of the top five questions posed by the applicants was on study design [11]. However, we did not assess the questions and the responses of the regulators specifically related to the NI design in more detail. Therefore, it is largely unknown whether companies often ask questions specifically related to NI trial design, and what the nature of and answers to these questions are.

In this study, we identified questions on NI trials that were posed by applicants of European SA in 2008 and 2009, and the responses given by the EMA, to identify potential issues that may benefit from a more explicit regulatory guidance.

METHODS

With the keyword 'inferior' we searched in confidential scientific advice letters from the EMA in the years 2008–2009 for advice documents dealing with NI trials. At the time of our study, information on SA in more recent years was not fully available. Data collection and analyses were conducted under the jurisdiction of confidentiality agreements between the parties involved (i.e. MEB, EMA and Utrecht University).

The following information was collected for each SA-application: whether it was a follow-up to a previous SA application, whether the drug was classified as orphan drug, and indication of the drug. The drugs were categorized by their therapeutic target group according to the Anatomical Therapeutic Chemical (ATC) classification system [12]. In case an ATC classification was missing, the anatomical main group was determined based on the intended indication of the product.

Each question-CP and CHMP response was scored according to the topic of interest. The topics of interest were divided into two types, "general" and "specific". General topics covered discussion about the strategic/overall development process of a drug. The specific topics consisted of NI trial unique topics and topics not related to NI trials. NI trial unique topic included questions on whether an NI trial should be conducted or not ("whether" question: NI study design) and topics that discussed technical issues about how an NI trial should be conducted ("how" questions; e.g. type of comparator, NI margin, NI sample size calculations, intention to treat (ITT) or per-protocol (PP) analysis; and switching (from non-inferiority to a superiority design or vice versa). NI trials not unique topics discussed aspects of a clinical trial that were not specific to NI trials, for example trial inclusion-exclusion criteria and type of endpoints (See Table 1 for further details and examples).

In each question-CP or CHMP response, multiple topics can be discussed. All topics were included separately in the analyses. Additional topics that were found in the CHMP response, but not in the accompanying question or company position were classified as "extra information".

Author GW searched and extracted all questions, company positions, and answers documents, while classification was done by both GW and MP. In case of discrepancies (n=5), AM-T and MK were consulted to reach consensus. Subsequently, data were analyzed by GW and MP in a descriptive way. In addition, the proportions of the topics according to their therapeutic target group were assessed.

RESULTS

Search result and general characteristics

In total, there were 350 final-advice documents in the year 2008 and 345 documents in 2009 and 166 of these contained the keyword "inferior" in the

Table 1. Examples of topics related to NI trials in question-CP-CHMP response units identified in final-advice letters

Topics			Definition	Example		
				Question	Company position	CHMP answer
Unique to NI trials	WHETHER - topic	NI study design	discusses NI trial design	Does the agency support the selected **non-inferiority** trial design for the phase 3 study in patients with YYY?	An open-labelled, randomised, multi-centre, parallel group study will be conducted in YYY adult patients for a period of 6-8 months.The primary objective of this study is to demonstrate that ABC is just as efficacious as DEF, the current therapy. The main inclusion and exclusion criteria , etc.	CHMP agrees with the non-inferiority design. However, a two-arm **non-inferiority** study is considered inadvisable due to concerns relating to assay-sensitivity. For these reasons, inclusion of a placebo control is strongly recommended in addition to the active control.
		Type of comparator	a) Discusses the type of comparator *or* b) the use of additional placebo arm in the trial	Does the agency agree on the use of DEF as the active comparator in this **non-inferiority** trial?	DEF is recommended by the XXX as the current therapy of choice for YYY.	The choice of active comparator is justified.
		NI margin	discusses the NI margin	Does the SAWP consider an X % **non-inferiority** margin acceptable?	Minimum clinical relevant difference to detect is suggested to X % (**non-inferiority** margin) preserving 2/3 of the effect of ABC vs. placebo on primary endpoint.	CHMP agrees
	HOW - topic	NI data analysis[$]	a) discusses data analysis of an NI trial, including sample size calculation for NI trial *or* b) Controlling type I error in NI trial	In this trial, the primary analysis is performed on the per-protocol population (with a secondary analysis performed on the intent-to-treat population), with sample size of ZZ patients.Does CHMP agree?	Sample size was calculated based on 5% better response rate in the ABC arm, a **non-inferiority** margin of X %, one-sided significance level 2.5%, and power of 80% .	CHMP disagrees. A sample size of ZYX patients is necessary to exclude a significant activity difference. We recommend to do the primary analysis in both PP and ITT analysis.
		ITT or PP [$]	discusses the choice of per-protocol (PP) or Intention to treat (ITT) analysis			
		Switching	discusses a plan to switch from NI to superiority or Superiority to NI	Is the test procedure - testing first for **non inferiority** followed by superiority – acceptable?	The sponsor believes that the described procedure is in line with EMEA/CHMP guidelines for switching between superiority and **non-inferiority**.	Switching from **non-inferiority** to superiority as proposed is acceptable.
Non-unique to NI trials			discusses topics related to conduct of the trial, that are not specifically related to NI trials	We propose modifying the primary composite endpoint to include hospitalization in this **non-inferiority** trial.	The proposal to exchange the two composite endpoints would address the lower than anticipated event rate and would still allow the assessment of the impact of ABC on a composite endpoint.	Reluctance exists from clinical grounds to agree to the proposal. Adding hospitalization would add a component that has a different relevance than the components that were originally agreed as making a valid composite primary endpoint.
General			discusses " Strategy question"	Does the Agency agree that a single Phase 3 study with the proposed primary endpoint and statistical evaluation will provide sufficient data for approval?	Since, at this stage, no approved drug is available for YYY patients, it is considered acceptable to base potential approval of ABC for this disease on the proposed Phase 3 program.	Approval of ABC based on the current program will be possible. A new agent or indication should have a safety/ efficacy profile **non-inferior** to marketed comparators.

Note : $ An example that in one question/CP multiple topics can be discussed
To ensure confidentiality, the data presented in the table are not the original sentences found in the SA applications

database (75 documents in 2008 and 91 documents in 2009). We excluded nine documents in 2008 and one document in 2009, because they were not related to NI trials. We finally included 156 documents in our analysis, consisting of 66 final-advice letters from 2008 and 90 final-advice letters from 2009. These final-advice letters were given to 94 different applicants. In total, the documents contained 278 question-CP-CHMP response units related to NI trials.

Characteristics of the documents and questions are described in Table 2. Of the therapeutic groups, antineoplastic and immunomodulating products were discussed most often (22% of included final-advice letters), followed by alimentary tract and metabolism products (17 %) and anti-infectives (16 %).

Table 2. General characteristics of scientific advice applications

	Based on number of documents n = 156 (%)	Based on number of questions n = 278 (%)
Follow up applications	36 (23)	51 (18)
Orphan drugs	14 (9)	23 (8)
Therapeutic target group		
Antineoplastic and immunomodulating products	34 (22)	63 (23)
Alimentary tract and metabolism	27 (17)	48 (17)
Anti – infective drugs	25 (16)	47 (17)
Blood and blood-forming organs	15 (10)	31 (11)
Respiratory system	10 (6)	19 (7)
Musculoskeletal system	13 (8)	16 (6)
Systemic hormonal preparations, excluding sex hormones and insulins	7 (5)	14 (5)
Nervous system	7 (5)	10 (3)
Others	18 (11)	30 (11)

Topics of discussion

Within the 278 questions-CP units related to NI trials, a total of 587 different topics were discussed. Of these, 101 were classified as general topics, asking advice regarding the overall development strategy which may include a non-inferiority RCT. Issues that were specific, but not unique to NI trial design were identified 132 times. The remaining 354 topics were unique to NI trials. In CHMP answers, a total of 400 different topics were discussed. Of those 242 topics were unique to NI trials.

Among the NI trial unique topics, both topics of "whether" and „how' to conduct an NI trial frequently appeared in the questions-CPs and CHMP answers, but ("how" questions (74% of total NI topics asked and 72% of total CHMP

answers) were more frequently asked than "whether" questions (26% of total topics asked and 28% of total CHMP NI unique answers). Among the ("how" topics the NI margin was most frequently discussed in questions-CP and CHMP answers (98 (28%) questions-CPs and 86 (36%) CHMP answers of all NI trial unique topics). In 42 out of 86 (49%) CHMP answers that discussed NI margin, the CHMP supported the NI margin proposal from the applicants; while in another 35 out of 86 (41%) answers, CHMP recommended a stricter margin. In the remaining 9 out of 86 (10%) CHMP answers that discussed NI margin) the justification of the NI margin was questioned by CHMP, but no specific advice on its magnitude was given. The topic of switching appeared least often in question-CP units (6% of total topics asked); and the topic of "ITT or PP" appeared least often in CHMP-answers (3% of total CHMP answers) (See table 3).

In addition, table 3 shows the differences and similarities in questions-CP and CHMP answers between the three most often discussed therapeutic target groups. Among anti-neoplastic and immunomodulating products and alimentary tract and metabolism products, the topics of NI data analysis (29% and 31% respectively within the therapeutic area) mostly appeared in question-CP, while for antiinfective drugs the NI margin was discussed most often (40% of total topics asked within the therapeutic area). Among other drugs, most questions-CPs were about NI study design (28% of total topics asked).

Among CHMP answers, the NI margin was the topic that mostly appeared in all three therapeutic target groups (38% of total CHMP answers in anti-neoplastic and immunomodulating drugs, 28% in alimentary and metabolism drugs and 57% in anti-infective drugs).The NI margin was also most often discussed in the CHMP answers for other drugs (35% of total CHMP answers).

"Extra information"(i.e. unsolicited answers) given by the CHMP, more often pertained to "how" to do an NI study rather than "whether" to perform an NI trial (data not shown). Only in alimentary tract and metabolism products, extra information is mostly given about "whether" to do an NI-trial.

DISCUSSION

Our content analysis of 2008 and 2009 scientific advice documents on NI trials provided by the EMA, showed that questions on "whether" and ("how" to conduct an NI trial were frequently asked by applicants. In addition, NI margin seems to be the main concern of EMA in NI trials.

Interestingly, more than 25% of the questions were "whether" questions, and thus it seemed that the doubts of the company about the need of an NI trial frequently exist. These results illustrate that more explicit guidance on fundamental issues in NI trials, such as in which situation an NI trial can or should be applied are necessary. However, we realize one general guideline may not be feasible for

Table 3. Frequency of topics unique to NI trials appearing in Question-CP- CHMP answers based on therapeutic target group

		All therapeutic groups N (% of total)		Antineoplastic and immunomodulating drugs N (% of total)		Alimentary tract and metabolism drugs N (% of total)		Anti – infective drugs N (% of total)		Other drugs N (% of total)	
Topic		**Q-CP**	**CHMP answers**	**Q-CP**	**CHMP answers**	**Q-CP**	**CHMP answers**	**Q-CP**	**CHMP answers**	**Q-CP**	**CHMP answers**
Whether topic	NI study design	92 (26)	67 (28)	21 (25)	11 (20)	11 (22)	10 (26)	4 (20)	3 (21)	56 (28)	43 (32)
	Type of comparator	34 (10)	22 (9)	8 (9)	5 (9)	4 (8)	6 (15)	4 (20)	1 (7)	18 (9)	10 (7)
	NI margin	98 (28)	86 (36)	21 (25)	21 (38)	15 (31)	11 (28)	8 (40)	8 (57)	54 (27)	46 (35)
HOW - topics	NI data analysis	87 (25)	50 (21)	25 (29)	15 (27)	15 (31)	10 (26)	3 (15)	2 (14)	44 (22)	23 (17)
	ITT or PP	22 (6)	8 (3)	5 (6)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	16 (8)	8 (6)
	Switching	21 (6)	9 (4)	5 (6)	3 (6)	3 (6)	2 (5)	1 (5)	0 (0)	12 (6)	4 (3)
TOTAL		354 (100)	242 (100)	85 (100)	55 (100)	49 (100)	39 (100)	20 (100)	14 (100)	200 (100)	134 (100)

all therapeutic areas, for example when efficacy of the current standard therapy against placebo is not fully established, e.g. anti-depressants [13].

Our second finding shows that NI margins and data analysis were the most frequently discussed specific topics. This finding applied to all therapeutic areas. Furthermore, in 40% of the CHMP answers on NI margins, a stricter margin was recommended. This concern was previously acknowledged by the European regulators [14,15]. The large proportion of ("how" questions confirms that the methodology of NI-trials, in particular NI margin determination, is not straightforward [2]. These facts strengthen the need of the applicants" additional guidance on technical issues such as previously given by the EMA guidance [6] and draft FDA guidelines on NI trials [7].

Our subgroup analysis showed that NI trial design for alimentary tract and metabolism products is of specific concern to CHMP since CHMP often recommends a NI design for these products, without the applicant asking for guidance on this point. Apparently, in this therapeutic area, the use of NI trials to confirm drug efficacy is still complex. Recently, CHMP released revised guidance in 2011 on anti-diabetic drugs [8] which recommends beside the use of superiority trials, the use of NI trials in diabetes patients. This may help to clarify in which cases NI trials should be performed.

In the 2011 guidance on anti-diabetic drugs described above, a recommendation on a NI margin of 0.3% HbA1C was included. A similar specific requirement was previously proposed by EMA for anti-infective drugs, where a specific value of NI margin (10%) was recommended [16]. Although the numbers are small, we found that the specific requirements still resulted in questions on the NI margin in anti-infective drugs. Recently, in a 2011 updated version, the value of 10% was replaced by a general statement in the guideline on how an NI margin should be determined [17]. This approach is in line with the draft FDA guideline 2010 [7] that recommends determining an NI margin based on historical data instead of using a single fixed value as an NI margin. Whether this new approach will lead to a reduction or an increase in scientific advice questions related to NI trials remains to be established. In the meantime, awareness of regulators about the difficulties faced by applicants is essential and dialogue between both parties, for example by means of the scientific advice process, can support the regulators in improving guidance on NI trials.

We conclude that difficulties still exist in selecting the appropriate methodology of NI trials. Straightforward and harmonized guidance on NI trials is needed, such as when to conduct NI trials and how to determine the NI margin. Regulatory guidelines (either as one general guideline or special sections on NI trials in disease-specific guidelines) may not be feasible to cover all therapeutic areas; in that case regulatory scientific advice may be used as an opportunity for tailored advice.

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3.3

SCIENTIFIC ADVICE AS WITNESSED AND PERCEIVED THROUGH AN SME LENS

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ABSTRACT

Scientific advice seems to be an excellent way for small and medium-sized enterprises (SMEs) to clarify complexities in drug development. It is questioned whether scientific advice is currently used in its most fruitful way. In this interview study we therefore evaluated the role of scientific advice in innovative drug development as witnessed and perceived by SMEs. We focused on three main research questions (i) What are reasons for you to request scientific advice? (ii) How did you perceive the scientific advice procedure? and (iii) What would be an optimal way of applying a scientific dialogue? A qualitative semi-structured interview study was held with eleven directors of Dutch SMEs, involved in the company's research strategy to obtain marketing authorisation between July and September 2012.

SMEs appeared to request scientific advice to retrieve regulators' reassurance of their development plan, to gain regulators' trust and to fill knowledge gaps where guidelines are lacking or unclear. SMEs appreciated the scientific advice procedure and acknowledged the complex role of regulatory assessors being scientific advisor and assessor at the same time. However, the dialogue is complicated by (i) the formal relation/status of the advice and uncertainty about assessors' decisions during the marketing authorisation application procedure and (ii) regulators' lack of expertise for highly innovative products in some cases. Suggestions for further optimizing the scientific dialogue included creating a constructive dialogue by addressing its formal status and by keeping regulators' expertise up to date, diminishing the administrative burden and explore opportunities for more informal interaction with regulators.

INTRODUCTION

For a pharmaceutical company, discovering a new medicine and bringing it to the market requires joint efforts of many experts within the company and large financial investments. Previous research shows that receiving marketing approval from drug regulatory agencies heavily depends on the study results, but also on an in depth knowledge of the drug candidate and an appropriate development plan [1].

In Europe, drug development is guided by general and disease specific regulatory guidelines indicating the elements of the development plan, such as the required type of studies and the design most suitable to assess the safety and efficacy of a medicinal product [2]. The last decade has witnessed a sharp increase in the development of guidelines resulting in hundreds of (draft) guidelines for specific therapeutic areas, for biotechnological products and for advanced-therapy medicinal products [3]. In innovative drug development, issues that are not addressed in existing guidelines are common. For example, choosing an endpoint for a new rare disease indication or the pharmacokinetic requirements of a medicine with a new administrative route. Besides, interpreting regulatory guidelines and translating general recommendations in guidance to a research project can be difficult. In addition, scientific guidelines do not have legal force and deviations are possible, provided that these are appropriately justified [2]. For these reasons, compiling development plans that are deemed appropriate by regulators can be demanding. Experience in drug development has been shown to contribute to a successful marketing authorisation procedure [4], which suggests that in particular small and medium-sized enterprises (SMEs) developing new medicines, may consider this challenging. SMEs have gained a relevant role in the development of innovative medicines, including biological and advanced therapeutic products and their role is expected to further increase in the near future [5,6]. To address the need of knowledge on drug development at SMEs, the European Commission adopted a specific regulation (provisions) in 2005 aimed at promoting innovation and the development of new medicinal products by SMEs [7]. As part of this regulation incentives for innovative drug development are offered to SMEs such as fee reductions, e.g. 90% for scientific advice [8].

In particular scientific advice – either at the national or European level - seems to be an excellent way to clarify issues that are not (completely) clear in existing guidelines or to discuss proposals for deviations [9,10]. A 2011 European Medicines Agency (EMA) survey among SMEs identified a lack of understanding of regulatory requirements and a lack of sufficient detailed guidance for highly innovative therapies in many therapeutic fields, which could be filled by up-to-date scientific advice [11]. In a previous study, however, we identified differences in requesting scientific advice between large pharmaceutical companies and SMEs. For example, large companies ask relatively more clinical questions than SMEs [12].

The proportion of marketing authorisation applications preceded by European scientific advice has increased in the last 5 years and was 46% in 2011 [13]. Still, it remains questionable whether scientific advice is currently used in the most fruitful way, especially by SMEs, that accounted for only 22% of all scientific advice given in 2010 [14]. In this interview study we therefore evaluated the role of scientific advice in innovative drug development as witnessed and perceived by SMEs. We focused on three main research questions (i) What are reasons for you to request scientific advice? (ii) How did you perceive the scientific advice procedure? and (iii) What would be an optimal way of applying a scientific dialogue?

Lessons learned may lead to recommendations on how to optimize the regulatory scientific advice procedure for SMEs in Europe.

METHODS

Study population

The EMA definition of SMEs was taken as an inclusion criterion to select SMEs: "an enterprise which employs fewer than 250 persons and which has an annual turnover not exceeding EUR 50 million, and/or an annual balance sheet total not exceeding EUR 43 million" [15].

For practical reasons we only included SMEs based in the Netherlands in our interview study. The persons selected for the interview were directors or management team members involved in the company's strategy to obtain marketing authorisation . We included one interviewee per SME and initially set out to include 10-15 SMEs in the study. The ultimate number of interviews was decided on during the interview study based on the amount of new or unexpected information from additional interviewees, until saturation and redundancy were concluded.

Data collection

The study was designed as a qualitative semi-structured interview. The selected persons were invited to participate in our study by means of a telephone call and letter of invitation by email. Before the start of the interview, additional information about confidentiality and interview methods were explained to the interviewee. One of the authors (MP) assured that the interview took place in accordance with ethical standards without any harm to participants, e.g. without mentioning the names of other interviewees. A confidentiality form was signed by MP and the interviewee or the confidentiality was agreed on by the interviewee by telephone. The interviews were performed face to face or by telephone by MP and did not take longer than 60 minutes.

Interviews were conducted using a semi-structured interview guide, based on the three main research questions. According to the guide, questions were asked in a predefined order, but the interviewer could divert from this order on a case

by case basis if needed. Follow-up questions were adjusted to the informant's initial responses. The interviews were conducted in Dutch and audio recorded and verbatim transcribed for analysis by independent transcribers.

Data analysis

In a deductive way, based on the themes and questions in the interview guide, the transcribed text was coded and categorized by MP. This analysis was conducted with use of the Nvivo 10 software program. Subsequently, another author (AM-T) read the transcribed interviews using an inductive approach and collected themes and topics from the interviewees' responses.

RESULTS

In 2012 in total 991 companies had the 'SME status' at the EMA, including 41 Dutch SMEs. Eleven interviews were held with heads of research of Dutch SMEs between July and September 2012. In nine of these SMEs, the heads of research had experience with requesting scientific advice. The majority of the companies were developing biologicals, including some advanced therapy medicinal products, either with or without orphan status. Most companies had developed at least one plan for a Phase II clinical study. In addition, four companies were developing new formulations for existing chemical entities. The number of employees in the Dutch SMEs varied from 2 to 85. The majority had less than ten employees, whereas two SMEs had about 25 employees and two others about 80 employees.

Reason for asking advice

Our study demonstrates that SMEs primarily asked scientific advice at the European Medicines Agency rather than at national agencies and were mainly driven by three goals: (i) to gain reassurance about their drug development plans, (ii) to discuss scientific issues with experts, and (iii) to introduce their product to decision makers.

Reassurance about development plans was pivotal to all companies; they typically requested feedback by the EMA on their complete drug development plan. In this way they aimed to identify crucial issues that needed to be addressed according to regulators. Moreover, such reassurance is relevant to convince potential investors that regulators support the development plan.

According to most SMEs, discussing development plans was preferably done at a very early stage, most often during the Chemical-Manufacturing and Control (CMC) phase in which the product formulation is created, assays for potency testing are developed and product specifications such as stability are assessed. Most companies approached regulatory agencies at predefined moments, commonly before starting CMC, before initiating trials in patients and before the start of phase

III (if applicable). However, due to long timelines of the scientific advice procedure in many cases, drug development plans were already initiated in practice.

To a lesser extent, SMEs also asked very specific questions, e.g. about the quality specifications of their product or the appropriateness of a clinical endpoint. The need for such specific questions depended on the availability of guidelines, although it was emphasized that even in the presence of guidelines, detailed questions were asked to discuss nuances and gain reassurance. Because limited guidelines are available for more innovative products, SMEs developing cell-based therapeutic products or other advanced therapy medicinal products considered a dialogue with regulators with appropriate expertise crucial to further develop their product and bring it to the market.

R1. "There is no such thing as a text book: usual aspects of registration like process validation and stability testing are all a bit different, so you really want to check those with the authorities. What we often do is present our plans with some specific questions."

R10. "In particular in drug development for rare diseases, we depend on the available expertise in the Netherlands as well as in the EU. Scientific advice helps to choose a broadly supported approach."

The third aim of SMEs was to meet the regulators that would (indirectly) be involved in decision making during the marketing authorisation application of their product. They emphasized the relevance of making regulators aware of their intention to develop a product and to inform them about the intended product development process.

R4. "Then they know that we are seriously developing a product, it would not be wise to just throw your dossier around the corner and see what happens."

Since many products were orphan medicinal products or advanced therapies, these would need to be approved via the European centralised marketing authorisation procedure. Therefore SMEs preferred to have a scientific dialogue with regulators at the European Medicines Agency, not only for their expertise on these products, but also to discuss the program with those regulators that in the end will decide about marketing approval.

R4. "The advantage of a centralised scientific advice procedure at EMA is that, in principle, experts look at the dossier, who hopefully will also later be involved in the marketing authorisation procedure. So that's why I always say: 'Let's go directly to EMA' rather than to the Dutch MEB."

Some SMEs considered scientific advice at national regulatory authorities useless because of perceived lack of relevant expertise and the time and additional costs that national procedures require. However, other interviewees did ask for advice at national agencies, preferably in a very early stage, 'to gain

a first impression' and learn about the 'enthusiasm' of national regulators about the intended product, indication and development plan in general and to identify early '*show stoppers*' (crucial issues that would put further development on hold).

R5. "We just want an advice about a certain concept: We want to do this, is that all right?"

R8. "To get an impression of what they think of it. What is their view on such a product?"

The selection of a specific national agency to seek scientific advice was based on the available expertise and the presumption of future (co-)rapporteurships in the centralised marketing authorisation procedure. It was emphasized that an overview of the expertise at the different national agencies was not clearly provided by the agencies themselves, but was obtained through drug developers' networks and by looking at (co-)rapporteurs for competitor products.

The scientific advice procedure as perceived by SMEs

SMEs want to be assisted by regulators but, according to the SMEs, the dialogue is complicated by (i) the formal relation/status of the advice and (ii) regulators' lack of expertise for highly innovative products in some cases. Regulators seem to be enthusiastic about innovative medicines in informal settings and willing to discuss development plans, but are more reluctant to give explicit answers in formal settings.

R1. "Last year I attended a conference. I presented our product development there and many regulators were present, from EMA and the Dutch authorities. The atmosphere was very good, there were excellent conversations about the development. They were very interested in what we do and we are interested in what they think of it. And yes these were fruitful conversations, just around the table. It was not as formal as I was used to."

The formal character of the scientific advice procedure in its current form seems to induce a conservative approach among regulators, more likely to yield an ambiguous scientific advice and ongoing additional evidence requirements. This conservative approach rather than the advice not being legally binding, was perceived as problematic.

R4. "Of course they say" scientific advice is not an assessment procedure". So all disclaimers are put on the advice document, saying that it is actually not an evaluation. Thus, because of the bureaucracy, it is quite difficult to get a good feeling about that."

R4. "Some advice you just follow, to maintain a good relationship, it is also a kind of a game you play. And some advice that you really think is useless, you just don't follow. We have done some animal studies for the FDA, which were really nonsense. But all right, you know, it is give and take and choose your battles."

The fact that scientific advice as provided is not legally binding was deemed acceptable from an SME perspective, since long time periods can exist between the scientific advice and the marketing authorisation application and science may evolve over time. SMEs recognized advice will never be unconditional, and that unexpected safety events or disappointing outcomes may lead to additional requests for evidence by regulators. In addition, companies prefer to decide themselves whether they would adhere to the given advice or opt for a better alternative.

R5. "It can be really annoying when you have done something and it suddenly becomes clear that it is no longer state of the art. But would you, as a company, want to have a product on the market that is not state of the art? I mean, you have to be conscious all the time and keep noticing what happens around you."

R6. "As long as it makes sense and is rationally acceptable, I can live with it."

R4. "On the one hand annoying that it is not binding, because then you do everything as they asked and then later on they will say something different. On the other hand, as a company you also want to be able to change your mind."

The above described ambiguous character that scientific advice can have and the fact that regulators always seem to ask for more data, even in a late stage of drug development, was a general complaint.

Another important perception was that expertise among regulators is a main condition for a fruitful dialogue. The SMEs considered themselves leading experts in the field, but expected a sufficient level of expertise from the regulator. They admitted that being well prepared before the meeting is also crucial for a successful scientific advice procedure: clearly explaining the intended drug development plan in a step by step approach to regulators led to clearer answers to their specific questions. In addition, expertise among regulators and an appropriate explanation by SMEs were both essential to gain support for deviations from guidelines. Experiences regarding the level of regulatory expertise in practice varied strongly. Whether regulators were willing to discuss innovative study designs seemed to depend on the type of product and the regulator. In particular when limited guidance was available, e.g. for advanced therapy medicinal products or orphan medicinal products, regulators appeared to be more open to solutions from the SMEs.

Suggestions for an optimal scientific dialogue

Overall, SMEs appreciated the opportunity to discuss development plans with regulators. SMEs were willing to adhere to the advice given as long as it is clear and a scientific rationale is provided. In line with the objectives and experiences described above, suggestions for an optimal scientific dialogue included considered creating a constructive dialogue despite the formal setting, diminishing the administrative burden and explore opportunities for informal interaction with regulators.

R5. "Once again, the phenomenon of scientific advice, I am very satisfied with it. In particular when you comply with the advice and really use it, it is an excellent tool to increase your chances for fast marketing approval."

R5. "But the regulators should be at our side of the table and look at the dossier with us, together..instead of them saying 'show your dossier and we will see whether we like it or not later on'."

A constructive dialogue about innovative drug development is facilitated by having sufficient expertise to recognize the value and limitations of an innovative drug development plan. FDA was mentioned as an example of best practice with much (clinical) expertise among regulators, due to the opportunities to specialization, while the fragmented organization of the EMA was considered to jeopardize its efficiency. As a solution to the ambiguous character and unexpected requests for more data, several respondents suggested to introduce binding agreements for confirmative/Phase II-III clinical trials, in line with the Special Protocol Assessment by the Food and Drug Administration.

R2. "Then you can only discuss and interpret the quality of the study: e.g. the study protocol was good, but its implementation was not. Or you have found results that you didn't expect: you have found more adverse effects or less efficacious results then you had hoped for. But then the product is the problem and no longer the protocol."

R11. "At some point, when the dossier gets more and more complete and you reach phase III, you need to know what your chances are. It cannot be the case that you finalize phase III and then again get called back, leading to two years of delay."

Secondly it was unanimously recommended to decrease the administrative burden of scientific advice procedures, in particular at the EMA level. The preparation of a scientific advice procedure was considered very demanding and time lines were perceived as long. It was emphasized that for SMEs the impact of these time lines on the delay of new investment decisions is significant as they often face more financial constraints in the development phase than large innovator companies. Considering both the formal character of the current relation between regulators and applicants and the time-consuming scientific advice procedures, it was recommended to also explore opportunities for more informal settings between regulators and applicants. A strong preference was expressed to have face-to-face contact to be able to respond to regulators' responses. National agencies were advised to let their ability to provide advice to SMEs to become better known and to offer opportunities for informal feedback in dialogues.

DISCUSSION

This qualitative study reveals that SMEs consider a scientific dialogue with regulators an essential element in their attempts to bringing a new medicine to the market. SMEs appear to request scientific advice to retrieve regulators' reassurance of their development plan, to gain regulators' trust and to fill knowledge gaps where guidelines are lacking or unclear. Regulatory agencies such as EMA have indicated that scientific advice is a main instrument to increase the number of approvals of needed medicines. The EMA Roadmap to 2015 states that EMA will encourage companies to request scientific advice and will optimize the scientific advice procedure [16]. The results of this study offers opportunities to optimize this procedure.

SMEs' views on and perceptions of scientific advice

The first two objectives demonstrate that SMEs see regulators mainly as decision makers. The first objective that SMEs expressed is in line with a 2011 SME survey result: regulatory feedback on the development plan is relevant to investors and the eventual aim is to gain information and start communication with regulators about the predictability of the assessment of the application [11]. EMA emphasizes that the scientific advice procedure is not a pre-assessment of the product for future marketing authorisation [9]. In practice SMEs consider reassurance of their development plan useful and sufficient to attract potential investors. However, the contribution of scientific advice to the predictability of the regulatory system could be improved. First, the reassurance received in scientific advice is currently challenged by regulators' requests for additional evidence in a subsequent advice or during the marketing authorisation procedure. The absence of a legal status allows additional evidence requests. In addition, its formal status was found to contribute to ambiguous scientific advice, that is not sufficiently explicit about the need for additional evidence. The ambiguous character may also be caused by the type of questions asked by SMEs. SMEs' strategies to receive reassurance about the development plan and to gain trust and credibility by introducing the product in an early stage, lead to discussions of a broad range of topics and more general questions. A previous study demonstrated that general questions (e.g. "*Do you think the proposed efficacy studies together are appropriate for a marketing authorisation?")* are indeed often asked in scientific advice procedures [12] and give rise to broad and less specific responses, not particularly useful to solve specific issues in drug development.

The SMEs' objective to let regulatory advice fill knowledge gaps demonstrates that SMEs also see regulators as scientific experts. This is more in line with EMA's vision that the scientific advice procedure is an important way to discuss protocols for drug development, in particular issues for which guidelines do not exist, or discuss proposals for deviations from scientific guidelines [9,10]. In practice

SMEs that develop products on cutting edge science seem to balance between being in need of scientific advice when guidelines are lacking *and* being the leading expert in the field, thus convincing regulators of alternative methods and negotiating about the development plan. According to SMEs, regulators tend to be conservative and stimulate adherence to available guidelines. This tendency may be the result of the formal character of the advice or due to insufficient expertise about highly innovative methods at regulatory agencies.

The interviews highlighted that regulators seem interested in pharmaceutical innovations and attempt to stay up-to-date with latest insights at scientific conferences and informal meetings. Meetings between regulators and SMEs at such events are highly appreciated by SMEs because of the opportunity to discuss scientific issues in a more informal environment. SMEs acknowledge the complex role of regulatory assessors being scientific advisor and assessor at the same time, but the perceived insufficiency of specific regulatory expertise on latest technologies and the uncertainty about assessors' decisions during the marketing authorisation application procedure hamper the current scientific dialogue between SMEs and regulators.

Suggestions for improvement

To meet SMEs' objectives, the scientific advice procedure could be improved by addressing its formal status and by keeping regulators' expertise up to date. Sufficient expertise and an open-minded attitude among both parties could enhance a constructive dialogue, because these reflect the two main elements of perceived trust: competence (ability) and benevolence [17]. Having trust in the knowledge source increases the chance that the knowledge receiver will learn from and absorb the knowledge transferred [17]. In scientific advice regulators and SMEs can only be *both* knowledge source *and* knowledge receiver if they both are benevolent and competent. Creating a more open-minded behavior seems possible: regulators could be more interested in alternative methods proposed by SMEs, and SMEs could learn from regulators' experience with similar products. Regarding competence or expertise SMEs should clearly and robustly substantiate their preference for alternative methodologies being key experts in their own research area, whereas regulators should have sufficient expertise to foster a real dialogue based on the latest scientific evidence. In particular for orphan and advanced therapy medicinal products, it is a challenge to find experts that comply with the strict conflict of interest policy in the EU [18].

Informal settings such as conferences were appreciated for exchanging knowledge in the *(early)* developmental phase. Literature confirms the strength of 'weak links' for exchange of knowledge between parties [17]. The EMA SME office does offer meetings with regulators in an informal setting such as workshops and theme meetings. Other than scientific advice such interactions are related to a

group of products e.g. for a certain therapeutic area, or special products such as orphan medicinal products and advanced therapy medicinal products [19]. It remains questionable whether a more informal dialogue is possible between an applicant and the regulators under the current scope of scientific advice.

The proposal to make binding agreements about clinical study designs (mainly phase III trials) in scientific advice, could increase the predictability of the marketing authorisation procedure. The benefit-risk evaluation for marketing authorisation would then only depend on the outcomes of clinical studies. If companies develop new products and aim to deviate from guidelines for valid, scientific reasons, companies should feel confident that the evidence generated on the basis of their development plan is still acceptable at time of marketing authorisation application. If this is not the case, companies will be inclined to 'play safe' and comply with all available guidelines, also those guidelines that companies consider a waste of time because of limited added value or the availability of better alternatives. The FDA does allow formal agreement on plans for phase III studies in their 'Special Protocol Assessment' procedure [20]. In this specific procedure regulators and the applicant agree explicitly on the design, execution, and analyses as proposed in a selected type of protocol. The FDA states that "it will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident"[20]. In particular for confirmatory clinical studies this approach could be further explored at EMA.

Potential limitations of the study

For logistic reasons, this study was conducted with 11 SMEs, all from the Netherlands. The results however, seem to be applicable to other SMEs requesting scientific advice in the EU. The participating Dutch SMEs represented companies with varying numbers of employees (2-85 employees) and a wide range of products. In addition, diverse indications were covered from orphan indications to potential blockbuster indications. Besides, the Netherlands is considered to be attractive for high level SMEs, because of a world-class medical infrastructure, new standards in innovation, and high level academic research and science parks according to international pharmaceutical industry [21]. The Netherlands belongs to the top 5 countries with the highest proportion of SMEs registered at EMA [22]. The responses given by the interviewees therefore, seem to offer an externally valid view of SMEs towards EMA scientific advice.

CONCLUSION

SMEs request scientific advice to gain regulators' support for their development plan, to build a relationship with regulators and to fill knowledge gaps where

guidelines are lacking or not clear. According to SMEs changing the formal status of scientific advice and improving regulators' expertise are key in optimizing the scientific advice procedure in the EU.

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4

GENERAL DISCUSSION

INTRODUCTION

The relevance of continuous development of needed medicinal products is publicly recognized, but the development and market launch of new medicines require increasing efforts and costs [1].There are many targets for improving patient access to innovative medicines, and this thesis focuses on the regulatory system that aims to guarantee and facilitate entering of efficacious, safe and high quality medicines to the European market.

An efficient and effective marketing authorisation system contains an acceptable balance between clinical evidence on a new medicines' beneficial and adverse effects required *pre*- and *post*-marketing approval [2,3,4]. Despite regulatory initiatives for more efficient marketing authorisation, current non-approval rates of new medicines are relatively high [5,6]. These high non-approval rates potentially have a negative effect on the prognosis of patients in need of new therapies and the pharmaceutical industries' R&D productivity. Another aspect is the clinical benefit newly developed medicines could bring, being innovative therapies [7] or incremental innovations only [8]. Evidence-based improvement of the regulatory system of innovative medicines requires an empirical evaluation of the current regulatory system and previous marketing approval decisions. We conducted such analyses to identify critical factors of successful marketing approval. The body of the thesis generated evidence from both a regulatory and industry perspective, by focusing on previous decisions on marketing approval and on regulatory scientific advice. In this chapter we will discuss how bottlenecks and factors for success we identified, can lead to evidence-based recommendations for improvement of marketing authorisation of new medicines.

DETERMINANTS FOR MARKETING AUTHORISATION OF NEW MEDICINES

In the EU the Committee for Medicinal Products of Human Use (CHMP) evaluates benefits and risks of new active substances and finally advises the European Commission about (non-) approval for market entry. The centralised procedure offers licensing in all member countries and is obliged for new active substances and for biotechnological products, medicinal products to treat cancer, HIV, neurodegenerative diseases, diabetes, and auto-immune and viral diseases [9]. In Chapter 2 we provide empirical analyses of CHMP's assessment of new active substances, including orphan medicinal products (OMPs), to explore underlying determinants of (non-) approval. As outlined in the introduction of this thesis, potential determinants for marketing approval can be divided in three main categories that follow the drug development cycle: (i) the drug development plan that the company has followed (ii) clinical efficacy and safety outcomes of

the confirmatory studies and (iii) medical need. All three phases contribute to the benefit-risk assessment. The studies in Chapter 2 address the association between these three categories of determinants and (non-)approval, and findings will be discussed in more detail below.

Learning in early drug development

Since efficacy and safety results are explicit elements of the benefit-risk assessment, their strong association with marketing as shown in chapter 2.1 is as expected. The analyses in this chapter demonstrate that non-approval is often not just the consequence of disappointing phase III study results, but also of the submitted development plan; i.e. *how* exploratory and confirmatory evidence is generated. Notably, the learning phase (or exploratory studies) of innovative drug development was an important driver of marketing approval; emphasizing the attention drug developers should pay to that phase. This is especially the case for evidence on the mode of action, clinical proof of concept and on the selection of appropriate doses for phase III confirmatory studies. Robust exploratory studies that demonstrate the mode of action or a clinical dose-response relation with an effect on a surrogate endpoint are particularly valuable for regulators when there is uncertainty regarding efficacy and safety results in benefit-risk evaluations, e.g. when multiple confirmatory efficacy studies yield contradictive results.

For *drug developers* exploratory proof of concept studies seem particular important to fuel go-no go decisions to move to next phases in drug development. Appropriate preclinical and early phase I and II studies reduce attrition rates later in drug development. PK/PD principles such as understanding the exposure to the drug target, target binding and functional pharmacological activity at the site of action have been associated with an improved chance of progression to phase III development [10]. Several recent studies in high impact journals advocated investments in proof of concept studies and better target validation to increase the success rate of phase II studies and R&D productivity in general [1,4,10,11].

Chapter 2.1 demonstrated that in regulatory practice the development of several new active substances was continued and a marketing authorisation application was submitted despite deficits in the learning phase. In 30 out of 68 regulatory assessments studied, major objections were raised about at least one aspect of the learning phase. The high proportion of applications of medicines with a deficit in the learning phase may be attributable to the current need for new marketing approvals that may make companies decide to progress into phase III despite only marginal statistically significant efficacy in phase II [11-14] or the fact that regulatory guidelines seem ambiguous in their requirements or vary between therapeutic areas. Guidelines for specific therapeutic areas may be reevaluated for their explicitness on mode of action, early proof of concept and dose finding requirements.

Another reason for lack of robust exploratory studies could be the lack of scientific knowledge on how to conduct such studies. For some diseases such as diabetes and osteoporosis, the pathophysiology is known and surrogate markers have been developed and validated that could be used in exploratory studies to demonstrate proof of concept and a dose-response curve. However, for some other indications like psychiatric disorders current knowledge is limited to potential target sites, their mode of action and the type of receptor binding. For these disorders future research [15] should offer the knowledge to guide proof of concept studies [16]. In the Escher-project several initiatives were taken to develop innovative surrogate endpoints, in particular to estimate long-term renal and cardiovascular outcomes [17,18]. The validation of surrogate outcome measures stands high on the research agenda of both EU and US public-private partnerships [19,20]. Importantly, regulators should be involved early in the discussion whether validated surrogate outcomes can be acceptable in regulatory practice [21].

Confirmatory drug development

An appropriate design of pivotal clinical studies ensures the validity and applicability of efficacy and safety results. In contrast to exploratory drug development, confirmatory drug development has more often been subject to empirical science studies. Van Luijn et al. demonstrated that only 48% of approved medicines between 1999 and 2005 had been compared with medicines available at the market at the moment of marketing authorisation [22]. In 2002 Pignatti et al. found that lack of randomized clinical trials were a major reason for marketing failure of innovative medicines. Concerns and objections were found in 43% of 110 marketing authorisation applications [23]. In chapter 2.1 we demonstrate that in 2009 and 2010 in 23 of 68 (34%) applications of new active substances regulators raised "concerns" or "major objections" related to the design of the clinical studies. Often, regulators emphasized the need for (active) comparative studies. A statistically significant association between "inappropriate" study design and non-approval could not be established, possibly because in most cases the major objections, measured at day 120 of the marketing authorisation procedure, were addressed at a later stage in the procedure. Our analysis in Chapter 3.2 demonstrates that companies also find it relevant to discuss with regulators whether and how to conduct non-inferiority (NI) trials with an active comparator. In 22% of all scientific advice requests at EMA, companies discussed whether and how to conduct such NI trials, e.g. how to determine the NI margin. A brief exploration of NI guidelines in Chapter 3.2 indicates that these could be more explicit and consistent among therapeutic areas.

Because of the criticism regarding the low quality of clinical studies underlying approval of OMPs [24,25], we stratified our marketing approval evaluations of new active substances on orphan status to assess whether lower standards are

applied compared to non-OMPs. This analysis demonstrates that EMA regulators equally often identify study design issues for both groups and, thus regulatory standards seem equally high for OMPs and non OMPs, albeit that the issues raised by regulators were different between the two groups. Importantly, however, lower quality of OMP study designs, e.g. single arm studies, was only allowed when alternative therapies were lacking and under the scope of conditional or exceptional approval.

Clinical Outcomes and Clinical relevance

Efficacy and safety outcomes of pivotal clinical studies are the core of the benefit-risk assessment and played a decisive role as shown by the analyses in Chapters 2.1, 2.2 and 2.3. These results provide evidence of the validity of our data. The finding that some products with disappointing efficacy or safety outcomes are still approved was remarkable. This occurred, for example, under the condition of label-restrictions, when a subpopulation benefited from the product, but not the initial study population.

Chapters 2.1 and 2.3 demonstrate that clinical relevance – although not formally considered in the benefit-risk assessment - is also an important determinant of marketing approval. 'Clinical relevance' was broadly defined by i) medical need: the availability of alternative therapies for the indication, or explicit remarks by the regulators in the final benefit-risk evaluation about ii) impressive clinical benefit or iii) a large effect size. From Chapter 2.1 it became evident that regulators also take the potential impact/benefit of the drug for clinical practice, including the size of the effect, into account. The fact that 38 (55%) met at least one of the "Clinical relevance" criteria, is at variance with the often heard criticism that new active substances hardly bring any pharmacological or clinical advantage [8].

Although in Chapter 2.3 the lack of alternative therapies was found a significant factor in approval decisions of OMPs that could help overcome deficiencies with regard to clinical outcomes, this was not confirmed in Chapter 2.2. Methodological challenges in data collection (see below) may account for this discrepancy.

Marketing authorisation of Orphan Medicinal Products

Over the last decades major progress has been made in bringing therapies for rare diseases to the market. The considerable proportion of OMPs among new active substances is in line with the fact that the Orphan Regulation is generally perceived as a success [26]. By May 2011, a total of 855 orphan designations had been granted [27]. An application for an orphan designation is considered a serious intention by a sponsor to initiate the development of a medicinal product for a rare disease, finally leading to marketing authorisation [28]. The incentive of market exclusivity [29] probably contributed considerably to the high number of orphan designations. Chapter 2.3 demonstrates that for 73 rare diseases (representing

a small proportion of the 6000-8000 rare diseases described) an OMP had been authorised for marketing in the EU since the introduction of this regulation.

The large difference between the number of orphan designations and submissions/marketing approvals illustrates that certain factors complicate the translation of rare disease research into clinical drug development. As previously discussed standards for drug development plans are relatively high and not meeting these standards is associated with non-approval. In chapter 2.3 we also studied factors related to experiences of regulators with the drug (previous approval of the drug outside the EU) and experience of the company in drug development. In a similar study of OMPs licensed at FDA, company size and experience was found to be associated with marketing approval [30]. Our study of marketing approval submissions of OMPs suggest that both initiation of OMP development and successful marketing authorisation depend on the disease category. Most marketing approval submissions of OMPs were in the field of oncology: 35% of all applications, of which 70% was approved. Uncommon cancers represent the highest number of orphan designations and marketing authorisations in both the EU and the US [26,31]. The high number of orphan designations for oncology indications is partly due to stratification of common cancers into molecular subsets to become 'uncommon or rare cancers' [32]. Research into these specific molecular subsets has led to valuable results for products with a specific target leading to marketing authorisation for rare and even more common cancers (e.g, epidermal growth factor receptor inhibitors in non-small cell lung cancer or the protein kinase inhibitor Glivec® that is currently licensed for six indications) [26,33].

Orphan designations are hardly requested for certain other types of rare diseases such as certain neurodegenerative diseases [26,34]. In chapter 2.4 the question why for only few of the many *exceptionally* rare diseases applications for orphan designations have been submitted to FDA and/or EMA is addressed, focusing on the role of public scientific knowledge. Our analysis of orphan designations for exceptionally rare metabolic diseases demonstrates that besides prevalence of the disease, published scientific knowledge on the preclinical proof of concept of a drug target is the main driver for a request for an orphan designation application. Fundamental research to better understanding the underlying disease that causes the symptoms is needed to find necessary drug targets for those therapeutic areas and diseases for which orphan designations are needed but for which a targeted drug is hardly ever submitted for regulatory assessment [28]. Such knowledge of the underlying disease and drug targets would not only be instrumental to receive an orphan designation, but according to the results of chapter 2.1, this could ultimately also increase the probability of obtaining marketing approval. In the EU Seventh Framework Programme (FP7; 2007-2013), the focus in rare disease research lies on strengthening the international collaboration between industry, universities and research centres in studying pathophysiology of rare diseases and translating these into therapeutic interventions [35]. Regulators

could further explore expanding opportunities for scientific advice *before* orphan designations are applied for, i.e. at the very early stage of preclinical proof of concept.

OPTIMIZING THE SCIENTIFIC ADVICE PROCEDURE

The scientific advice regulation of the EMA was renewed in 2006 to enable companies to discuss development plans with regulators on a broader scope of issues [36]. Scientific advice has also been included in various regulations to facilitate drug development, e.g. in the regulation of OMPs, the paediatric regulation and the regulation for advanced therapy medicinal products [29,37,38]. Regnstrom et al demonstrated that compliance with scientific advice is associated with a higher rate of successful marketing authorisation [39]. The relevant role of (early) drug development as described in Chapter 2, also illustrates that scientific advice can be effective. Chapter 2.1 shows that in 2009 and 2010 45 of 68 (66%) new active substances were preceded by scientific advice. Our analysis in Chapter 2.3 demonstrates that protocol assistance (the special form of scientific advice available for companies developing designated OMPs for rare diseases) was only received in 48% of OMPs that were submitted for marketing approval by 2010. For the numerous diseases for which orphan designations exist, but clinical development is a major challenge, regulatory protocol assistance seems a useful tool and should be more strongly advocated. The results of Chapter 3 indicate that opportunities to optimize this procedure lie in the objective, timing, and formal character of regulatory scientific advice.

Objective of scientific advice

The EMA emphasizes that scientific advice aims to discuss development plans prospectively and not to pre-evaluate study results to support a marketing authorisation application. During scientific advice, issues related to all phases of medicine development can be discussed, e.g. quality (manufacturing, chemical, pharmaceutical and biological testing), preclinical (toxicological and pharmacological tests) or clinical issues (early and confirmatory clinical studies pre- and post-approval), as well as opportunities for conditional or exceptional approval [36]. Chapter 3.1 demonstrates that, no matter their size and thus experience, all companies request scientific advice primarily to be reassured that ongoing clinical development plans sufficiently comply with regulatory requirements and guidelines. Chapter 3.2 focuses on scientific advice on a specific topic in current innovative drug development: the non-inferiority (NI) study design. Also in this study general questions to gain reassurance on the development plan are frequently asked. In the qualitative analysis in chapter 3.3 heads of research of small and medium sized enterprises (SMEs) confirm that gaining reassurance was one of the major reasons to request scientific advice. It

also revealed SME's objective to (indirectly) show decision makers their serious intentions to develop a new product. Scientific advice is used to a lesser extent for specific questions about development plans in cases where guidelines provide insufficient detail. This current practice of scientific advice by pharmaceutical companies is not fully in line with the EMA's expectation that scientific advice can help to optimize development plans. Regulators should therefore more clearly communicate the primary goals of regulatory scientific advice.

Timing of scientific advice

The EMA does not specify timelines for scientific advice but companies can seek scientific advice as often as deemed necessary and during all phases of the product lifecycle: from the initial development phase of the medicine to the post-marketing phase. Since 2006, follow-up advice can be applied for, with additional questions rather than further discussions pertaining to previously provided scientific advice. Follow-up advice includes post-marketing advice on risk management plans [36]. According to the EMA Roadmap to 2015, scientific advice should be expanded to provide *continuous* scientific support during the development of a medicine, combined with *earlier* appointment and involvement of (co-)rapporteurs, which would augment the interaction between regulators and sponsors during the development of medicines [40].

Chapter 3.1 indicates that current scientific advice is neither provided at an early stage nor a continuous process. Most questions are asked about the later stages of the pre-authorisation phase, e.g. discussion on the interpretation of phase III guidelines when phase III studies are already on-going. Advice concerning early development is asked less frequent in general, and more often by small companies. SMEs explained that because of long timelines of the procedure, studies may have been initiated at the time the study is discussed with regulators (chapter 3.3). Chapter 3.1 demonstrates that companies ask scientific advice from different national regulatory agencies, rather than seek follow-up advice at the Dutch Medicines Evaluation Board. Chapter 3.2 showed that for non-inferiority design, follow-up advice requests to EMA, was high (23%).

The results of Chapter 2.1 support that early and continuous scientific advice can be beneficial for pharmaceutical innovation. However, it is questionable whether this is feasible when maintaining the current demanding and costly procedure. Although SMEs benefit from fee reductions for scientific advice at EMA, Chapter 3.3 demonstrates that the current fee can still be considerable, particularly in an early phase of drug development when scientific advice can be most relevant but future return on investment is most uncertain. Further evaluation of this procedure could point out to what extent a continuous scientific dialogue can be implemented. An alternative solution may be additional scientific interaction of a more general nature such as workshops, information days, and

guideline consultation procedures. Some of these activities are organized by regulatory agencies, such as EMA, to discuss scientific issues, including novel study designs and draft guidelines, but this could be expanded [41].

Formal character of scientific advice

Companies are not obliged to follow the advice: scientific advice is not legally binding with regard to a future marketing authorisation application, neither for companies nor for authorities [36]. Companies, however, have to justify deviations from scientific advice to the CHMP when applying for marketing authorisation. Similarly, any deviation from previous regulatory scientific advice has to be explained by the CHMP during the review of a marketing authorisation application [42]. Chapter 3.3 demonstrates that companies often perceive the conservative approach of regulators as problematic, especially when this results in ambiguous advice and requests for additional evidence during drug development. The consequence is that companies are inclined to 'play safe' and comply with all available guidelines, also with those guidelines that companies consider a waste of time because of limited added value or the availability of better alternatives. According to SMEs reaching some sort of binding agreement with regulators about their confirmatory development plan, with room for adjustments based on new scientific developments, is preferable. Such a procedure may be a solution to the ambiguous advice sometimes provided by regulators and to the current complex dual role of regulators, being an advisor and (indirectly) an assessor at the same time. Sufficient expertise among regulators would be essential for the success of such a binding procedure. Further research could identify opportunities and challenges for regulatory agencies to offer such a procedure to applicants, possibly taking the FDA Protocol assessment as an example [43].

REGULATORY SCIENCE: METHODOLOGICAL CHALLENGES IN EMPIRICAL SYSTEM ANALYSIS

The analyses presented in this thesis are examples of 'drug regulatory science'. Leading regulatory agencies worldwide have endorsed regulatory science as an approach to increase the efficiency of the drug regulatory system. There is no uniform definition of regulatory science; FDA defines it as *"the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products"* [44,45]. According to EMA regulatory science consists of the areas of science that are used in the assessment of the quality, safety and efficacy of human and veterinary medicines throughout their life-span, as well as the scientific areas used in regulatory decision-making [46].

Our empirical analyses add to this relatively unexplored field of research. In particular, the application of epidemiological methods to quantify the association

between various determinants and marketing (non-)approval is relatively new in this area. Until now, the EMA only provides descriptive results of main marketing authorisation procedures and scientific advice on an annual basis in reports [6,47]. In addition, most frequent themes of major objections are sometimes presented in these reports or in presentations on conferences by regulators [48]. Only few studies so far explored (causal) relations between relevant determinants and regulatory approval [22,30,49,50]. Most of these studies are based on publicly available assessment reports and only occasionally on confidential regulatory documents such as the scientific advice documents studied in chapters 3.1 and 3.2 and the major objections assessed in chapters 2.1 and 2.2. In order to continue empirical analyses for evidence based improvement of the regulatory system, these and other regulatory documents that are currently confidential, should be available for research by independent researchers. Whether these documents can become publicly available or via confidentiality agreements on request only, is a topical issue that is currently being worked on by EMA [51]. For future studies using such assessment reports and scientific advice documents, the lessons learned and challenges encountered during our endeavors can be helpful and will be discussed in more detail below.

Defining determinants

First of all clear definitions of relevant determinants are essential. Definitions should clearly include the scope of the topic, e.g. comments on preclinical and/or clinical safety pharmacology studies, on trial duration, or on the design of one or more of the pivotal trials. In principle this is facilitated by predefined phases in drug development: from quality tests, through preclinical, clinical phase I, II, III, to ultimately post-marketing studies. However, we noticed that in the assessment reports included in Chapter 2.1 such a distinction was not always obvious for the exploratory clinical studies in (mostly) phase I and II.

To study these exploratory studies we had to study the dossiers submitted by the applicant. Considerable variety existed in the number and type of exploratory studies submitted, which may be explained by (i) the type of product (biotechnological, advanced therapy medicinal products or new chemical entity) or (ii) the combination of multiple study objectives for efficiency reasons in one clinical study (proof of concept can be demonstrated in a phase II dose-ranging study or during the conduct of PK/PD studies). The relevant role of exploratory studies as demonstrated in Chapter 2.1 calls for more clear inclusion of assessment results in publicly available assessment reports.

In Chapter 2, a central element of our analysis was the measurement of comments from regulatory review. This approach highlights a second relevant issue when defining determinants: how to recognize a regulatory concern in (withdrawal) European public assessment reports (EPARs and WEPARs)? Major objection

documents consist of briefly described objections listed with bullet points, but recognizing concerns in public assessment reports is more complex. Although in the preceding years, assessment reports evolved towards structured documents with standard formats and subheadings, variation exists among the reports, in particular among those before 2007. In order to recognize regulatory concerns from these documents and minimize subjective scoring, definitions of determinants should not only include the scope of the topic but also mention when to consider a comment a "concern". Having a second review of (a sample of) the data collection is commendable to reduce subjectivity in scoring of these determinants.

Consistency of determinants

Measurement of comments from regulatory review rather than the data itself depends on the assumption that regulatory review is done in a consistent way. Figure 1 depicts the steps taken from dossier submission to decision making and demonstrates how this approach depends on consistency in regulators' reviews. The dossiers submitted by applicants are heterogeneous in development plans and clinical study outcomes (step 1). In step 2 bias could occur in the regulatory review in the way any deficits were identified and worded in the assessment reports. For example, a major objection could in one case refer to the use of 'response rate' as primary endpoint in a pivotal study of an oncological product or in another case to the use of 'progression free survival' rather than 'overall survival'. This variety is not a problem for our study as long as 'response rates' or 'progression free survival' are recognized as being insufficient by each regulator. In particular in Chapter 2.2 this could have been an issue when comparing OMPs and non-OMPs dossiers. We assume that regulators review submitted dossiers in a consistent way, also for OMPs. The association of regulators' comments with the final marketing approval decision then provides what regulators' consider most relevant for marketing approval (step 3).

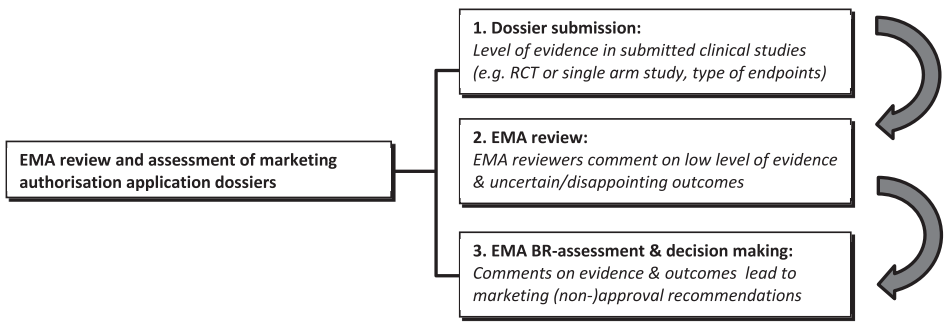

Figure 1. EMA review & assessment of marketing authorisation application dossiers

Other limitations

Major challenges in the type of studies we performed are the relatively small number of products included in our study and the heterogeneity of the products. The small sample sizes partly resulted from the time involved in scrutinizing the information of a single application or scientific advice. In addition, the limited number of OMPs approved to the EU market was low. The variety in products is the consequence of looking at all new active substances or OMPs in a certain time span, rather than taking all new active substances for a specific therapeutic area over a considerable number of years. In our analyses we aimed to demonstrate crucial factors in *recent* approval decision making. Despite these differences between medicines, their approval decision is largely based on similar requirements of efficacy, safety and quality. Thus, despite the wide confidence intervals and variety among products, we believe our study does yield valuable evidence to base further recommendations on.

The added value of qualitative research

The results in most chapters of this thesis describe the association between determinants and marketing approval in a quantitative way, but do not reveal the reasons behind regulatory concerns or asking scientific advice. Such reasons can be explored with qualitative research, as was done for the case of clinically relevant differences in approval decisions for oncology medicines between the EMA and FDA by Trotta et al. [52]. Our qualitative analysis of Chapter 3.3 demonstrated additional scientific objectives to those retrieved from scientific advice questions in Chapters 3.1 and 3.2. Insight in the reasons why SMEs ask scientific advice yielded valuable information to optimize the scientific advice procedure. These results encourage continuation of qualitative studies of specific elements in the drug regulatory system.

IMPLICATIONS FOR FUTURE MARKETING AUTHORISATION OF NEW MEDICINES

The results presented in this thesis may be used to improve the drug regulatory system. In the last decade many (regulatory and research) initiatives have been taken to increase the efficiency of the system and to stimulate the development of medicines urgently needed in daily clinical practice [37,38,53,54]. In addition new proposals are introduced by researchers and policy makers such as adaptive marketing approval [55,56] and supportive instruments for benefit-risk assessments [57-59]. Besides, further collaboration between leading regulatory agencies and health technology assessment bodies is part of the agenda of the regulators [40]. How would the results of this thesis fit into these proposals for improvement and which topics warrant further research?

First, several parties recently suggested to transform the current system into a more adaptive licensing approval system, based on stepwise learning under conditions of acknowledged uncertainty, with continuous data collection and regulatory evaluation [55]. These proposals emphasize that knowledge about medicines is not binary but continues to evolve over time [55,56]. With improved knowledge in the early stages of drug development, the marketing authorisation and the further development of knowledge about the product could be prospectively planned. One approach is for example an early determination of efficacy in an RCT in a small well-defined population. Including an additional safety endpoint in such a small study could detect early safety problems [55]. In line with Chapter 2.1 such an adaptive approach of marketing authorisation calls for a more pivotal role for learning studies, which could function as a robust basis of evidence on how the product works and which patients are most likely to benefit from the new treatment. Having an early scientific dialogue between regulators and applicants provides an opportunity to tailor evidence requirements for initial marketing approval. Continuing this dialogue during drug development enables discussion of further efficacy *and* pharmacovigilance requirements in later phases.

Secondly, quantitative scientific methods enabling decision-making have gained attention in the last few years. Different approaches are being studied to standardize benefit-risk assessments and therefore enhance transparency and consistency of the decision process, of which multi criteria decision analysis is an example (MCDA) [57-58]. One of the Escher-projects has developed software for MCDA: the Aggregate Data Drug Information System (ADDIS) [59-60]. In the ADDIS software efficacy and safety outcomes of confirmatory trials of multiple comparators can be compared. Clinical relevance is taken into account when regulators attribute priorities to beneficial and adverse effects. This thesis demonstrates that clinical relevance is currently an essential element of weighing benefits and risks, but measuring the role of clinical relevance in current decision making is challenging and warrants further research. Instruments for benefit-risk assessment could help to clarify and (re)align judgments about clinical relevance. Their role in optimizing the benefit-risk assessment should be explored further [61].

Third, global marketing authorisation is now current practice for both large *and* small pharmaceutical companies. Thus, they increasingly also have to meet requirements of for example the US Food and Drug Administration (FDA), the Japanese Pharmaceutical and Medical Devices Area (PMDA) as well as EMA. Differences in marketing approval decisions between regulatory agencies occur, based on the same application dossier, as was demonstrated in an analysis of FDA and EMA approval decisions on anticancer drugs [52]. EMA and FDA have established a cooperation by offering parallel scientific advice to applicants on request. The goal of parallel scientific advice is to provide a mechanism to exchange views on scientific issues during the development phase of new

medicinal products (new human drugs and biologics) between EMA and FDA regulators [62]. Although scientific information is exchanged between the two agencies, an independent advice is given to the applicant by both agencies [62]. It would be worth studying opportunities for increased interaction between these two agencies and applicants from the beginning of the lifecycle of a new product. Besides regulatory science studies could assess to what extent differences in scientific advice and marketing authorisations occur and what the practical implications of these differences would be. Moreover, the possibility to harmonize marketing approval decisions or for joint decisions by multiple registration authorities could be explored.

Not only the regulatory system changed in the last decade, the world around this system also changed. Regulatory marketing authorisation may no longer be the (only) crucial step for access to medicines. Especially in the European setting, marketing authorisation is followed by a process of reimbursement decisions at the national level [63]. Health Technology Assessment (HTA) bodies evaluate the cost-effectiveness of new medical technologies such as medicines, as input for reimbursement decisions. The relative effectiveness of a new medicine constitutes an important element of cost-effectiveness assessments, it compares beneficial effects of interventions when provided under the usual circumstances of health care practice. [64] Studies comparing decisions from regulatory and reimbursement agencies may yield important information on the criteria applied by these agencies and could be instrumental to further optimize the path from drug development to prescription in daily practice.

Without some alignment of requests for evidence by marketing authorisation agencies and health technology assessment bodies, reimbursement may be unnecessarily rejected. EMA and the HTA bodies collaborating in EUnetHTA Joint Action have begun to explore how scientific advice could be harmonized with advice given by HTA bodies, and to establish the evidence that both groups require [65,66]. Stimulating scientific advice may be an important, early and continuous, tool to align assessors from several bodies involved in assessing the value of new drugs and may well contribute to more efficient allowing of new medicines to the market. Further research could establish for which part of drug development harmonization of scientific advice is needed most.

CONCLUSIONS AND FINAL CONSIDERATIONS

This thesis offers empirical analyses of the drug regulatory system in the EU to facilitate future evidence-based improvement of the regulatory system. The analyses provide insights for both pharmaceutical industry and regulators that may increase approval rates and ensure that clinically relevant medicines are approved to the market.

This thesis demonstrates the role of learning and gaining scientific knowledge in the early phase of drug development. Pharmaceutical companies should put more effort in (pre-)clinical exploratory studies to enhance approval rates. In addition, they are encouraged to prepare comparative confirmatory studies in a well-described population, even for OMPs. Seeking regulatory scientific advice, earlier and continuously during drug development to support the design of appropriate development plans can further increase approval rates. This thesis also shows that clinical relevance has become an important part of current benefit-risk evaluations, complementing efficacy, safety and quality standards. This should stimulate pharmaceutical companies to develop medicines that are most needed by society.

For regulators, this thesis provides insight in their current practice of benefit-risk evaluations and scientific advice. Regulatory decision makers could better communicate the relevance of exploratory studies for marketing approval, for example by including main findings more explicitly in public assessment reports. Regulators' attention to understanding how the medicine actually works connects well with potential future adaptive licensing approaches. Regulators are strict on comparative phase III study designs with clinically relevant endpoints, even for OMPs, which is a step in the right direction to stimulate clinically relevant products and minimize the efficacy-effectiveness gap. To support future innovative methods in development plans much effort should be put in early scientific advice by regulators with (expert understanding of) state of the art science. In addition, a more formal status of scientific advice could be reconsidered to optimize the applicant-regulator dialogue. Finally, regulatory documents should be opened for empirical scientific research to support evidence-based improvements of the regulatory system.

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5

SUMMARY AND SAMENVATTING

5.1

SUMMARY

SUMMARY

Marketing approvals of new medicinal products can count on large interests of both patients in need of new medicinal therapies and the pharmaceutical industry. Drug regulatory authorities, such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) act as independent governmental third parties that decide about marketing authorisation. The EU regulation of marketing approval of medicinal products aims on the one hand to protect public health by preventing that low-quality, unsafe, or inefficacious products enter the market. On the other hand the regulation aims to promote public health by ensuring that patients gain access to medicines without unnecessary delay. Indeed with this regulatory system many valuable safe and efficacious medicines were brought to the market. **Chapter 1** demonstrates that there are also important challenges that this system has to face in the future, to ensure that a continuous flow of innovative medicines will enter the market without unnecessary delay and to have those medicinal products developed that are most needed by society. Currently there is a trend of rising research and development (R&D) expenditures, but no increase in the number of newly developed medicines submitted to regulatory agencies. The non-approval rates of new active substances at EMA usually lies around 25%, but was 40% in 2009. According to pharmaceutical companies one of the reasons for the decline in efficiency of the development of innovative medicines is regulators being overly cautious, resulting in rising R&D expenditures and long drug development timelines. Over the years, regulatory agencies have acknowledged the need to facilitate and encourage innovations for medicines most needed by society and introduced incentives and regulations to achieve this. However, it is still not clear what the determinants of successful marketing authorisation are. In addition, the role of newly developed tools and incentives, such as scientific advice, has not been studied in detail. In order to further improve the marketing authorisation system there is a need for empirical studies to gain insight in the way benefits and risks are evaluated and approval decisions are made by regulatory authorities. This thesis, which is part of the Escher-project, offers empirical analyses of the drug regulatory system in the European Union to facilitate future evidence-based improvement and provides both a regulatory and industry perspective.

In **Chapter 2**, we identified determinants of marketing approval of new medicines, with a special focus on orphan medicinal products (OMPs) to treat rare diseases. In **Chapter 2.1** we presented a detailed analysis of all marketing applications for new active substances considered for approval at the EMA in 2009-2010. We assessed to what extent the design of the development plan (specified in learning and confirming phase), the clinical outcome (efficacy and safety results) and clinical relevance according to the EMA Committee for

Medicinal Products for Human use (CHMP), were associated with licensing failure. For these three categories, we identified key variables and the presence of regulators' concerns or major objections about these variables. For the category development plan we distinguished between 'learning-phase studies' (early-stage trials, for which we assessed the variables mode of action, proof of concept, pharmacokinetics, dose finding and safety pharmacology) and 'confirmatory studies' (late-stage trials, for which we assessed study design, choice of primary end point, target population, trial duration and statistical analysis). Data were retrieved from European Public Assessment Reports (EPARs) and confidential dossiers in the EMA database (original preclinical and clinical study assessment reports and lists of major objections on day 120 of the application procedure). Of all 68 applications evaluated by the CHMP, 45 (66%) were approved, whereas 23 (34%) were not; 6 received a negative opinion and 17 were voluntarily withdrawn by the applicant before a final opinion was made. Univariate and multivariate logistic regression analyses demonstrated that a disappointing assessment of the clinical outcome (defined as no convincing statistical significant effect on primary endpoints and/or when serious safety concerns were raised during the 210 days of the procedure) was the major driver for non-approval (odds ratio (OR) 21.7; 95% confidence interval (CI) 5.0–94.0). Non-convincing clinical relevance contributed less to the likelihood of non-approval (OR 4.6; 95% CI 1.1–20.0) than a disappointing clinical outcome. Conversely, positive scores on clinical relevance can help overcome deficiencies with regard to clinical outcome, particularly when good alternative treatment options are lacking for the disease. In addition, this study demonstrated the relevance of the underlying development plan (learning and confirming) for increasing the likelihood that a medicinal product is approved (OR 6.1; 95% CI 0.9–42.7). More in-depth analysis of the learning-phase studies identified that insufficient evidence on the mode of action, proof of concept and dose finding were significantly associated with licensing failure. This study indicates that relevant learning-phase studies are valuable in reducing the number of failed dossiers and speeding up pharmaceutical innovation. Drug developers are encouraged to increase investments in such studies before moving to large and more costly Phase III trials.

Given the complexities in clinical drug development for rare diseases, the question arises which factors determine their marketing authorisation and whether the clinical evidence supporting the licensing of OMPs can meet the same standards of scientific proof as compared to non-OMPs. In **Chapter 2.2** we compared orphan and non-orphan marketing authorisation reviews evaluated by the EMA in the period 2009-2010. We studied whether differences existed in the number and type of deficits brought forward during the EMA review, regarding the clinical development plan, clinical outcome and medical need and studied whether these deficits were similarly associated with marketing approval in the

EU. In the study period, 17 OMPs and 51 non-OMPs were reviewed by the EMA of which 12 OMPs (71%) and 33 non-OMPs (65%) were approved. There were differences between OMPs and non-OMPs related to the clinical development plan: in study design (i.e. use of single arm studies), clinically relevant endpoint (i.e. more challenging for OMPs) and finding the appropriate target population (i.e. less a challenge for OMPs than for non-OMPs), related to clinical outcome in the safety profile (i.e. for OMPs doubts were raised about *potential* risks rather than concerns about *identified* risks in Phase III studies), and related to acknowledged high medical need (i.e. in two thirds of OMP dossiers and in one fifth of the non-OMP dossiers). But overall these differences did not result in differential weighing of the benefit-risk for marketing approval of both OMPs and non-OMPs. In an aggregated analyses of the three categories and their association with marketing authorisation, RERI (relative excess risk due to interaction)-outcome measures demonstrated strong overall similarity of regulatory decision making in the study period, underlining that regulatory standards are equally high (clinical development plan (RERI -0.20; 95% CI -0.8-0.4), clinical outcome (RERI -0.09; 95% CI -0.8-0.6), medical need (RERI -0.08; 95% CI -0.5-0.4). Our results therefore encourage future OMP developers to search for opportunities to meet the high standards of clinical drug development e.g. for comparative study designs and validated clinically relevant endpoints.

For most of the 6000-8000 rare diseases no effective treatment exists, which makes OMP development an important public health issue. Possible determinants for marketing approval of OMPs in the EU were therefore further studied in **Chapter 2.3.** In this chapter we assessed all approved and non-approved marketing applications for OMPs in the EU since the orphan drug regulation was established in 2000 aiming at learning from ten years of regulation on OMPs. Potential determinants for marketing authorisation that were studied were related to drug substance, indication, clinical development plan, company and dialogue with the EMA. Data were collected from EPARs. Univariate ORs and 95% CIs of marketing authorisation were calculated applying logistic regression analyses. All variables with a univariate OR with a p-value <0.20 were included in a multivariate logistic regression model to calculate adjusted odds ratios (ORadj). This analysis of all marketing applications for OMPs in the EU has shown that demonstrating convincing evidence of a beneficial effect on the primary endpoint (ORadj 53.9; 95% CI 8.4–345.2) was associated with marketing approval, but also clinical trial characteristics such as the selection of a clinically relevant endpoint (ORadj 15.0; 95% CI 2.9–77.8), providing RCT data as pivotal study evidence (ORadj 6.9; 95% CI 1.3–36.1) and sufficient learning from dose finding (ORadj 8.1; 95%CI 1.6–41.2) were critical success factors. In addition, high medical need, defined as lack of an alternative therapy for the disease, seems to counterweigh uncertainties about the scientific evidence in the benefit-risk assessment of OMPs (ORadj 4.6;

95%CI 1.1–20.4). Thus, although OMPs have their inherent challenges in terms of development and assessment of benefit-risk, robust data on the real clinical benefit for the patients with a rare disease remain pivotal. Besides, taking the high medical need for drugs that target rare diseases into account is an important factor when building and evaluating OMP dossiers.

Both FDA and EMA have systems in place that offer incentives and scientific support for the development of possibly promising medicinal products for treating rare diseases. These medicines can receive a so-called orphan drug designation. Development of orphan designated products can benefit from incentives such as market exclusivity, fee reductions and protocol assistance. An application for an orphan designation can be seen as a proxy for the intention to initiate the development of a drug for the rare disease leading to marketing authorisation. Considering that the majority of low prevalence rare diseases remain without therapy, we studied in **Chapter 2.4** to what extent the level of scientific knowledge on exceptionally rare metabolic inherited diseases and their potential OMPs was associated with enterprises deciding to apply for an orphan designation. All metabolic diseases with a genetic cause and prevalence of 9 patients per 1 million of the population or less were selected from the 'Orphanet database of Rare diseases'. The outcome of interest was the first application for an orphan designation for one of these rare diseases at FDA or EMA. The level of *publicly available* knowledge of the disease and drug candidate was described by the following determinants: whether a protein function corresponding with the pathologic gene was known, whether an appropriate animal study was identified for the disease, whether the preclinical proof of principle was ascertained and whether data in men were available. Other determinants included in the study were metabolic disease class, the prevalence of the disease, disease prognosis and time of first description of the rare disease in the scientific literature. Univariate relative risks (RRs) and 95% CIs of an orphan designation application were calculated for each of these determinants. In addition, a multivariate Cox regression analysis was conducted (Forward LR). In total, 166 rare metabolic genetic diseases were identified and included in the analysis. For only 42 (25%) of the diseases at least one orphan designation was applied for at either FDA or EMA before January 2012. The multivariate results identified preclinical proof of concept of potential medicinal products as major determinant of an orphan designation application (RRadj 5.0; 95% CI 2.3-11.1) and confirmed that prevalence of the disease is also associated with filing an application for an orphan designation (RRadj 2.5; 95%CI 1.3-4.9). To expand drug development for low prevalence rare diseases future incentives should aim at stimulating fundamental research to elucidate the pathophysiology of the disease as well as the identification of drugable targets.

In **Chapter 3** we evaluated the current role and content of regulatory scientific advice, an important regulatory tool in drug development that provides an

opportunity for pharmaceutical companies to discuss development plans with regulators. Such analyses also allow for the identification of bottlenecks related to all phases of medicine development according to pharmaceutical companies.

In **Chapter 3.1** we provided an overview of scientific advice questions discussed with the Dutch Medicines Evaluation Board (MEB) in 2006–2008 and assessed whether the content of these questions addressed to a national drug regulatory agency was associated with company size. Definition of company size was based on ranking by total revenues (Scrip's Pharmaceutical Company League Tables 2008). The content of each scientific advice question was scored according to predefined domains (quality, nonclinical, clinical, regulatory, and product information), their subdomains (e.g., efficacy), and a selection of additional content variables (e.g., endpoints, choice of active comparator). In total, 201 scientific advice documents including 1,087 questions could be identified. Small, medium-sized, and large companies asked for scientific advice 110 (54.7%), 40 (19.9%), and 51 (25.4%) times, respectively. Clinical questions were asked most often (65.9%), mainly including efficacy (33.2%) and safety issues (24.0%). The most frequently discussed topics were overall efficacy and safety strategy, implying companies tried to gain reassurance for their confirmatory development plan including multiple confirmatory efficacy and safety studies. Small companies asked quality and nonclinical questions more often ($p<0.001$) and clinical questions less frequently than large companies ($p=0.004$). Small companies asked significantly more clinical questions about pharmacokinetics, including bioequivalence, than medium-sized and large companies ($P<0.001$). In conclusion, the array of topics addressed in scientific advice reveals that large companies considers the Phase III trial package and specific Phase III characteristics the most relevant issues in drug development worthwhile to discuss with regulators, whereas small companies more often aimed to discuss early drug development.

In **Chapter 3.2** we zoomed in on scientific advice on a specific Phase III trial design that has gained popularity in recent years: the non-inferiority (NI) design, which is a trial design to assess whether a new medicine is not worse than a currently available alternative medicine.. In this analysis, we identified questions on NI trials that were posed by applicants of European scientific advice in 2008 and 2009, and the responses given by the EMA to identify potential issues that may benefit from more explicit regulatory guidance. We included 156 scientific advice documents given to 94 different applicants. Our analysis of final advice letters in 2008 and 2009 yielded two major findings: (1) questions on 'whether' and 'how' to conduct an NI trial were frequently asked by applicants, but 'how' questions were more frequently posed than 'whether' questions (74 % vs. 26 %); (2) the choice of the NI margin seemed to be EMA's main concern in NI trials (36 % of total regulatory answers). In 40% of the answers, the CHMP recommended the use of a stricter margin, and in 10% of the answers on NI margin they questioned

the justification of the proposed NI margin. We conclude that difficulties still exist in selecting the appropriate methodology for NI trials. Straightforward and harmonized guidance on NI trials is needed, such as when to conduct NI trials and how to determine the NI margin. Regulatory guidelines (either as one general guideline or special sections on NI trials in disease-specific guidelines) may not be feasible to cover all therapeutic areas. In that case regulatory scientific advice may be used as an opportunity for tailored advice.

Scientific advice is generally considered an essential instrument within the regulatory system and it is increasingly being advocated. An increasing proportion of applications for marketing authorisation has been preceded by scientific advice: in 2011 this was the case for 76% of all marketing authorisation applications. Scientific advice seems to be an excellent way for small and medium-sized enterprises (SMEs) to clarify complexities in drug development. It is questioned whether scientific advice is currently used in its most fruitful way. In **Chapter 3.3**, we therefore evaluated the role of scientific advice in innovative drug development as witnessed and perceived by SMEs. We focused on three main research questions (i) What are reasons for you to request scientific advice? (ii) How did you perceive the scientific advice procedure? and (iii) What would be an optimal way of applying a scientific dialogue? A qualitative study was undertaken, conducting semi-structured interviews between July and September 2012 with eleven directors of Dutch SMEs involved in the company's research strategy to obtain marketing authorisation. SMEs appeared to request scientific advice to retrieve regulators' reassurance of their development plan, to gain regulators' trust and to fill knowledge gaps where guidelines are lacking or unclear. SMEs appreciated the scientific advice procedure and acknowledged the complex role of regulatory assessors being scientific advisor and assessor at the same time. However, the dialogue was deemed complicated by (i) the formal relation/status of the advice and uncertainty about assessors' decisions during the marketing authorisation application procedure and (ii) regulators' lack of expertise in highly innovative products in some cases. Suggestions for further optimizing the scientific dialogue thus included creating a constructive dialogue by addressing its formal status and by keeping regulators' expertise up to date, but also diminishing the administrative burden and exploring additional opportunities for informal interaction with regulators.

The body of this thesis offered empirical analyses of previous regulatory decisions on marketing approval and of scientific advice. In **Chapter 4** we discussed how factors for success that we identified, can lead to evidence-based recommendations for improvement of marketing authorisation of new medicines. This thesis demonstrates the role of learning and gaining scientific knowledge in the early phase of drug development. Pharmaceutical companies are encouraged to put more effort in (pre-)clinical exploratory studies to enhance approval rates. Besides, the analyses demonstrate that regulators are strict on comparative Phase

III study designs with clinically relevant endpoints. Pharmaceutical companies are recommended to prepare comparative confirmatory studies in a well-described population, even for OMPs. This thesis also underlines that clinical relevance has become an important part of current benefit-risk evaluations, complementing efficacy, safety and quality standards. This should stimulate pharmaceutical companies to develop medicines that are most needed by society.

Regulatory decision makers could better communicate the relevance of exploratory studies for marketing approval, for example by including main findings more explicitly in public assessment reports. The association of an appropriate development plan with marketing approval implies that scientific advice on the design of appropriate development earlier in and continuously during drug development could increase approval rates. To optimize scientific advice, regulatory authorities should also put effort in expertise in state of the art science in scientific advice. In addition, a more formal status of scientific advice could be reconsidered to optimize the scientific dialogue with regulators.

In order to continue gaining insight in the regulatory system, regulatory documents should be opened for empirical scientific research to support evidence-based improvements of the regulatory system.

5.2

SAMENVATTING

SAMENVATTING

De toelating van nieuwe geneesmiddelen tot de markt is van groot belang voor patiënten, met name met aandoeningen waarvoor geen effectieve farmacotherapeutische behandeling beschikbaar is, en voor de farmaceutische industrie. Registratieautoriteiten zoals de European Medicines Agency (EMA) en de Food and Drug Administration (FDA) in de Verenigde Staten (VS) beslissen over de markttoelating van nieuwe geneesmiddelen volgens specifieke wet- en regelgeving. De Europese regulering van geneesmiddelen heeft enerzijds tot doel de volksgezondheid te beschermen door het waarborgen van de kwaliteit, effectiviteit en veiligheid van geneesmiddelen die tot de markt worden toegelaten. Anderzijds wordt met deze regulering beoogd de volksgezondheid te bevorderen door bijvoorbeeld nieuwe geneesmiddelen zonder onnodige vertraging tot de markt toe te laten.

Dit gereguleerde systeem heeft er aan bijgedragen dat veel waardevolle werkzame en veilige geneesmiddelen tot de Europese markt zijn toegelaten. **Hoofdstuk 1** beschrijft dat er echter ook belangrijke uitdagingen zijn voor het systeem. Zo moeten er bijvoorbeeld ook in de toekomst voortdurend innovatieve geneesmiddelen zonder onnodig tijdsverlies tot de markt worden toegelaten en moeten geneesmiddelen die het meest nodig zijn in de klinische praktijk daadwerkelijk worden ontwikkeld. In het afgelopen decennium zijn de kosten voor de ontwikkeling van nieuwe geneesmiddelen gestegen, maar het aantal innovatieve geneesmiddelen dat wordt aangeboden en toegelaten tot de markt is gelijk gebleven. Het percentage geneesmiddelen dat wordt afgekeurd door de EMA schommelt rond de 25% en was zelfs 40% in 2009. Volgens de farmaceutische industrie is een van de redenen voor de verminderde efficiëntie in de ontwikkeling van nieuwe geneesmiddelen de risicomijdende houding van beoordelaars bij registratie-autoriteiten, die maakt dat er voornamelijk eisen aan het ontwikkelprogramma van geneesmiddelen worden toegevoegd met stijgende kosten en langer durende ontwikkelprogramma's tot gevolg. In de afgelopen jaren hebben registratie-autoriteiten de noodzaak gesignaleerd om de ontwikkeling van innovatieve geneesmiddelen te bevorderen en daartoe nieuwe regelgeving en stimulerende maatregelen geïntroduceerd. Het is echter onduidelijk wat de belangrijkste determinanten van markttoelating van nieuwe geneesmiddelen zijn. Ook is het onvoldoende duidelijk wat de rol en de effecten van deze nieuwe maatregelen en instrumenten als wetenschappelijk advies zijn. Voor toekomstige verbetering van het systeem van markttoelating van nieuwe geneesmiddelen is empirisch onderzoek nodig dat inzicht verschaft in de afweging van baten en risico's van geneesmiddelen en in overige potentiële factoren die meewegen in een advies over markttoelating. Dit proefschrift, dat onderdeel uitmaakt van het Escher-project, bevat dergelijk empirisch onderzoek om toekomstige verbeteringen in het regulatoire systeem van markttoelating van geneesmiddelen in de EU wetenschappelijk te onderbouwen.

In **hoofdstuk 2**, hebben we determinanten van markttoelating van nieuwe geneesmiddelen bestudeerd en van weesgeneesmiddelen voor zeldzame aandoeningen in het bijzonder. In **hoofdstuk 2.1** hebben we een gedetailleerde analyse beschreven van alle aanvragen voor markttoelating van 'nieuwe actieve stoffen' die in 2009 en 2010 zijn beoordeeld door de Committee for Medicinal Products for Human use (CHMP) van de EMA. We hebben onderzocht in welke mate eigenschappen van (i) het ontwikkelprogramma (met daarbij onderscheid makend tussen een verkennende fase en bevestigende fase), (ii) de klinische resultaten van de bevestigende studies (effectiviteit en veiligheid) en (iii) de klinische relevantie van de resultaten volgens de CHMP, waren geassocieerd met een negatief advies over markttoelating. Deze drie categorieën zijn beschreven aan de hand van een aantal specifieke variabelen, waarvoor is vastgesteld of er sprake was van tevredenheid, bezorgdheid of bezwaren bij de CHMP. Binnen de categorie 'ontwikkelprogramma' werd de verkennende fase beschreven met de variabelen werkingsmechanisme, farmacodynamiek/proof of concept, farmacokinetiek, het vinden van de meest geschikte dosering(en) voor de bevestigende fase en preklinisch veiligheidsonderzoek. De bevestigende fase (fase III onderzoek) werd beschreven met de variabelen type (vergelijkende, gerandomiseerde, geblindeerde) studie, het primaire eindpunt, de studiepopulatie, de duur van de studies en de statistische analyse. De data werden verzameld uit Europese beoordelingsrapporten (European Public Assessment Reports) en vertrouwelijke dossiers uit de EMA database (originele (pre)klinische studiedossiers en de lijst met bezwaren op dag 120 van de toelatingsprocedure). Van alle 68 aanvragen die beoordeeld werden door de CHMP werden er 45 (66%) goedgekeurd, en 23 (34%) niet (hiervan kregen er 6 een negatief advies en werden er 17 vrijwillig vroegtijdig teruggetrokken uit de toelatingsprocedure). Univariate en multivariate logistische regressieanalyses toonden aan dat een tegenvallend resultaat ten aanzien van werkzaamheid (niet-significant) of veiligheid ((potentieel) ernstige bijwerkingen) de belangrijkste factor was voor een negatief advies over markttoelating (odds ratio (OR) 21.7; 95% betrouwbaarheidsinterval (BI) 5.0–94.0). Afwezigheid van klinische relevantie droeg minder bij aan de kans op een negatief advies (OR 4.6; 95% BI 1.1–20.0). Echter, wanneer er overtuigend sprake was van klinische relevantie (bijvoorbeeld bij gebrek aan een alternatieve behandeling) kon dit tegenvallende resultaten op het gebied van effectiviteit en veiligheid compenseren. Misschien wel het interessantste resultaat van deze studie is de relevantie van een volledig en robuust ontwikkelprogramma voor markttoelating (OR 6.1; 95% BI 0.9–42.7). Een verdergaande analyse van het verkennende ontwikkelprogramma toonde aan dat onvoldoende kennis over het werkingsmechanisme, de farmacodynamiek/proof of concept en de meest geschikte dosering(en) voor de bevestigende fase significant geassocieerd waren met een negatief resultaat ten aanzien van markttoelating.

Gezien de beperkingen van klinisch geneesmiddelonderzoek voor zeldzame aandoeningen, ontstond de vraag welke factoren bepalend zijn voor markttoelating

van weesgeneesmiddelen en of het klinisch dossier kan voldoen aan dezelfde maatstaven voor wetenschappelijk onderzoek die gelden voor reguliere geneesmiddelen. In **hoofdstuk 2.2** vergeleken we de beoordelingen van dossiers voor markttoelating in 2009 en 2010 van reguliere en weesgeneesmiddelen. We bestudeerden of het aantal en type bezwaren met betrekking tot (i) het klinisch ontwikkelprogramma, (ii) de klinische studieresultaten ten aanzien van werkzaamheid en veiligheid en (iii) de beschikbaarheid van alternatieve farmacotherapeutische behandelingen bij de beoordeling verschillend was voor weesgeneesmiddelen en reguliere geneesmiddelen en of mogelijke bezwaren in gelijke mate geassocieerd waren met markttoelating. Zeventien weesgeneesmiddelen en 51 reguliere geneesmiddelen werden beoordeeld door de CHMP, waarvan er respectievelijk 12 (71%) en 33 (65%) werden goedgekeurd. Verschillen waren er met betrekking tot het klinisch ontwikkelprogramma: in soort studie (bijv. het gebruik van eenarmige studies bij weesgeneesmiddelen), klinisch relevantie van het gekozen primaire eindpunt (vaker een probleem bij weesgeneesmiddelen) en het selecteren van een representatieve studiepopulatie (vaker een probleem bij reguliere geneesmiddelen). Ten aanzien van de klinische resultaten was er een verschil in veiligheid (vaker potentiële risico's op ernstige bijwerkingen voor weesgeneesmiddelen) en klinische relevantie (bij weesgeneesmiddelen vaker geen alternatieve behandeling beschikbaar). Deze verschillen leidden echter niet tot een differentiële wijze van beoordelen van dossiers voor markttoelating. In een geaggregeerde analyse van de drie categorieën en hun associatie met markttoelating toonden RERI (relative excess risk due to interaction) uitkomstmaten aan dat deze factoren gelijk geassocieerd waren met een positief advies over markttoelating voor weesgeneesmiddelen en reguliere geneesmiddelen (klinisch ontwikkelprogramma (RERI -0.20; 95% BI -0.8-0.4), klinische studieresultaten (RERI -0.09; 95% BI -0.8-0.6), beschikbaarheid alternatieve farmacotherapeutische behandelingen (RERI -0.08; 95% BI -0.5-0.4). Deze resultaten kunnen bedrijven die weesgeneesmiddelen ontwikkelen stimuleren om een klinisch ontwikkelprogramma te ontwikkelen dat voldoet aan de standaard die voor reguliere geneesmiddelen wordt gesteld, zoals inclusie van een vergelijkende studie-arm en het meten van gevalideerde klinisch relevante eindpunten.

Voor de meeste zeldzame aandoeningen bestaat geen effectieve behandeling, wat deze groep geneesmiddelen extra relevant maakt voor het bevorderen van de volksgezondheid. Mogelijke determinanten voor markttoelating van weesgeneesmiddelen zijn daarom verder onderzocht in **hoofdstuk 2.3.** In dit hoofdstuk werden alle beoordelingen bestudeerd van in de EU toegelaten en niet-toegelaten weesgeneesmiddelen sinds de inwerkingtreding van de Europese Wet en regelgeving rond weesgeneesmiddelen in 2000. Potentiële determinanten voor markttoelating in deze studie hadden betrekking op het geneesmiddel, de indicatie, het klinisch ontwikkelplan, het bedrijf en de dialoog met de EMA. Data

werden verzameld uit Europese beoordelingsrapporten. Univariate odds ratio's en 95% betrouwbaarheidsintervallen werden berekend met behulp van logistische regressie. Alle variabelen met een univariate OR met een p-waarde< 0.20 werden geïncludeerd in een multivariaat logistisch regressiemodel. Deze analyse van alle aanvragen voor markttoelating van weesgeneesmiddelen in de EU liet zien dat een overtuigend vastgesteld werkzaam effect op het primaire eindpunt een belangrijke determinant was van markttoelating (ORadj 53.9; 95% BI 8.4–345.2), maar ook dat kenmerken van het klinisch ontwikkelprogramma zoals het gebruik van een klinisch relevant eindpunt (ORadj 15.0; 95% BI 2.9–77.8), het uitvoeren van een gerandomiseerde, gecontroleerde trial (ORadj 6.9; 95% BI 1.3–36.1) en voldoende aandacht voor het vaststellen van de meest geschikte dosering(en) voorafgaand aan bevestigende studies significante succesfactoren waren. Bovendien kon gebrek aan een farmacotherapeutische behandeling voor een zeldzame aandoening tegenwicht bieden aan onzekerheid rondom bewijs voor werkzaamheid en veiligheid (ORadj 4.6; 95% BI 1.1–20.4). We concluderen dat robuust wetenschappelijk bewijs over de klinisch baten voor de patiënt gevraagd wordt voor weesgeneesmiddelen, ondanks de uitdagingen in dit klinisch onderzoek die inherent zijn aan het zeldzame karakter van de indicatie. Het gebrek aan alternatieve mogelijkheden is bij de markttoelating echter ook een belangrijke factor.

Zowel de FDA in de VS als de EMA bieden stimuleringsmaatregelen en wetenschappelijke begeleiding bij het ontwikkelen van geneesmiddelen voor zeldzame aandoeningen. Aan deze geneesmiddelen kan de 'weesgeneesmiddelstatus' worden verleend. Ontwikkelaars van weesgeneesmiddelen met een dergelijke status profiteren van voordelen als marktexclusiviteit, kortingen op tarieven van diverse procedures gerelateerd aan markttoelating en 'protocol assistance', advies over het wetenschappelijke ontwikkelprogramma. Een aanvraag voor de weesgeneesmiddelstatus kan gezien worden als een intentie om een weesgeneesmiddel te ontwikkelen en naar de markt te brengen.

Gezien het feit dat voor de meerderheid van zeer zeldzame aandoeningen geen farmacotherapeutische behandeling bestaat, stelden we ons in **hoofdstuk 2.4** de vraag waarom voor sommige aandoeningen wel een weesgeneesmiddelstatus voor een product is aangevraagd en voor andere aandoeningen niet. We onderzochten of de beschikbaarheid van kennis over zeer zeldzame erfelijke metabole aandoeningen en mogelijke geneesmiddelen in de wetenschappelijke literatuur was geassocieerd met het initiatief om een "weesgeneesmiddelstatus" voor een product aan te vragen. Alle metabole aandoeningen met een genetische oorzaak en een prevalentie van 9 patiënten per 1 miljoen van de populatie of minder werden geselecteerd uit de 'Orphanet database of Rare diseases'. De uitkomst van deze studie was de eerste aanvraag van een weesgeneesmiddelstatus voor een van deze zeer zeldzame aandoeningen bij de FDA of EMA. Mogelijke determinanten met betrekking tot beschikbare wetenschappelijke kennis over de

ziekte en mogelijke geneesmiddelen die we hebben onderzocht waren: of de eiwitfunctie behorend bij het pathologisch gen bekend was, of er een geschikt diermodel beschikbaar was, of preklinisch de 'proof of concept' van een middel was vastgesteld en of een medicijn in de mens getest was voor de zeer zeldzame ziekte. Andere determinanten waren de ziektecategorie, de prevalentie van de aandoening, de (meest ernstige) prognose van de ziekte en de periode waarin de aandoening voor het eerst beschreven was in de wetenschappelijke literatuur. Univariate relatieve risico's (RR) en 95% betrouwbaarheidsintervallen werden berekend voor elk van deze determinanten. Vervolgens werd een multivariate Cox regressieanalyse uitgevoerd (Forward LR). In totaal werden 166 zeer zeldzame erfelijke metabole aandoeningen geselecteerd. Voor januari 2012 was voor 42 (25%) van deze aandoeningen minimaal 1 'weesgeneesmiddelstatus' aangevraagd. De multivariate analyse liet zien dat wetenschappelijke kennis over de 'preclinical proof of concept' van een geneesmiddelkandidaat is geassocieerd met een aanvraag voor een weesgeneesmiddelstatus (RRadj 5.0; 95% BI 2.3-11.1). Deze analyse bevestigde ook dat de prevalentie van de aandoening is geassocieerd met de aanvraag van een weesgeneesmiddelstatus (RRadj 2.5; 95% BI 1.3-4.9). Om geneesmiddelontwikkeling voor zeer zeldzame aandoeningen te stimuleren zouden toekomstige stimuleringsmaatregelen gericht moeten zijn op fundamenteel onderzoek naar de pathofysiologie van de ziekte, het identificeren van aangrijpingspunten van nieuwe geneesmiddelen en het testen van mogelijke geneesmiddelkandidaten.

In **hoofdstuk 3** evalueerden we de 'wetenschappelijk advies' procedure, een belangrijk instrument van registratie-autoriteiten dat geneesmiddelontwikkelaars de mogelijkheid biedt een wetenschappelijke dialoog aan te gaan over (pre-)klinische studies om de kwaliteit, veiligheid en werkzaamheid van een geneesmiddel aan te tonen. De vragen die geneesmiddelontwikkelaars stellen tijdens wetenschappelijk advies bieden inzicht in onduidelijkheden in alle fasen van de geneesmiddelontwikkeling.

In **hoofdstuk 3.1** bestudeerden we de aard van de vragen die gesteld werden tijdens wetenschappelijk advies aan de Nederlandse registratie-autoriteit in de periode 2006-2008. Bovendien onderzochten we of de inhoud van de vragen was geassocieerd met de omvang van het bedrijf. De omvang van het bedrijf (groot, middelgroot, klein) was gebaseerd op de Scrip's Pharmaceutical Company League Tables 2008 van totale bedrijfsomzet. De inhoud van elke vraag werd gecategoriseerd in vooraf gedefinieerde categorieën (kwaliteit, preklinisch onderzoek, klinisch onderzoek, regulatoire aspecten, productinformatie) en bijbehorende subcategorieën (bijv. werkzaamheid en veiligheid als subcategorieën van de categorie 'klinisch onderzoek') en een selectie van specifieke onderwerpen (bijv. eindpunt, keuze van vergelijkend geneesmiddel in een trial). In totaal werden 201 wetenschappelijke adviezen geanalyseerd,

met een totaal van 1087 vragen. In 110 (54.7%) gevallen werd wetenschappelijk advies gevraagd door kleine bedrijven, in 40 (19.9%) gevallen door middelgrote bedrijven en 51 (25.4%) keer door grote bedrijven. De meest vragen die werden gesteld behoorden tot de categorie 'klinisch onderzoek' (65.9%), voornamelijk de subcategorieën werkzaamheid (33.2%) en veiligheid (24.0%). De meest gestelde vragen waren weinig specifiek en vooral gericht op bevestiging van de geschiktheid van het algehele onderzoeksprogramma naar effectiviteit en veiligheid voor markttoelating. Kleine bedrijven stelden vaker dan grote bedrijven specifieke vragen over preklinisch onderzoek ($p<0.001$) en minder vaak over klinisch onderzoek ($p=0.004$). De klinische vragen die kleine bedrijven stelden gingen vaker over farmacokinetiek en bio-equivalentie dan middelgrote en grote bedrijven ($p<0.001$). We concludeerden dat de keur aan onderwerpen die bedrijven aan de orde laten komen in wetenschappelijk advies laat zien dat grote bedrijven fase III studies en bijbehorende specifieke eigenschappen het meest belangrijk vinden om met registratie-autoriteiten te bespreken, terwijl kleine bedrijven vaker tot doel hebben de dialoog aan te gaan over de vroege fase van geneesmiddelonderzoek.

5.2

In **hoofdstuk 3.2** bestudeerden we wetenschappelijk advies van een specifiek type fase III studie: de 'non-inferieure studie'(een studie waarin wordt aangetoond dat een nieuwe geneesmiddel niet minder goed werkzaam is dan een geneesmiddel dat al tot de markt toegelaten is). In deze analyse selecteerden we vragen én antwoorden over non-inferieure studies die besproken werden in wetenschappelijk advies van de EMA in 2008-2009, met als doel het beschrijven van de belangrijkste issues in dit type onderzoek en het identificeren van mogelijkheden voor verduidelijking van wetenschappelijke richtlijnen. In totaal werd 156 keer wetenschappelijk advies gegeven over non-inferieure studies aan 94 verschillende partijen. Onze analyse van deze 156 documenten uit 2008 en 2009 heeft tot twee belangrijke resultaten geleid: (1) bedrijven vroegen zowel 'of' non-inferiority onderzoek nodig was voor markttoelating als vragen over 'hoe' dit onderzoek uitgevoerd zou moeten worden, maar 'hoe' vragen werden vaker gesteld dan 'of' vragen (74% vs. 26%); (2) de keuze van de marge voor non-inferieuriteit leek de prioriteit van de EMA (36% van alle antwoorden behandelde dit onderwerp). In 40% van deze antwoorden werd een kleinere marge aanbevolen dan het bedrijf had voorgesteld en in 10% van de antwoorden werd gevraagd om een verdere toelichting op de keuze voor de marge. De conclusie van de analyse van wetenschappelijk advies over studies met een non-inferieur design was dat bedrijven de keuze voor de juiste methodologie complex vinden. Er lijkt behoefte aan heldere en eenduidige richtlijnen over non-inferieure onderzoeken, bijvoorbeeld wanneer dit type onderzoek nodig is en wat de juiste keuze voor de NI-marge is. Voor therapeutische gebieden waarin specifieke richtlijnen niet mogelijk zijn, is wetenschappelijk advies in het bijzonder geschikt.

Wetenschappelijk advies wordt beschouwd als een essentieel instrument van het regulatoire systeem. Een toenemend aantal aanvragen voor markttoelating wordt voorafgegaan door wetenschappelijk advies, in 2011 was dat het geval voor 76% van alle aanvragen in de EU. Wetenschappelijk advies lijkt een geschikt instrument voor kleine en middelgrote bedrijven om complexe vragen over geneesmiddelontwikkeling te verduidelijken. Het is echter de vraag of wetenschappelijk advies optimaal wordt toegepast. In **hoofdstuk 3.3** evalueerden we de rol van wetenschappelijk advies volgens kleine en middelgrote bedrijven door middel van een kwalitatief onderzoek. Een semi-gestructureerd interview werd gehouden met elf leden van management teams van middelgrote en kleine farmaceutische bedrijven in Nederland in de periode juli-september 2012. Deze mensen waren allen betrokken bij de strategie van hun bedrijf om markttoelating te verkrijgen. We stelden drie onderzoeksvragen (i) Wat zijn de belangrijkste redenen voor u om wetenschappelijk advies te vragen? (ii) Hoe ervaart u de 'wetenschappelijk advies' procedure? (iii) Hoe kan de wetenschappelijke dialoog worden geoptimaliseerd? De belangrijkste reden om wetenschappelijk advies aan te vragen was om bevestiging te krijgen van de registratie-autoriteiten van de geschiktheid van het ontwikkelprogramma, om het vertrouwen van beoordelaars te winnen en om kennis te verkrijgen over onderwerpen waarvoor richtlijnen niet bestaan, onvolledig of onduidelijk zijn. De middelgrote en kleine bedrijven hechtten veel waarde aan de mogelijkheid tot het vragen van wetenschappelijk advies en erkenden de complexe dubbelrol van beoordelen en adviseren van de registratie-autoriteiten. Echter, de dialoog werd bemoeilijkt door (i) de formele status van het wetenschappelijk advies en onzekerheid over latere beoordelingen van het ontwikkelprogramma gedurende de markttoelatingsprocedure en (ii) gebrek aan expertise over zeer innovatieve methoden en producten bij registratie-autoriteiten. Suggesties voor een optimale wetenschappelijke dialoog omvatten het creëren van een constructieve dialoog door het aanpassen van de formele status van advies over bevestigende klinische studies en door het waarborgen van de expertise over meest recente onderzoeksmethodes en technieken bij registratie-autoriteiten, maar ook het verminderen van de administratieve last en het verkennen van mogelijkheden voor informeel overleg.

In hoofdstuk 2 en 3 van dit proefschrift presenteerden we empirisch onderzoek naar besluitvorming met betrekking tot markttoelating van nieuwe geneesmiddelen en naar wetenschappelijk advies. In **hoofdstuk 4** bediscussieerden we hoe inzicht in determinanten voor succesvolle markttoelating en wetenschappelijk advies kunnen leiden tot evidence-based aanbevelingen voor verbetering van het regulatoire systeem voor de toelating van nieuwe geneesmiddelen tot de Europese markt.

Dit proefschrift liet de relevantie zien van de verkennende fase van geneesmiddelontwikkeling voor markttoelating. Geneesmiddelontwikkelaars wordt aanbevolen om meer aandacht te besteden aan (pre)klinische verkennende

studies om de kans op markttoelating te vergroten. Bovendien toonden onze analyses aan dat registratie-autoriteiten veel waarde hechten aan vergelijkende studies in de bevestigende ontwikkelingsfase, met klinisch relevante eindpunten. Farmaceutische bedrijven worden aangemoedigd om vergelijkende studies uit te voeren in een representatieve en nauwkeurig omschreven studiepopulatie, juist ook voor weesgeneesmiddelen.

Dit proefschrift wijst ook uit dat klinische relevantie een rol gekregen heeft in de afweging van baten en risico's en de besluitvorming rond markttoelating, in aanvulling op de criteria kwaliteit, werkzaamheid en veiligheid. Dit zou farmaceutische bedrijven moeten aanmoedigen geneesmiddelen te ontwikkelen waarvoor de maatschappelijke behoefte groot is.

Registratie-autoriteiten kunnen op hun beurt het belang van de verkennende studies beter communiceren, bijvoorbeeld door belangrijke resultaten van deze studies expliciet te vermelden in beoordelingsrapporten. De associatie tussen een geschikt ontwikkelprogramma en markttoelating pleit voor een belangrijke rol voor het herhaaldelijk aangaan van de wetenschappelijke dialoog, vanaf een vroege fase van het ontwikkelprogramma, om de kans op markttoelating te vergroten. Om de 'wetenschappelijke advies' procedure te optimaliseren, zouden registratie-autoriteiten zich moeten richten op het waarborgen van expertise op het gebied van de laatste innovatieve methoden en technieken bij de beoordelaars. Bovendien kan de mogelijkheid tot het maken van formele afspraken over het ontwerp van bevestigende studies in de late fase van het ontwikkelprogramma in wetenschappelijk advies worden overwogen. Om inzicht in het regulatoire systeem te vergroten en om wetenschappelijk onderbouwde verbeteringen van het systeem in de toekomst mogelijk te maken, is het nodig documenten over de beoordeling van geneesmiddelen beschikbaar te stellen voor empirisch onderzoek.

6

ADDENDUM

6.1

DANKWOORD

DANKWOORD

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6.2

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6.3

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Putzeist M, Mantel-Teeuwisse AK, Aronsson B, Rowland M, Gispen-de Wied CC, Vamvakas S et al. Factors influencing non-approval of new drugs in Europe. *Nature Reviews Drug Discovery* 2012; 11(12):903-4.

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6.4

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Michelle Putzeist was born in Sittard on August 10,1983. She graduated at the Jeanne d' Arc College in Maastricht in 2001 and obtained a Bachelor's degree in Pharmacy at Utrecht University in 2004 and a Pharmacist degree (PharmD) in 2008. She wrote her Master thesis about self-regulation of the promotion of medicines at the World Health Organisation in Geneva. From September 2008 she worked on the studies presented in this thesis as a PhD student at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences, Faculty of Science of Utrecht University under the supervision of Prof. Dr. H.G.M. Leufkens, Prof. Dr. A.W. Hoes, Dr A.K. Mantel-Teeuwisse and Dr. C.C. Gispen-de Wied. In parallel she obtained a Master's degree in Epidemiology at the Graduate School of Life Sciences, Utrecht University. She also participated in the 'Master class of Corporate Entrepreneurship' organized by Utrecht University and Rabobank. From July 2012- April 2013 Michelle worked as a consultant at Exon consultancy.