EXPLORING THE REGULATORY DECISION-MAKING PROCESS FOR MEDICINES

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EXPLORING THE REGULATORY DECISION-MAKING PROCESS FOR MEDICINES

Het besluitvormingsproces rondom
de toelating van geneesmiddelen
(met een samenvatting in het Nederlands)

Il processo decisionale per i farmaci
a livello regolatorio
(con riassunto in italiano)

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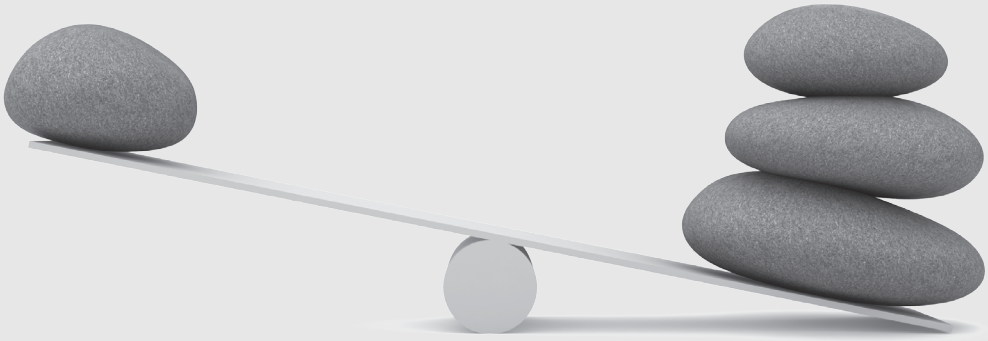
CHAPTER 1

General introduction



Background

The basis of regulatory decisions is the benefit/risk assessment, a complex process that requires the evaluation of quality, non-clinical and clinical data submitted by the pharmaceutical company. It is the core task of drug regulatory agencies to make sure that the benefits of a new medicine outweigh the risks and that only products with a positive benefit/risk balance are brought to the public. One of the main challenges faced by regulatory agencies today is the act of balancing the need for rapid market access to new drugs with the need for comprehensive data on the benefits and risks of the new drugs.[1] Unfortunately the scientific evidence supporting the use of a new product is always incomplete and therefore decisions have to be made under conditions of uncertainty. The less information available, the greater the uncertainty and, in turn, the risk of 'getting it wrong', which can compromise the credibility of the decision making process and fuel scepticism among patients, prescribers, industry and the public.[2]

The basis and process of the regulatory decisions should be both implicit and explicit. This in turn creates a problem of communicating the reasons and the rationale for regulatory decisions. A properly conducted benefit/risk assessment should be a rational process of combining objective elements (data and uncertainties) with subjective elements, leading to consistent decisions and should occur in a transparent process, communicable to the various stakeholders.[3]

The level of evidence needed for regulatory decisions

There is a great demand on pharmaceutical companies to generate the appropriate data for marketing authorization, leading to large investments and long timelines for medicines development.[4,5] It is not infrequent to hear ethical appeals in order to shorten the validation process of a new health technology, but ethical considerations are difficult to reconcile with studies that have essentially a commercial aim. Opinions on an earlier-than-ideal endpoint in the drug approval path vary from those who view it as an important step in improving public health by ensuring that beneficial drugs are made available as quickly as possible to those who see it as a dangerous shortcut that might jeopardise consumer health due to unsafe and ineffective drugs being marketed and prescribed. [6] The European Union has introduced two instruments that regulate early market access: approvals under exceptional circumstances (ECs)[7] and conditional approvals (CAs)[8]. As an additional strategy for early licensing, the International Conference on Harmonisation guidelines allow the use of interim analyses to stop clinical trials early.[9] However, recent studies showed that neither CAs nor ECs have accelerated the approval process for innovative drugs up until now[10], while there is still no consensus within the scientific community as to whether the level of evidence provided by interim analyses can be considered adequate. [11-14]

On the other hand it is not known to what extent the data requested by regulatory authorities to pharmaceutical companies are an effective and efficient investment of resources

for the promotion of public health.[15] This leads to challenging question such as: are randomized clinical trials always necessary for regulatory decisions? There may be cases when evidence can be extrapolated from existing data without necessarily performing additional studies. This approach is particularly relevant to deal with the off-label use of medicines in different therapeutic areas, patient populations and age groups.

Transparency

Transparency, consistency, auditability, and public accountability of regulatory decisions are under increasing scrutiny.[16] Communicating the rationale of benefit risk decisions to the public is crucial to promote trust in the regulatory system. Therefore full disclosure of information on internal discussions, minutes and assessment reports related to regulatory decision making is needed. Transparency about the outcomes of marketing authorisation procedures has gained importance, also for the purpose of building up a better understanding of the reasons why certain procedures for the approval of new active substances and indications tend to result in either a successful or a failed application.[17]

Consistency/divergence in regulatory decisions

Regulatory evaluation of medicinal products involves determining the balance between the benefits promised by the product and the attending potential harms. This process requires reviewing the clinical data submitted by the product manufacturer and determining the likelihood of benefits and the probability of harm, but in doing so the assessors' belief systems and values are also engaged, giving rise to variability among assessors and contributing to divergent opinions.[18]

The problem of consistency under conditions of uncertainty is that a threshold of acceptability cannot be described by a single metric.[1,2] Although the regulation of medicines is largely driven by scientific considerations, it must also operate within other frameworks – legal, cultural, public health and temporal, which may vary in different parts of the world. Therefore different regulatory authorities may take different decisions based on the same applications for marketing approval and this may generate confusion both at the level of health professionals and society at large. These differences are reflected in information supplied by agencies for medical practitioners and patients, variously called the label, the summary of product characteristics and the patient information leaflet. The importance of these differences is not which agency is correct and which is wrong in its decisions at a specific point in time but rather why the differences exist and what the policy implications are for these differences. [19]

Regulatory dynamics leading to decisions

Research so far on benefit/risk decision making has shown that multiple criteria are involved depending on product characteristics, disease/medical need, intended use,

alternative therapies and so on.[20] Given the multidimensional nature of this process and the ample uncertainty regarding virtually all these dimensions, regulators often tend to request additional data, post-approval commitments or restrictions in therapeutic indications.[21,22] A restriction of therapeutic indications aims at identifying the specific patient's population that may benefit most from the medicine. However, this kind of approval tends to be tailored to restricted patient populations and is potentially distant from the actual clinical needs, empowering third parties (e.g., scientific societies, reimbursement authorities) to define the real place in therapy of a new medicine.

The focus on anticancer medicines

Most of the research articles included and discussed in this thesis are related to anticancer medicines. This is due to several reasons. First of all, cancers claimed 8 million lives in 2010, 15.1% of all deaths worldwide, 38% more than two decades ago.[23] It has been estimated that over one-quarter of the global burden of cancer incidence occurs in Europe, despite the fact that persons living in Europe comprise only approximately one-eighth of the world's population.[24]

In oncology there are still many unmet medical needs and new therapeutic opportunities are often immediately translated into clinical practice. Today's emerging anticancer therapies are designed to block the growth and spread of cancer by interfering with specific molecules involved in tumour growth and progression. Targets can be polymorphic, have variable expression or be subject to somatic mutations that affect drug response. Based on these targeted therapies, a personalised approach to cancer management has been developed with the goal to enable identification and treatment of only those patients most likely to respond. This concept has gained momentum in recent years with the development of successful therapies such as imatinib mesylate for chronic myeloid leukaemia and gastrointestinal stromal tumours and trastuzumab for breast and gastric cancers.[25] These agents target specific molecular alterations, which are now used as predictive biomarkers of response, thereby allowing these drugs to be targeted to individuals with the appropriate tumour characteristics. In this evolving scenario guidelines on the evaluation of anticancer drugs are subject to continuous revision and important changes have been made in terms of trial design and conduct.[26] These factors have simplified and shortened the process of development of a new anticancer drug. Given the serious and life-threatening nature of cancer and patients' expectations, quicker clinical development has been required by both patients and clinicians, but this has led to an unclear and poorly defined benefit/risk balance of new drugs.

The fact that new anticancer drugs reach the market with a lack of complete and sound evidence has complicated the decision-making process for oncology medicines. Analysis of past regulatory decisions supports the notion that the level of acceptable uncertainty is not constant across all therapeutic indications. Regulators are generally willing to accept

a higher level of uncertainty around the benefit/risk assessment for life-threatening or otherwise severe conditions for which there is a high unmet medical need such as cancer, as opposed to less severe conditions or where an effective treatment already exists.[1] These factors make the analysis of the regulatory decision-making process in oncology more interesting than in other therapeutic areas.

The increasing costs of new anticancer drugs represents an additional issue. For instance, a year's treatment with vemurafenib, recently approved by the European Medicines Agency (EMA) for late-stage melanoma, would cost $91,000 by itself. Even though the manufacturer has offered an undisclosed discount, the UK's National Institute for Health and Clinical Excellence will not have the National Health Service pay for it. No health service will be able to afford to put a patient on two or three such targeted drugs at the same time.[27]

Conceptual framework

We designed a conceptual framework for the decision-making process of anticancer medicines (see Figure 1). The first step is the structural and legislative framework. At this stage the decision-makers are involved in determining the main policy directions on which regulatory requirements will be based. Regulatory requirements, through various guidelines, establish the data package that must be submitted by companies to the regulatory authorities, and define specific aspects such as the appropriate trial designs and endpoints for specific drugs and diseases. The assessment step is when the evaluation of the benefit/risk profile of a new drug or a new indication takes place. The assessors make their decisions on the basis of "formal" factors such as the clinical relevance of the dossier data, the absence of alternative options or the safety profile, and "informal" factors which are related to ethical and socio-cultural aspects. The whole process leads to the final regulatory decision, which consists in a yes or no decision on marketing authorisation.

This thesis will mainly focus on the regulatory and the assessment steps leading to either a positive or a negative evaluation of the benefit/risk balance for a new medicine or a new therapeutic indication. The analyses included in this thesis fit into the larger context of research in regulatory science developed under the umbrella of the Utrecht-WHO Collaborating Centre for Pharmaceutical Policy and Regulation.

Goals and objectives of this thesis

Overall aims: to analyse the decision-making process and regulatory dynamics that lead to the approval or refusal of a new medicinal product or a new therapeutic indication. This research mainly focuses on the regulatory system of the European Union (EU) and critically analyses pitfalls, challenges and avenues for improvement from a public health perspective. Research related to pharmacovigilance issues is beyond the scope of this

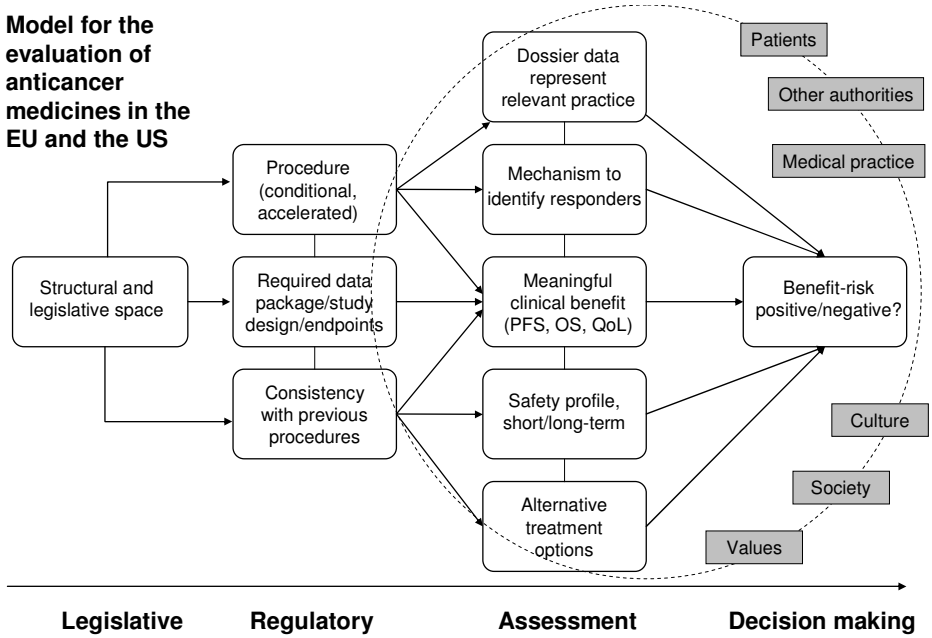


Figure 1: A conceptual framework for regulatory decision-making

Legend: PFS: Progression-Free Survival; OS: Overall Survival; QoL: Quality of Life. The area encircled by the dashed line embodies the criteria in the assessment process that lead to the final regulatory decision on benefit/risk. This process is shaped by both formal and informal factors. The white boxes contained within the dashed line indicate the formal factors guiding the assessment of a new drug. The grey boxes on the dashed line itself represent informal factors mediating a regulator's assessment of the formal factors

thesis. However, research focussing on the post-authorisation stage and safety-related regulatory actions has been developed within the context of this research group in regulatory science.[28-35]

Thesis outline and preview

This thesis contains six studies divided in two chapters, which reflect both the regulatory and the assessment steps of our conceptual framework, leading to the final regulatory decision (see Figure 1).

Chapter 2 focuses on the level of evidence needed by the regulators to take their decisions and the importance of transparency in communicating their decisions to the world. We will discuss the cases when the available evidence may be sufficient to make regulatory decisions without performing further clinical studies, such as the case of proton pump inhibitors (PPIs) in children. In fact we will demonstrate that due to the existence

of a large body of clinical evidence on the use of PPIs in children, trial replication may be unnecessary in this patient population.

We will see that over the last decade, Europe has made major steps forward in transparency compared to other regulatory agencies. Indeed, unlike major agencies such as the Food and Drug Administration (FDA) or Health Canada, EMA is required by EU legislation to disclose information on drug applications withdrawn prior to the conclusion of the evaluation process or refused at the end of it. Analysing this information, we will investigate the determinants leading to a negative regulatory decision.

In **Chapter 3** we will focus on the controversial issue of oncological clinical trials that are truncated early following interim analyses. The analysis will critically elucidate methodological and ethical aspects related to the use of interim analyses in randomised controlled trials testing new anticancer drugs, and it will assess how often trials prematurely stopped as a result of an interim analysis are used for registration purposes.

We will also quantify the time needed for anticancer drugs approved by the EMA to get an extension of indication, the rates and characteristics of extensions approved, and we will explore the regulatory process leading to the definition of new indications. We will analyse the differences between the EU and the US regulatory systems comparing the approaches of the EMA and the US FDA in the evaluation and approval of new anticancer indications in order to identify possible clinical implications associated with these differences. We will search for possible causes for these differences through an interview study that involves EMA and FDA regulators who are part of the decision-making process for the assessment of new anticancer drugs.

In **Chapter 4** we will discuss the key findings from the earlier chapters, placing them into the general context of the current challenges of medicines development and regulations. Finally, we will identify key lessons learned from each study and future research areas in regulatory science.

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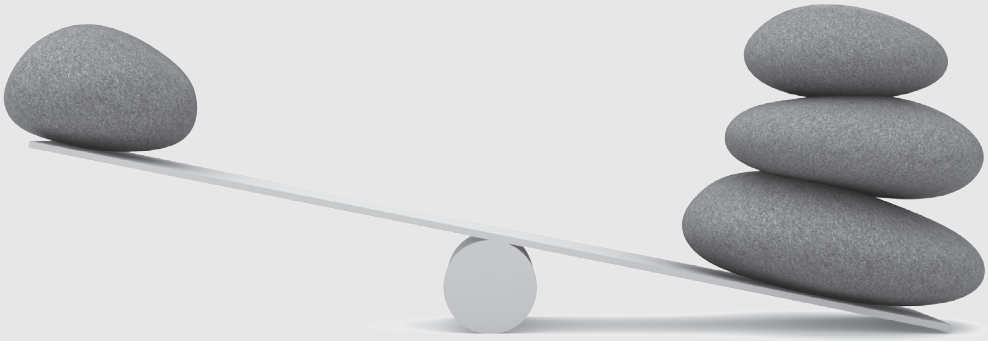
CHAPTER 2

Regulation and transparency



CHAPTER 2.1

Off-label use of medicines in children: can available evidence avoid useless paediatric trials?

The case of proton pump inhibitors for the treatment of gastroesophageal reflux disease

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Eur J Clin Pharmacol 2009;65(2):209-16.

ABSTRACT

Purpose In some cases of drug therapy, the available evidence might be sufficient to extend the indications to children without further clinical studies.

Methods We reviewed the available evidence for one of the categories of drugs most frequently used off-label in children: proton pump inhibitors (PPIs) used for the treatment of gastroesophageal reflux disease (GERD). A classification of the appropriateness of off-label use of PPIs in children with GERD was also performed.

Results Of the five PPIs evaluated, only omeprazole has a paediatric indication in Europe. Overall, 19 clinical trials were retrieved and evaluated on the basis of pharmacokinetics, efficacy and safety data. The off-label use of omeprazole, esomeprazole and lansoprazole in children was evaluated as appropriate given the consistent available evidence retrieved in literature.

Conclusion This study demonstrates the existence of a large body of clinical evidence on the use of PPIs in children. Regulatory agencies and ethical committees should cope with this issue for ethical reasons to avoid unnecessary trial replication.

INTRODUCTION

The use of unlicensed and off-label medicines in children is widespread and has raised an increasing concern over the last years. In the European Union (EU), 50% or more of the medicines used in children have only been studied in adults, and not necessarily for the same indication.[1] The general lack of information and appropriate pharmaceutical formulations for use in children may expose them to unwanted adverse events or underdosing without the expected efficacy. The need for more studies to obtain paediatric information for medicines used in children is now a matter of consensus on a global basis.[2,3] The awareness of off-label drug usage in the daily practice by paediatricians and the need to identify specific off-label clinical priorities in paediatrics have been documented in an observational study conducted in 32 Italian Departments of Paediatrics.[4]

The policy implemented in the USA, culminating in the Pediatric Research Equity Act of 2003, paved the way for the new European legislation (the 'Paediatric Regulation'), which was adopted in January 2007 with the objective to guide the development and authorisation of medicines for use in children aged 0–17 years.[5–7] This legislation was designed to better protect the health of children in the EU. A Paediatric Committee was established within the European Medicines Agency (EMEA) with the intent to provide scientific opinions on any development plan for paediatric medicines. The Committee has identified therapeutic areas where clinical studies on medicinal products for children are considered both a priority and a prerequisite for granting a paediatric indication.[8]

A recent draft guidance has been issued by the U.S. Food and Drug Administration (FDA) with the aim to effectively manage the off-label phenomenon, enabling sponsors to distribute publications about off-label use of approved drugs to prescribers.[9] The potential pros and cons of this approach have been strongly debated among the scientific and regulatory community at the international level.[10]

The current scenario on paediatric research and regulation raises a new challenging question: is it always necessary to perform additional clinical studies in children? Our hypothesis is that, in some instances, the evidence already available may be sufficient to extend the indications to children without further clinical studies. This would allow the translation of the existing evidence into clinical practice, minimising regulatory hurdles and avoiding the unethical replication of trials.

To test this hypothesis we reviewed the available evidence for one of the categories of drugs most frequently used off-label in children: proton pump inhibitors (PPIs) for the treatment of gastroesophageal reflux disease (GERD). The rationale for choosing PPIs

stems from the following considerations. The role of PPIs for the treatment of GERD is identified as a paediatric need by the EMEA PaediatricCommittee.[8] However, although PPIs do not have an indication for GERD in infants, clinical guidelines from the North American Society for Pediatric Gastroenterology and Nutrition address the use of PPIs for this age group.[11] Which line of action should be followed to better protect paediatric patients? This question is of particular importance given the enormous increase in the use of PPIs in infants for presumed GERD that has been documented (in the 6 years from 1999 through 2004, there was a more than sevenfold increase) and the largely inappropriate prescription of PPIs in children presenting physiological GERD that has been recently reported.[12, 13]

The aim of the study was to review the clinical evidence available in the published scientific literature concerning the use of PPIs for the treatment of GERD in the paediatric population in order to establish whether the absence of authorised indications can be justified. An additional aim of the study is to describe possible differences in the PPI-approved indications for the treatment of GERD in the paediatric population in the two largest regulatory agencies, EMEA and FDA.

METHODS

We performed a preliminary search to determine the regulatory status of approved PPIs (omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole) in Europe and the USA. The European summaries of product characteristics (SPCs) were retrieved from the EUDRANET database (http://ec.europa.eu/idabc/en/document/2291); the U.S. patient information leaflets were retrieved from the FDA website (www.fda.gov). The update of these documents was surveyed until June 2008. Information on paediatric indications was abstracted from such documents, and a comparison between Europe and the USA was then carried out.

A comprehensive search on the MEDLINE and EMBASE databases (January 1990–June 2008) was performed. All clinical trials on the off-label use of PPIs for the treatment of GERD in children (age 0–17 years) were considered eligible for inclusion. For the purpose of this analysis, the following parameters were assessed: study design, trial information (country, centres), objectives (endpoints), patients population, study duration, posology, formulation and main findings (as reported by the authors). Given the objective of the study, the analysis was restricted to the trials conducted on patients' age ranges not already included in approved EU indications (e.g. for omeprazole, only studies including children aged 0–2 years were analysed).

We defined a priori a common data acquisition form to be completed using the information collected from the selected articles.[14–32] The information was used to assess the available evidence on the pharmacokinetics (PK), efficacy and safety of each drug. The safety profile of each drug was evaluated through a comparison of adverse events (AEs) for adults listed in SPC versus the AEs reported in paediatric trials. A specific search on the MEDLINE and EMBASE databases was performed in order to retrieve safety data collected through reviews and observational studies.

On the basis of the retrieved evidence, a classification of the appropriateness of off-label use of PPIs in children with GERD was performed. Each drug was ranked as having a high, moderate or scarce appropriateness when administered in children, depending on the fulfilment of three pre-specified criteria. Specifically, a high appropriateness was attributed to a compound when at least two efficacy trials and two PK studies were retrieved and a comparable safety profile versus adults was assessed. Lack of compliance with one or more of the above-mentioned criteria leads to a decrease in the ranking of appropriateness. For the classification of appropriateness, strength of the endpoints and robustness of the study designs have been also considered as two additional criteria. The use of 24-h pH monitoring and/or endoscopy, although surrogate endpoints, are considered to be acceptable predictors of efficacy.[33] Double-blind randomised controlled trials were considered the highest level of evidence for testing medicines.

RESULTS

The five PPIs currently marketed in the EU—omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole—were approved through a mutual recognition procedure. Of these five PPIs, only omeprazole has a paediatric indication (i.e. children aged ≥2 years). Esomeprazole, which is the S-isomer of omeprazole, does not formally have any paediatric indication, although the approved European SPC contains information on posology in children under the age of 12 years. At the end of June 2007 further information on the treatment of GERD was added for the pantoprazole SPC. However, no changes were included in the therapeutic indication section of the SPC.

The scenario in the USA appears to be different: three out of five compounds (omeprazole, esomeprazole, lansoprazole) are currently authorised for children, although with the exclusion of infant and neonate age groups (Table 1). It is noteworthy that lansoprazole and esomeprazole are approved for children aged 1–17 in the USA but not in the EU. The most recently marketed PPIs (rabeprazole and pantoprazole) are not indicated for use in children in the USA nor in the EU.

Table 1: Approved indications of PPIs for the treatment of GERD in the European Union and the USA

Drug	EU indication	US indication
Omeprazole	GERD ≥2 years	GERD 2-16 years
Esomeprazole	Not authorized in children*	GERD 1-17 years
Lansoprazole	Not authorized in children	GERD 1-17 years
Pantoprazole	Not authorized in children*	Not authorized in children
Rabeprazole	Not authorized in children	Not authorized in children

PPI, Proton pump inhibitors; GERD, gastroesophageal reflux disease. *Information on posology in adolescents (≥12 years) with GERD is available in the summaries of product characteristics (SPC)

Nineteen clinical trials testing PPIs in the treatment of GERD in children were retrieved; these are summarised in Table 2. Of these, eight were multicentre trials. More than 40% of the trials evaluated were conducted in the USA. Findings on omeprazole consisted of six efficacy trials, two also focussing on the PK profile. The study duration ranged from 7 days to 3 months, and a total of 151 children were enrolled; three studies were randomised controlled trials (RCTs).The evidence for lansoprazole consisted of six studies (one was a RCT), testing efficacy and PK, with a study duration ranging from 5 days to 3 months. Overall, 282 patients were enrolled. Four RCTs on esomeprazole were retrieved: these were aimed at defining the PK, efficacy and safety profile, with a total of 257 enrolled children. The improvement of GERD symptoms was investigated in two efficacy trials (one was a RCT) with pantoprazole. The population enrolled consisted of 68 children with a mean study duration of 1.5 month. Finally, for the latest marketed PPI, rabeprazole, only one trial investigating PK and safety was retrieved, with a population involving 24 children.

All PK studies were designed with the aim of determining doses. The posology adopted was homogeneous across trials testing the same compound, and it was reported on a milligram/kilogram per day basis, which is appropriate in children. On the other hand, heterogeneity in terms of formulations was observed across all of the evaluated trials. It should also be highlighted that none of these studies was designed as a comparative trial testing different PPIs. For omeprazole and esomeprazole, evidence on efficacy and PK emerged from at least three RCTs (in many cases, the trials had a double-blind design).

Table 2: Clinical trials testing PPIs in children with GERD[14-32]

Drug	Study design	Trial information (country, centre)	Objective (End-point)	Patients population (N, age)	Posology	Study duration	Formulation	Main findings (as reported by authors)
omeprazole	RCT	Italy single-centre	Efficacy (24h pH monitoring, endoscopy, histological evaluation, and GERD symptom assessment chart)	N=32; 6 months to 13,4 years	40 mg/ die/1,73 m^2	8 weeks	Capsule content or capsule	Efficacious reduction of intragastric acidity and intra-oesophageal acid exposure. Healing of oesophagitis and relief of symptoms.
	RCT, double-blind, placebo controlled, crossover	Australia, single-centre	Efficacy (24h pH monitoring, and GERD symptom assessment chart)	N=10; 50 ± 9 days	0,7 mg/Kg/die	7 days	Liquid intravenous formulation administered via naso-gastric tube	Significantly effective in normalizing pathological acid GERD. Not significantly effective in reducing symptom frequency.
	RCT, double blind, placebo controlled, crossover	Australia, multicentre	Efficacy (24h pH monitoring and Cry/fuss diary and visual analogue scale of irritability)	N=30; 3-12 months	5-10Kg: 10mg/ die; >10Kg: 10 mg/ bid	2 weeks	Microspheres in apple juice	Despite effective acid suppression omeprazole failed to suppress symptoms of irritability
	CT, open- label	Multinational,multicentre	PK and efficacy (main PK parameters, 24h pH monitoring, endoscopy, and standardized questionnaire)	N= 57; 1-16 years	0,7 - 3,5 mg/ kg/die	12 weeks	Capsule in children, microgranules in infants	Highly effective for treatment of erosive esophagitis and symptoms of GERD. Doses required much greater than those required for adults.
	CT open- label	Belgium, single-centre	Efficacy (24h pH monitoring, endoscopy, and Cry/fuss reports)	N=12; 2.9 ± 0.9 months	0,5 mg/kg/die	6 weeks	Capsule content in milk or water	Marked decrease in symptoms, endoscopic and histological signs of esophagitis, and intragastric acidity.
	CT open- label	UK, single-centre	PK and Efficacy (main PK parameters, 24h pH monitoring)	N=10; 1.25-20 months	0,7 mg/kg/die	2 weeks	Microgranules in alcaline vehicle	Effective treatment for GERD in children younger than 2 years. The majority respond to a dosage of 0,7 mg/kg/die

Table 2: Clinical trials testing PPIs in children with GERD[14-32] *(continued)*

Drug	Study design	Trial information (country, centre)	Objective (End-point)	Patients population (N, age)	Posology	Study duration	Formulation	Main findings (as reported by authors)
	CT, open -label	USA, multicentre	Efficacy (endoscopy, investigator interview, and patients daily diary)	N=87; 12-17 years	15 or 30 mg/ die	8 weeks	capsule	15 or 30 mg reduced symptoms of GERD
	CT open-label	France, single-centre	PK and efficacy (main PK parameters, 24h pH monitoring, endoscopy)	N=23; 3 months to 13,4 years	0,8-1,4 mg/ kg/die	7 days	Capsule in children, microgranules in infants	The optimal effective starting dosage is 1,4 mg/Kg/die. PK is similar to adults.
	CT open-label	Italy, single-centre	Efficacy (24h pH monitoring, endoscopy)	N=35; 3-15 years	Group A: 1,3 to 1,5 mg/kg/die Group B:0,8 to 1,0 mg/kg/die	12 weeks	Capsule or microgranules in acid vehicle	Effective in healing esophagitis and improving GERD symptoms. An initial dose of 1,5 mg/kg/die is suggested.
lansoprazole	CT, open-label	USA, multicentre	PK/PD (main PK parameters, 24h pH monitoring, investigator interview)	N=8; 13-24 months	15 mg die to bid	8-12 weeks	N.A.	PK and PD properties were similar to those observed in older children and adults.
	CT, open-label	USA, multicentre	PK and efficacy (main PK parameters, 24h pH monitoring, GERD symptoms assessment)	N=66; 1-12 years	15 mg/die if ≤ 30kg; 30 mg/ die if > 30 kg (mean dose 0.9mg/kg/die)	8-12 weeks	N.A.	Effective symptom relief dose is 1,2 mg/kg/die. PK properties were similar to those previously observed in adults
	RCT, double-blind	USA, multicentre	PK and efficacy (main PK parameters, 24h pH monitoring and GERD symptoms assessment)	N=63; 12-17 years	15 vs 30 mg/ die	5 days	tablet	PK properties were similar to those previously observed in adults. 15 or 30 mg effectively relieves symptoms of GERD

Table 2: Clinical trials testing PPIs in children with GERD[14-32] *(continued)*

Drug	Study design	Trial information (country, centre)	Objective (End-point)	Patients population (N, age)	Posology	Study duration	Formulation	Main findings (as reported by authors)
esomeprazole	RCT, open-label	USA, single-centre	PK (main PK parameters)	N=31; 1-11 years	1-5 years: 5 vs 10 mg/die; 6-11 years: 10 vs 20 mg/die	5 days	capsule	PK properties may be both dose and age dependent. Younger children (1-5 y) might have more rapid metabolism. Well tolerated at all doses.
	RCT, open-label	USA, single-centre	PK (main PK parameters)	N=28; 12-17 years	20 vs 40 mg/ die	8 days	capsule	PK properties were dose and time dependent. Well tolerated at both doses.
	RCT, single-blind	Australia, single-centre	PK and efficacy (main PK parameters, 24h pH monitoring, infant GERD questionnaire)	N=50; 1-24 months	0,25 vs 1 mg/ Kg/die	1 week	capsule content in applesauce	0,25 and 1 mg/Kg/die provided dose-related acid suppression and decreased esophageal acid exposure.
	RCT, double blind	Multinational, multicentre	Efficacy and safety (GERD symptoms assessment with diary, physical examinations, clinical laboratory evaluations, evaluation of adverse events	N=148; 12-17 years	20 vs 40 mg/ die	8 weeks	capsule	20 or 40 mg were well tolerated and GERD-related symptoms were significantly reduced
pantoprazole	RCT, double-blind	USA, multicentre	Efficacy (CSS, biopsies, and endoscopy)	N=53; 5-11 years	10 vs 20 vs 40 mg/die	8 weeks	tablet	20 and 40 mg were significantly more effective than 10 mg in reducing GERD symptoms
	CT, open-label	Mexico, single-centre	Efficacy (24h pH monitoring, endoscopy)	N=15; 6-13 years	20 mg (0,5 to 1,0 mg/Kg/die)	4 weeks	tablet	Partial clinical improvement of GERD symptoms.

Table 2: Clinical trials testing PPIs in children with GERD[14-32] *(continued)*

Drug	Study design	Trial information (country, centre)	Objective (End-point)	Patients population (N, age)	Posology	Study duration	Formulation	Main findings (as reported by authors)
rabeprazole	CT, open-label	USA, multicentre	PK and safety (main PK parameters and evaluation of adverse events)	N=24; 12-16 years	10 vs 20 mg/ die	1 week	tablet	10 and 20 mg were well tolerated

N.A, Not available; RCT, randomised controlled trial; CT, clinical trial; PK, pharmacokinetics; PD, pharmacodynamics; CSS, composite symptoms score; die, daily; bid, twice daily

Of note, in more than 70% of the efficacy trials, the activity of each drug was evaluated on end points based on the 24-h pH monitoring, often accompanied by an endoscopy.

On the basis of the AEs reported in the trials included in the analysis, all compounds presented a safety profile in children that was comparable with one described in adults. Only in the case of omeprazole were AEs of the respiratory system reported more frequently in children aged 0–2 years than in adults. This is also confirmed by recent literature data.[34] Two reviews confirmed our findings in terms of the comparability of the omeprazole, lansoprazole, esomeprazole and pantoprazole safety profiles between children and adults.[33,35] A retrospective observational study that evaluated the long-term safety and efficacy of omeprazole and lansoprazole and involved 166 children reported that PPIs are efficacious and well tolerated for continuous use for as long as 11 years in children.[36]

The off-label use of omeprazole, lansoprazole and esomeprazole in children was evaluated as highly appropriate given the consistent available evidence on PK, efficacy and safety (Table 3). Moderate appropriateness was attributed to pantoprazole, due to the lack of PK data and insufficient efficacy trials. Since no adequate evidence was available for rabeprazole, its off label use was considered to be scarcely appropriate in children.

Table 3: Appropriateness of off-label use of PPIs in children with GERD

Criteria used for classification of appropriateness	Drugs				
	Omeprazole	**Lansoprazole**	**Esomeprazole**	**Pantoprazole**	**Rabeprazole**
Availability of clinical trials for efficacy	Yes	Yes	Yes	Yes	No
Availability of PK data	Yes	Yes	Yes	No	No
Comparability of safety profile in children versus adults	Yes	Yes	Yes	Yes	No
Appropriateness	High	High	High	Moderate	Scarce
Comments	The available evidence supports the use in children aged 0-2 years	The available evidence supports the use in children	The available evidence supports the use in children	Pharmacokinetic studies should be conducted to support use in children	Insufficient evidence available in children

DISCUSSION AND CONCLUSIONS

Of the five authorized PPIs in Europe only one, omeprazole, has a paediatric indication. Consequently, any use of PPIs for the treatment of GERD in patients under the age of 2 years and the paediatric use of all PPIs but omeprazole in patients between 2 and 17 years are to be considered off-label in the EU. Our findings also highlight the discrepancies between regulatory agencies in terms of approved indications (i.e. PPIs for the treatment of GERD in children). Wide discrepancies between the EU and the USA were observed regarding paediatric indications of three compounds, esomeprazole, lansoprazole and pantoprazole. Whereas esomeprazole and lansoprazole are only authorised by the FDA for the treatment of GERD in children aged 1–17 years, pantoprazole was recently reviewed in terms of children posology only in the EU. This heterogeneity could be overcome through the integrated efforts of different regulatory authorities to share more information on the regulatory decision-making process for paediatric drugs. In addition, the incoherence between the posology section and the clinical indication section of the same SPC represents potentially misleading information for prescribers.

According to our analysis, omeprazole, esomeprazole and lansoprazole showed a satisfying level of clinical evidence for paediatric use in the age ranges that are not covered by a formal indication. Those compounds fulfilled all of the criteria for a high appropriateness for administration in children.
A robust clinical data package, i.e. at least two efficacy and two PK trials, and a comparable safety profile between children and adults represent the required level of evidence for avoiding that further paediatric trials are carried out solely for registration and regulatory purposes. This is also in line with the EMEA recommendations on clinical drug development.[37–39] Analysing the available clinical data prior to conducting further trials could be one approach for avoiding the well-known practical and ethical problems related to testing drugs in children. Even when the clinical data package is not robust enough, as in the case of pantoprazole, further testing could be limited only to the missing information.

The case of omeprazole and rabeprazole, respectively evaluated as highly and scarcely appropriate in children, raises further research questions and ethical concerns. In fact, the amount of information available for omeprazole makes the performing of further trials on a molecule of the same class, such as rabeprazole, useless and unethical unless within comparative trials.

It is often reported that the lack of clinical trials in children can be attributable to ethical, methodological and financial issues. However, our analysis shows a different scenario: although there is a consistent amount of published paediatric trials for this specific condi-

tion, the use of PPIs for GERD is still considered off-label. Our study also showed the existence of a large amount of clinical evidence on the use of PPIs in children and, therefore, that performing trials in children is feasible.

We believe that the evaluation we carried out on the appropriateness of off-label use of PPIs in children could be easily extended to other classes of drugs or other special populations. Similar analyses could be helpful for prescribers. This would at least allow a more evidence-based approach to off-label prescribing. Moreover, this model could help regulatory authorities identify research priorities for a specific compound (e.g. a further PK study) and require specific mandatory studies for those important questions of efficacy or safety which still remain unresolved. However, most of the retrieved trials were not RCTs and were based on small sample sizes. Regulatory bodies should promote and support the conducting of few large and well-designed trials instead of a multiplicity of small trials with weak methodology. This could contribute to a better protection of the patients from the potential hazards of the off-label use of drugs.
There are two main limitations to our analysis. Firstly, the evaluation of safety in children for each compound was based on information retrieved in published studies (i.e. clinical trials, reviews, observational studies). Given the small number of patients enrolled in clinical trials, only the more frequent events could have been observed and reported in each trial. Secondly, we identified the heterogeneity of formulations used as a potential limitation. However, such heterogeneity is a common problem in studies involving children.

In conclusion, the use of medicines that have not been studied and assessed fully in children is a common situation in Europe as well as the rest of the world.

This study was prepared from a public health perspective. A review of the literature with the aim of searching out published findings can be a useful tool for regulators and policy-makers within the framework of granting children simplified access to medicines. Translating clinical evidence into clinical practice and health-care decision-making could be a useful strategy to fill the gap between regulatory bodies and patients, thereby ensuring an equal and quicker access to medicines.

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CHAPTER 2.2

In reply to: Knowledge of developmental pharmacology and modeling approaches should be used to avoid useless trials in children

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We agree with de Wildt et al. on the need to take children's developmental changes into consideration when assessing the clinical evidence in order to waive additional studies.

In reviewing the available evidence on the use of proton pump inhibitors (PPIs) in the treatment of gastroesophageal reflux disease (GERD) in children, we focused on the age ranges for which no labeled indication was approved in theEU.[1] For example, in the case of omeprazole (authorized for the treatment of GERD in Europe for children ≥ 2 years), we searched for scientific literature based on children younger than 2 years. We found four trials entirely dedicated to children aged 0–2 years. The remaining two trials, although not strictly dedicated to that target population, also enrolled children between 0 and 2 years.

Our review intended to deal with the general issue of off-label use of drugs in the pediatric population, to verify whether drugs not formally approved for use in a specific population may nonetheless present sufficient evidence supporting their (off-label) use. If the 0- to 2-year range is still considered too large to take into account the impact of developmental changes on a drug risk/benefit profile, further studies focusing on more specific age groups are clearly needed. Prior biological knowledge, or new data, are critical factors in deciding whether the available evidence is insufficient to guide clinical practice in a specific population sub-group.

However, we should also use a pragmatic and prioritizing approach, considering that requiring separate trials for each patient sub-group–in pediatrics as well as in other populations–may not be always feasible. For instance, in the case of the elderly, the combination of different age strata, co-morbidities, and concomitant use of different drugs may create an enormous number of potential different groups. The issue of how to generalize data deriving from a specific population to a wider population is inevitably to be considered on a case-by-case basis. Mathematical modelling may provide a contribution though, again, the applicability of existing evidence to different patient groups will continue to carry various degrees of uncertainty.

With regards to who should assess the use of off-label medicines in children, we agree on the importance of regulatory agencies in reviewing the available evidence to support clinical practice and to identify research priorities (a "to do" list). In the effort to deal with this issue, different strategies and approaches have been used at the regulatory level. In Europe, the EMEA Paediatric Committee has identified the needs in different therapeutic areas where there should be research and development of medicinal products for children.[2] In the U.S., the FDA has recently released specific guidelines allowing drug manufacturers to distribute reprints of articles from medical journals that describe unapproved uses of their products, a practical attitude that can be of help in regulating evidence-based off-label drug use.[3]

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CHAPTER 2.3

Disclosure of grounds of European withdrawn and refused applications: a step forward on regulatory transparency

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ABSTRACT

Background The need for a greater transparency in the process of how regulatory authorities evaluate new medicines has been advocated by the public and the scientific communities. Transparency about the outcomes of marketing authorization procedures is important for the purpose of a better understanding of the reasons why certain procedures tend to result in either a successful or a failed application. While the Food and Drug Administration is not obliged to disclose information on drug applications withdrawn prior to the conclusion of the evaluation process or refused at the end of it, European Union legislation requires the European Medicines Agency (EMA) to do so. Indeed, the EMA publishes on its website assessment reports of withdrawn and refused applications.

Objective The primary objective of this study is toidentify rationale and grounds leading to the withdrawal or refusal of a drug application as processed through the European centralized procedure.

Methods Public assessment reports on withdrawals and refusals of applications related to all therapeutic categories were retrieved from the EMA website for the period 2005-2010. Post-approval withdrawals were beyond the scope of the study and were therefore excluded from the analysis.

Results A total of 86 drug applications could be identified with either a withdrawal (70 out of 86) or a refusal (16 out of 86). The majority of these applications represented four therapeutic categories: i) oncology/immunology (29 out of 86, 34%), ii) Central Nervous System (15 out of 86, 17%), iii) cardiovascular/metabolic diseases (14 out of 86, 16%), and iv) infectious diseases (12 out of 86, 14%). The reasons leading to a withdrawal or refusal could be related to all the three critical criteria for approval, i.e. quality, safety and efficacy issues; sometimes a combination of the three. Within the scope of efficacy-related major objections, five main categories could be identified: i) lack of clinical relevance (44 out of 106), ii) methodological issues (23 out of 106), iii) Pharmacokinetics issues, including bioequivalence (20 out of 106), iv) lack of statistical significance (13 cases), v) five cases were related to major Good Clinical Practice issues.

Conclusions Over the last decade Europe has made a step forward in disclosing such information on withdrawal and refusal. However, this should not be the end of improving transparency. More regulatory science is needed to gain better insight and understanding on failed drug development.

BACKGROUND

Requests directed to drug regulatory authorities (e.g. European Medicines Agency, Food and Drug Administration and other) for full disclosure of information on internal discussions, minutes and assessment reports related to regulatory decision making, are becoming increasingly pertinent. In particular both public, clinical and scientific communities seem to be interested in: i) agenda and minutes of scientific committees' meetings held, ii) discussions held with the pharmaceutical industry, iii) internal reports on safety and/or efficacy issues of approved and yet to be approved drugs.[1-3] Transparency about the outcomes of marketing authorisation procedures has gained importance, also for the purpose of building up a better understanding of the reasons why and how certain procedures for the approval of new active substances and indications tend to result in either a successful or a failed application.[4] It is noteworthy that not only regulatory authorities can come to a negative opinion regarding a submitted application, but also pharmaceutical companies themselves may decide to withdraw an application, often after serious objections have been identified by the authorities during the procedure.

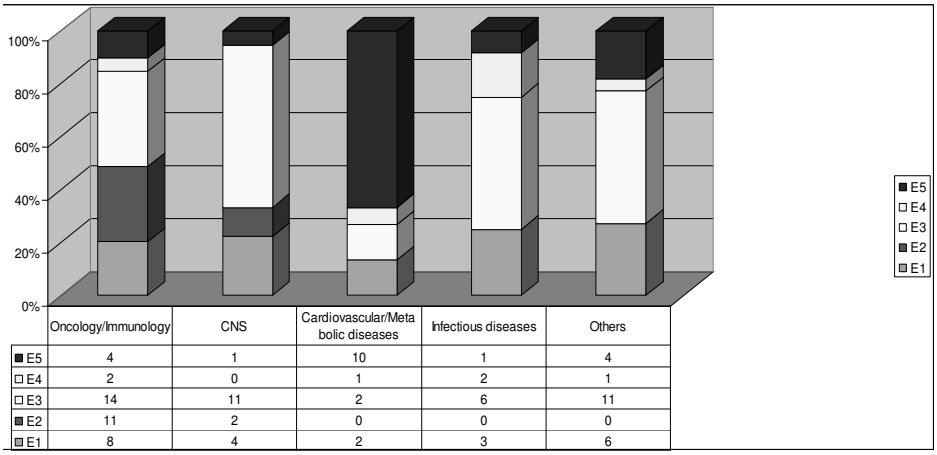
While the Food and Drug Administration (FDA) is not obliged to disclose information on drug applications withdrawn prior to the conclusion of the evaluation process or refused at the end of it[3], European Union (EU) legislation requires the European Medicines Agency (EMA) to do so.[5] In fact, the EMA makes this information publicly available through the refusal or withdrawn European Public Assessment Reports (EPARs) published on the Agency's website.
This offers a unique opportunity to explore the reasons behind approval failures and possibly understand the most critical deficiencies or uncertainties in either the drug product or its development.

The primary objective of this study is toidentify rationale and grounds leading to withdrawal or refusal of a drug application as processed through the European centralized procedure. Public assessment reports on withdrawals and refusals (i.e. a negative opinion by the EMA Committee for Medicinal Products for Human Use, the CHMP) of these applications were retrieved from the EMA website for the period 2005-2010. Post-approval withdrawals were beyond the scope of the study and were therefore excluded from the analysis.

RESULTS

A total of 86 drug applications could be identified with either a withdrawal (70 out of 86) or a refusal (16 out of 86). The majority of these applications represented four therapeutic categories: i) oncology/immunology (29 out of 86, 34%), ii) Central Nervous System (CNS) (15 out of 86, 17%), iii) cardiovascular/metabolic diseases (14 out of 86, 16%), and iv) infectious diseases (12 out of 86, 14%).The vast majority of these compounds were new active substances (54 out of 86, 63%). In 13 cases of out 86, the application consisted of an existing product in search of a new indication (e.g. cyclosporine for vernal keratoconjunctivitis). The remaining were mainly generics or biosimilars.

The reasons leading to a withdrawal or refusal could be related to all the three critical criteria for approval, i.e. quality, safety and efficacy issues; sometimes a combination of the three. Overall, 156 quality, safety and efficacy major objections were raised by the CHMP: 106 objections were due to efficacy deficiencies, while 27 to safety and 23 to quality, respectively. Within the scope of efficacy major objections, five main categories could be identified: i) lack of clinical relevance (44 out of 106, 41.5%), ii) methodological issues (23 out of 106, 21.6%), iii) Pharmacokinetics (PK) issues, including bioequivalence (20 out of 106, 18.8%), iv) lack of statistical significance (13 cases, 12.2%), v) major Good Clinical Practice (GCP) issues (5 out of 106, 4.7%) (see Figure 1). Methodological issues were equally distributed among drug classes, accounting for about 20% of all efficacy objections in each class. Issues related to lack of statistical significance occurred only



	Oncology/Immunology	CNS	Cardiovascular/Metabolic diseases	Infectious diseases	Others
E5	4	1	10	1	4
E4	2	0	1	2	1
E3	14	11	2	6	11
E2	11	2	0	0	0
E1	8	4	2	3	6

Figure 1: Types of efficacy deficiency per therapeutic area

Legend: E1: methodological issues; E2: lack of statistical significance; E3: lack of clinical relevance; E4: GCP issues; E5: PK issues/Bioequivalence

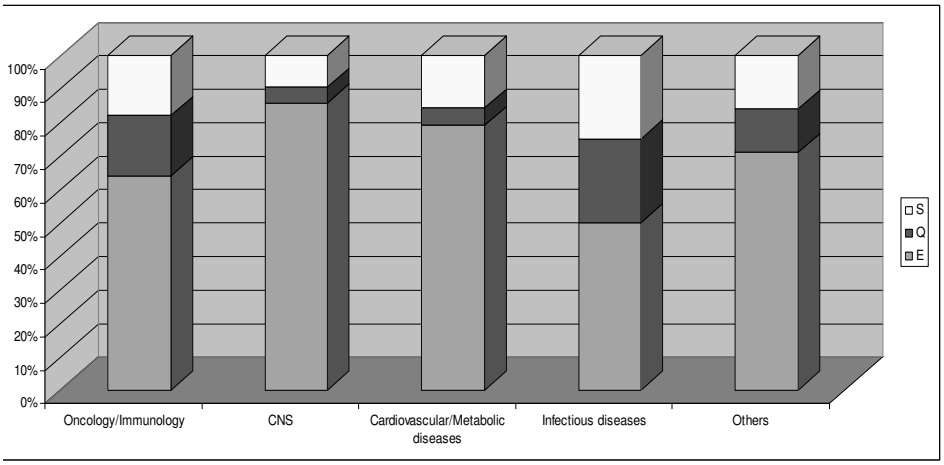


Figure 2: Rate of efficacy, safety and quality deficiencies per therapeutic area
Legend: S, Q and E are related to safety, quality and efficacy deficiencies respectively

for oncology/immunology and CNS drugs. The lack of clinical relevance was the most frequent objection in all failed applications, accounting for approximately 50% of all efficacy objections. Non-inferiority was a key issue for failed applications on cardiovascular/metabolic diseases, accounting for 60% of all efficacy objections within this class.

Within the safety objections, two main categories were identified: the first related to clinical safety (e.g. increased risk of adverse drug reactions and potential risk identified) in 23 out of 27 cases (85.2%). Only in four cases (14.8%), the objections concerned non-clinical safety/toxicological issues. Within the quality objections, two categories were identified: one related to drug substance and/or drug product issues (19 cases, 82.6%) and one related to Good Manufacturing Practice (GMP) issues (4 cases, 17.4%). Safety and quality issues both significantly concur with withdrawals in the case of drugs for oncology/immunology and infectious diseases (see Figure 2). It is noteworthy that only in two cases (Docetaxel Mylan and Mycrograb) withdrawal was solely due to quality issues. In none of the cases however, was a withdrawal solely due to safety (clinical and non-clinical). In all cases the grounds for withdrawal were due to a multiplicity of factors, in which the efficacy component consistently played the major role.

With regard to the time of withdrawal, in 17 cases out of 70, the application was withdrawn before Day 120 (the day when a preliminary evaluation by the CHMP is issued); the majority of the applications (41 out of 70) were withdrawn between Day 121 and Day 210, when a more consolidated CHMP evaluation is made available; 12 applications were withdrawn at a very final stage (after the end of procedure, i.e. after Day 210). Out of these

12, a total of 10 concerned applications for which a negative opinion was expected to be issued by the CHMP, while for the remaining two (Ratioepo and Lunivia) despite a positive opinion having been issued, the company decided to withdraw.

This analysis revealed a series of interesting scenarios in four cases with an initial refusal (i.e. Cimzia, Valdoxan/Thymanax, Yondelis) and a subsequent second submission leading to a positive opinion by CHMP. In one case (i.e. Cimzia) the indication approved at a later stage differed from the one which received an initial negative opinion. For the multiple applications of Valdoxan/Thymanax (both contain agomelatine as active substance) the grounds for refusal were mainly based on lack of demonstrated long-term efficacy. Two years after the refusal, the applicant submitted a new study with 492 patients and the results of this study were sufficient enough to convince CHMP about the positive benefit-risk of these products. The case of Yondelis could not be evaluated in much detail since no public refusal report was made available for this specific product. Therefore in 4 out of 16 refusal cases a negative opinion of the CHMP was evidently not the end of the story.

DISCUSSION

We evaluated 86 cases of withdrawn or refused applications for a European license of a medicinal product in the period 2005-2010. Disclosure of the grounds behind such failed applications is a step forward on regulatory transparency and can be considered as a positive implementation of EU legislation 726/2004. We also queried several other regulatory authorities in a sample of countries across the world in order to check whether they have similar transparency measures in place on failed drug applications. Apart from Europe, only Australia seems to have such a disclosure system (Table 1). The Australian authorities started to publish withdrawal information not prior to the end of 2009. Other important regulatory agencies, including the Swiss Medic, US FDA or Health Canada do not make this kind of information publicly available. The process for an increased transparency in Europe has been further strengthened with regard to pharmacovigilance.[6] In July 2012 the EMA announced that it will systematically publish all of its committees' agendas and minutes before the end of 2013.[7] We believe that information on withdrawals and refusals can be considered an important transparency indicator in the interest of public health and innovation.

Our analyses of the grounds of failed drug applications revealed that (lack of) efficacy is a main predictor for success or failure of an application. These findings are in line with previous analyses which investigated the most frequently objections and outcomes of drug applications at the EMA.[8] A clear propensity of a positive CHMP opinion seems to

Table 1: Query on disclosure of withdrawal and/or refused drug applications directed to a sample of drug regulatory authorities in various countries

Country	Replied to query (Y/N)	Disclosure of withdrawal/-refusal report (Y/N)
Argentina	Y	Not assessable
Australia	Y	Y
Brazil	N	Not assessable
Canada	Y	N
Chile	N	Not assessable
China	Y	N
Cuba	N	Not assessable
EU	Y	Y
India	N	Not assessable
Japan	Y	N
Mexico	N	Not assessable
Morocco	N	Not assessable
Namibia	N	Not assessable
New Zealand	Y	N
Russia	N	Not assessable
Saudi Arabia	Y	N
South Africa	Y	N
Switzerland	Y	N
US of America	Y	N

Legend: The Regulatory Authorities (RAs) were chosen across developing and developed countries on the basis of the availability of a valid email for contacts. In addition, contacts with RAs of emerging economies were privileged because these were expected to have more defined and organised regulatory systems. The Argentinean authority has provided a response, thus technically included among responders. However, it provided a list of links totally unrelated to the research question. Therefore it was labelled as not assessable.

be a good and robust clinical trial program, with a good rationale, and a targeted and efficient trial performance. In fact, this analysis also shows that statistical significance alone is not sufficient enough to acquire an approval for a marketing authorization, but most importantly clinical relevance must be demonstrated. It seems additionally important to evaluate clinical safety prior to registration (i.e. within clinical trials) since in 23 out of 60 cases the reason for withdrawal was due to safety concerns. In contrast, in none of the withdrawal cases were non-clinical data the main driver. This finding also fuels further reflection on how to bridge and integrate better non-clinical and clinical data. Non-clinical data with little to no link in terms of what this means for clinical practice, seems to be rather useless. On the other hand, non-clinical, mechanistic insight is indispensable for a better understanding of variance in drug response, also in the post-approval period of a drug's lifecycle.

In conclusion, developing medicinal products means acquiring robust data on quality, efficacy and safety. Regulators have the legal task to evaluate this data and to come to an informed decision about the benefit-risk of the product under review. Withdrawn or

refused applications provide an important insight into what may go wrong in bringing a product from bench to the clinic, and what could be improved in future applications. Over the last decade Europe has made a step forward in disclosing such withdrawal and refusal information. However, this should not be the end of improving transparency. More regulatory science is needed to gain better insight and understanding on failed drug development.

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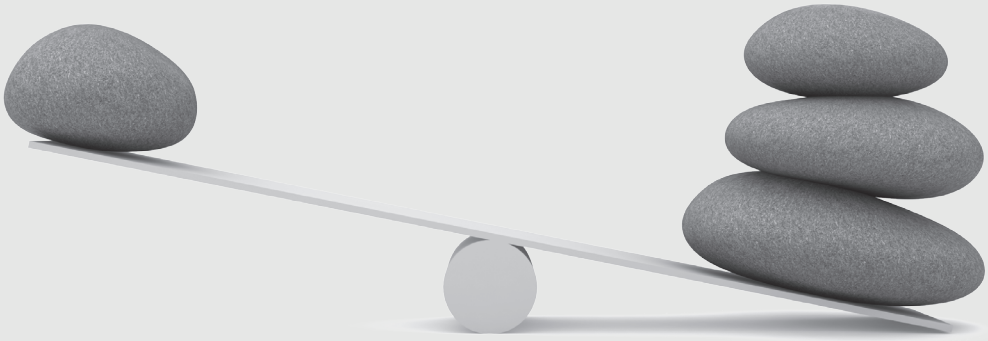
CHAPTER 3

Regulatory dynamics in oncology



CHAPTER 3.1

Stopping a trial early in oncology: for patients or for industry?

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ABSTRACT

Background The aim of this study is to assess the use of interim analyses in randomised controlled trials (RCTs) testing new anticancer drugs, focussing on oncological clinical trials stopped early for benefit.

Materials and methods All published clinical trials stopped early for benefit and published in the last 11 years, regarding anticancer drugs and containing an interim analysis, were assessed.

Results Twenty-five RCTs were analysed. The evaluation of efficacy was protocol planned through time-related primary end points, >40% of them overall survival. In 95% of studies, at the interim analysis, efficacy was evaluated using the same end point as planned for the final analysis. As a consequence of early stopping after the interim analysis, ~3300 patients/events across all studies were spared. More than 78% of the RCTs published in the last 3 years were used for registration purposes.

Conclusion Though criticism of the poor quality of oncological trials seems out of place, unfortunately early termination raises new concerns. The relation between sparing patients and saving time and trial costs indicates that there is a market-driven intent. We believe that only untruncated trials can provide a full level of evidence which can be translated into clinical practice without further confirmative trials.

BACKGROUND

European legislation in pharmaceuticals has been recently revised. In line with the path of the United States Food and Drug Administration (FDA), new procedures for granting marketing authorisation now include accelerated and conditional approvals, leading to quicker access of new drugs to patients. In this evolving scenario, guidelines on the evaluation of medicinal products are subject to continuous revision. This is especially the case for anticancer drugs, for which important changes have been made in terms of trial design and conduct.[1] These factors have simplified and shortened the process of development of a new drug, particularly in oncology.

Previous analyses of new anticancer compounds, approved by both the European Medicines Agency (EMEA) and the FDA, highlighted methodological concerns in terms of lack of comparative trials, use of surrogate end points, lack of evidence for establishing the added value, and lack of blinding/masking.[2–5] In addition, a recent systematic review covering different therapeutic areas found that the number of randomised trials stopped early for benefit had more than doubled since 1990.[6]

Interim analyses pose the ethical dilemma of safeguarding the interests of patients enrolled in clinical trials while also protecting society from overzealous premature claims of treatment benefit. Trials stopped early because of harm (toxicity) or futility tend to result in prompt discontinuation of useless or potentially harmful interventions. In contrast, trials stopped early for benefit may result in the quick identification, approval, and dissemination of promising new treatments.

Given the serious and life-threatening nature of cancer and patients' expectations, quicker clinical drug development is required by both patients and clinicians, but this may lead to an unclear and poorly defined benefit/risk balance of new drugs.

OBJECTIVE

The aim of this study is to assess the use of interim analyses in randomised controlled trials (RCTs) testing new anticancer drugs, focussing on oncological clinical trials stopped early for benefit. A second aim is to estimate how often trials prematurely stopped as a result of an interim analysis are used for registration purposes. Our study presents an updated overview of this growing phenomenon in the specific field of oncology, which is subject to continuous change. The analysis focussed on trials that were halted after an interim analysis found the treatment carried out better than the control arm.

MATERIALS AND METHODS

All clinical trials published from January 1997 to October 2007, regarding anticancer drugs and containing an interim analysis, were retrieved through Medline. The following strategy was adopted: publications containing the words 'interim' and 'analys*', and limited to humans, clinical trials, cancer, and English language, were searched. A total of 231 reports were found.
In order to test the sensitivity of the research methods, we did an extra search for articles, that might have been missed in the first search, published in the three main peer reviewed journals (The Lancet, The New England Journal of Medicine, and The Journal of Clinical Oncology) from October 2006 to October 2007; this produced two more reports. These three journals were chosen on the basis of how frequently they had reported the articles retrieved through the Medline search.

To increase the specificity, articles were initially screened on the basis of the abstract. Of the 233, 140 reports were excluded as not relevant according to predefined inclusion and exclusion criteria (see Figure 1). In particular, phase I trials, trials testing growth factors, and those based solely on surgery or radiotherapy were considered not pertinent, so were excluded. Furthermore, studies comparing different dose regimens and schedules of the same drugs and studies on the basis of palliative/supportive therapies (e.g. antiemetics) were excluded. Study protocols were also excluded.

Only papers on the basis of trials of anticancer medicinal products and containing an interim analysis were initially considered eligible for analysis (93 papers describing 93 trials). Out of these 93 papers, 65 were subsequently excluded for the following reasons: 4 trials were stopped after an interim analysis because of harm (toxicity) and 28 because of futility (lack of efficacy). Another 33 papers were excluded because the trials were not actually stopped after the interim analysis and were thus considered ongoing.

Twenty-eight papers met the inclusion criteria, i.e. clinical trials testing anticancer medicinal products truncated for benefit after an interim analysis. However, one was unretrievable, and in two separate cases two papers reported the same study in two different journals. In both cases, only the paper published earlier was included. Following these corrections, a final sample of 25 papers describing 25 trials was obtained.
For the purpose of this analysis, the following parameters were assessed: disease, study duration, date of publication, presence of a 'Data and Safety Monitoring Committee' (DSMC), type of end point(s), sample size, rationale for interim analysis and type of analysis carried out, consequences of the interim analysis on the RCT and on the patients, and characteristics of the control group. We reported both the primary end point planned

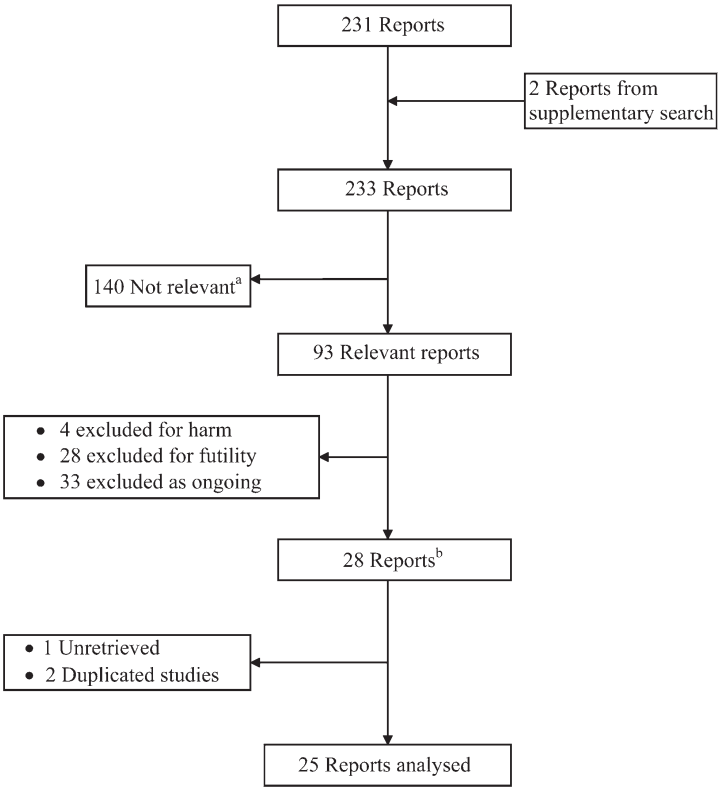

Figure 1: Flow chart

[a] Exclusion criteria:

1. phase I trials
2. trials testing growth factors
3. trials based solely on surgery or radiotherapy
4. studies comparing different dose regimens and schedules of the same drugs
5. studies based on palliative/supportive therapies.
6. study protocols

[b] Inclusion criteria: clinical trials testing anticancer medicinal products truncated for benefit after an interim analysis.

for final efficacy analysis and the end point used for the interim analysis. The same was done for sample size. In a few cases, certain study characteristics were not reported in the data acquisition form because they were not specified in the analysed articles. The investigators defined a priori a common data acquisition form to be completed. FT and GT independently evaluated all the selected papers and filled the respective forms. The

results were then cross-checked, leading to a joint document. In the case of disagreement, the final decision was taken through a consensus process reached following a discussion.

RESULTS

Of the 93 papers, initially selected as having been stopped after an interim analysis, 28 (30%) were stopped early for benefit, 28 (30%) for futility, and 4 (4%) for harm.

As described above, 25 of 28 papers were actually included in the analysis (see Figure 1). All 25 were RCTs, on a variety of different cancers (Table 1). In 16 trials, the control arm used an active comparator and in four used a placebo, while in five no treatment was given. In no case was information provided about trial design in terms of superiority, non-inferiority, or equivalence.

More than half of the selected trials (56%) were published in the last 3 years (2005–2007), 11 of them (79%) were used to support an application for marketing authorisation at the EMEA and FDA (Table 2).

The evaluation of efficacy was protocol planned through time-related primary end points, >40% of them overall survival (10 of 23, as information was unavailable in two cases). In two cases, publications lacked a clear definition of the primary end points, for both the final and the interim analyses. In 95% of studies (22 of 23), at the interim analysis, efficacy was evaluated using the same end point as planned for the final analysis. There was no DSMC in 24% (6 of 25) of the studies.

Table 1: Summarised data on oncological trials (N = 25) stopped early for benefit[7–31]

Treatment	Disease	Trial starting date vs end of the enrolment vs date of publication	DSMC	Primary endpoint vs endpoint used in interim analysis	Planned vs interim sample size	Rationale for planning interim analysis	Interim analysis consequences	Control group
Melphalan + prednisone + thalidomide*	Multiple Myeloma	May 2000 vs Aug 2005 vs Oct 2007	Y	OS vs OS	500 vs 447 patients	n. of enrolled patients	Stop enrolment	A
Temsirolimus*	Advanced renal-cell carcinoma	Jul 2003 vs Apr 2005 vs May 2007	Y	OS vs OS	600 vs 446 events	n. of events	Disclosure of results	A
Sunitinib*	Metastatic renal cell carcinoma	Aug 2004 vs Oct 2005 vs Jan 2007	Y	PFS vs PFS	471 events vs NA	cut-off date	Crossover to treatment group	A
Sorafenib*	Advanced clear-cell renal-cell carcinoma	Nov 2003 vs Mar 2005 vs Jan 2007	Y	OS vs PFS	540 vs 363 events	n. of events	Crossover to treatment group + Stop enrolment	P

Table 1: Summarised data on oncological trials (N = 25) stopped early for benefit[7–31] (*continued*)

Treatment	Disease	Trial starting date vs end of the enrolment vs date of publication	DSMC	Primary endpoint vs endpoint used in interim analysis	Planned vs interim sample size	Rationale for planning interim analysis	Interim analysis consequences	Control group
Paclitaxel + Carboplatin + Bevacizumab*	Non-Small-Cell Lung Cancer	Jul 2001 vs Apr 2004 vs Dec 2006	Y	OS vs OS	650 vs 455 events	n. of events	Disclosure of results	A
Lapatinib + Capecitabine*	HER-2 positive metastatic breast cancer	Mar 2004 vs NA vs Dec 2006	Y	TTP vs TTP	266 vs 114 events	n. of events	Crossover to treatment group + Stop enrolment	A
Sunitinib*	Advanced gastro-intestinal stromal tumour	Dec 2003 vs Jan 2005 vs Oct 2006	Y	TTP vs TTP	281 vs 149 events	n. of events	Crossover to treatment group	P
FU + Leucovorin + oxalilplatin (FOLFOX4)*	metastatic colorectal cancer	Apr 2001 vs Apr 2002 vs Jul 2006	Y	TTP vs TTP	550 vs 305 patients	n. of events	Stop enrolment	A

Table 1: Summarised data on oncological trials (N = 25) stopped early for benefit[7–31] (*continued*)

Treatment	Disease	Trial starting date vs end of the enrolment vs date of publication	DSMC	Primary endpoint vs endpoint used in interim analysis	Planned vs interim sample size	Rationale for planning interim analysis	Interim analysis consequences	Control group
Uracile + Tegafur	Stage III rectal cancer	Oct 1996 vs Apr 2001 vs Apr 2006	Y	RFS vs RFS and OS	400 vs 274 patients	cut-off date	Disclosure of results	NT
Carboplatin	Epithelial ovarian cancer	Nov 1994 vs Jul 1998 vs Jan 2006	Y	TTP vs TTP	190 vs 120 events	n. of events	Stop enrolment	A
Methotrexate, vinblastine, doxorubicine/ epirubicine, cisplatin	Advanced bladder cancer	May 1987 vs Dec 1990 vs Jan 2006	N	PFS vs PFS	NA	NA	Stop enrolment	NT
Trastuzumab + adjuvant chemotherapy*	HER-2 positive breast cancer	May 2003 vs Nov 2004 vs Oct 2005	Y	DFS vs DFS	710 vs 394 events	n. of events	Stop enrolment + Disclosure of results	A

Table 1: Summarised data on oncological trials (N = 25) stopped early for benefit[7–31] (*continued*)

Treatment	Disease	Trial starting date vs end of the enrolment vs date of publication	DSMC	Primary endpoint vs endpoint used in interim analysis	Planned vs interim sample size	Rationale for planning interim analysis	Interim analysis consequences	Control group
Trastuzumab (1 year arm + 2 year arm)*	HER-2 positive early-stage invasive breast cancer	Dec 2001 vs Mar 2005 vs Oct 2005	Y	DFS vs DFS	951 vs 347 events	n. of events	Disclosure of results	NT
Bevacizumab + (irinotecan, FU, leucovorin) and Bevacizumab + (FU, leucovorin)*	Metastatic colorectal cancer	NA vs NA vs May 2005	Y	OS vs OS	after 313 patients enrolled	n. of enrolled patients	Stop enrolment	A+ P
Letrozole*	Adjuvant therapy in receptor-positive breast cancer	Aug 1998 vs Sep 2002 vs Nov 2003	Y	DFS vs DFS	515 vs 171 events	n. of events	Disclosure of results	P
Gemcitabine	Advanced or metastatic adenocarcinoma of the pancreas	Dec 1997 vs Jul 1999 vs Sep 2003	Y	OS vs OS and PFS	350 patients vs 140 events	n. of events	Stop enrolment + Crossover to treatment group	A

Table 1: Summarised data on oncological trials (N = 25) stopped early for benefit[7–31] (*continued*)

Treatment	Disease	Trial starting date vs end of the enrolment vs date of publication	DSMC	Primary endpoint vs endpoint used in interim analysis	Planned vs interim sample size	Rationale for planning interim analysis	Interim analysis consequences	Control group
Bevacizumab	Metastatic renal-cell carcinoma	Oct 1998 vs Sep 2001 vs Jul 2003	Y	TTP, RR vs TTP	120 vs 110 patients	cut-off date	Crossover to treatment group	P
Idoxifene	Postmenopausal Metastatic breast cancer	Dec 1996 vs May 1999 vs Feb 2003	N	RR, TTP vs RR, TTP	440 vs 321 patients	n. of enrolled patients	Trial stopped for economic consideration	A
ChlVPP/EVA hybrid	Hodgkin's disease	Sep 1992 vs Sep 1996 vs Jul 2002	N	NA	80 vs 60 events	n. of events	Stop enrolment	A
Irinotecan + cisplatin	Metastatic small-cell lung cancer	Nov 1995 vs Nov 1998 vs Jan 2002	Y	OS vs OS	230 vs 230 patients	n. of enrolled patients	Stop enrolment	A

Table 1: Summarised data on oncological trials (N = 25) stopped early for benefit[7–31] (*continued*)

Treatment	Disease	Trial starting date vs end of the enrolment vs date of publication	DSMC	Primary endpoint vs endpoint used in interim analysis	Planned vs interim sample size	Rationale for planning interim analysis	Interim analysis consequences	Control group
Vinblastine + doxorubicin + irradiation	Hodgkin's disease	NA vs Apr 2000 vs Nov 2001	Y	FFS vs FFS	420 vs 348 patients	n. of enrolled patients	Stop enrolment	A
Gemcitabine + vinorelbine	Advanced non-small cell lung cancer	Jun 1997 vs May 1999 vs Jul 2000	Y	OS vs OS	240 vs 120 patients	n. of enrolled patients	Stop enrolment	A
Gemcitabine + vinorelbine + cisplatin	Advanced non-small-cell lung cancer	Apr 1997 vs Apr 1999 vs Apr 2000	N	OS vs OS	240 vs 120 patients	n. of enrolled patients	Stop enrolment	A
lipiodol iodine-131	Adjuvant in Resectable hepatocellular carcinoma	Apr 1992 vs Aug 1997 vs Mar 1999	N	Recurrence rate, recurrence sites, DFS, OS vs DFS	120 vs 43 patients	n. of enrolled patients	Stop enrolment	NT

Table 1: Summarised data on oncological trials (N = 25) stopped early for benefit[7–31] (*continued*)

Treatment	Disease	Trial starting date vs end of the enrolment vs date of publication	DSMC	Primary endpoint vs endpoint used in interim analysis	Planned vs interim sample size	Rationale for planning interim analysis	Interim analysis consequences	Control group
Doxorubicin or ethoglucid	Adjuvant in superficial transitional cell bladder carcinoma	Dec 1979 vs Dec 1983 vs Aug 1997	N	NA	NA vs 206 patients	n. of enrolled patients	Stop enrolment	NT

*Registration trial at the EMEA/Food and Drug Administration.

A, active controlled group; ChlVPP/EVA, Chlorambucil, vinblastine, procarbazine, and prednisolone/etoposide, vincristine, and doxorubicin; DFS, disease-free survival; DSMC, Data and Safety Monitoring Committee; FFS, failure-free survival; FOLFOX, Fluorouracil, leucovorin, oxaliplatin; FU, fluorouracil; HER-2, human epidermal growth factor receptor; N, no; NA, not available; NT, control group receiving no treatment; OS, overall survival; P, control group receiving placebo; PFS, progression-free survival; RFS, relapse-free survival; RR, response rate; TTP, time to progression; Y, yes

Table 2: Key characteristics of randomised controlled trials stopped early for benefit (N = 25)

Characteristics	No. (%)
Type of stop	
Crossover to treatment group	3 (12)
Stop enrolment	12 (48)
Disclosure of results	5 (20)
Stopped for economical consideration	1 (4)
Crossover to treatment group + Stop enrolment	3 (12)
Stop enrolment + Disclosure of results	1 (4)
DSMC	
Present	19 (76)
Absent	6 (24)
Discrepancy in endpoint used (planned vs interim)	
Same	22 (88)
Different	1 (4)
Not available	2 (8)
Study purposes	
Registration trial	12 (48)
Non registration trial	13 (52)
Date of publication	
2005-2007	14 (56)
1997-2004	11 (44)

DSMC, Data and Safety Monitoring Committee

All RCTs reported consequences after the interim analysis. Those fell into three groups: cross-over to the treatment group, stopping enrolment, and disclosure of results (Table 2).

The criteria for planning an interim analysis were based either on a cut-off date (3 of 24, as in one case information was missing) or on the number of observed events (12 of 24) or on a preset number of patients enrolled (9 of 24). In 15 RCTs, interim analysis was done when ≥50% of the planned sample size for final efficacy analysis was reached. Five, however, reported an interim analysis conducted on a sample ≤43% of that planned for the final analysis. This information was not assessable for the remaining five RCTs.

The full sample size initially planned was ~8000 patients/ events across all trials retrieved. As a consequence of early stopping after the interim analysis, ~3300 patients/events across all studies were spared.

The mean study duration was 30 months (range 12–64 months). The median time lag between the end of enrolment (which coincides approximately with study termination)

and the date of publication of the results in peer-reviewed journals was 22 months (range 3 months to 15 years).

DISCUSSION AND CONCLUSIONS

Truncated RCTs reported as having been stopped early for benefit are becoming more frequent. Our findings highlight a consistent increase (>50%) in prematurely stopped trials in oncology during the last 3 years in comparison to whole period analysed (1997–2007).

Ethical reasons also play a role in the decision to stop a trial, since there is a responsibility to minimise the number of people given an unsafe, ineffective, or clearly inferior treatment. On the other hand, an interim analysis may also have drawbacks, since stopping trials early for apparent benefit will systematically overestimate treatment effects.[32]
The studies analysed were formally well designed; all were randomised, controlled, on the basis of robust endpoints, and with a large sample size. Though criticism of the poor quality of oncological trials seems out of place, unfortunately early termination raises new important concerns. Our findings lead to a new awareness: oncological trials are now formally better designed than in the past, but they are too often stopped prematurely. This may cause harm resulting from unreliable findings prematurely translated into clinical practice. More than 78% of the RCTs published in the last 3 years with an interim analysis ending the trial were used for registration purposes. This suggests a commercial component in stopping trials prematurely.

Regarding the methodology used to conduct the interim analyses, sample sizes used to obtain the interim efficacy results varied widely. Substantial concern is raised by five studies which enrolled <40% of the sample planned for final analysis. It is obvious that the risk of overestimating treatment effects increases markedly when the sample is small. Therefore, it is very important to insist that a large number of events must occur before investigators or DSMCs examine interim data, although that cannot guarantee data reliability in any case. In addition, the heterogeneity in sample sizes indicates that these committees enjoy ample discretion in advising or deciding whether to stop a clinical trial early for benefit.

Statistical simulations have shown that RCTs can overestimate the magnitude of the treatment effect depending on the timing of the decision to stop (i.e. the fraction of the total planned sample size or expected number of events).[33] Furthermore, repeated interim analyses at short intervals raise concern about data reliability: this strategy risks looking as though it is seeking the statistical significance necessary to stop a trial. In addition,

repeated analyses on the same data pool often lead to statistically significant results only by chance.[34, 35]

If a trial is evaluating the long-term efficacy of a treatment of conditions such as cancer, short-term benefits, no matter how significant statistically, may not justify early stopping. Data on disease recurrence and progression, drug resistance, metastasis, or adverse events, all factors that weight heavily in the benefit/risk balance, could easily be missed. An early stop may reduce the likelihood of detecting a difference in overall survival (the only relevant end point in this setting) because of the small sample, the possibility of crossing-over the experimental drugs, and contamination with other treatments.
Interim analysis data should always be evaluated by a DSMC, which should be independent in the sense that the members should have no interests in the study and should not directly participate in it. Although the majority of RCT reports stated there was a DSMC, we believe that its independence should always be reported. Stopping a trial after an interim analysis is often motivated by ethical considerations. The large number of patients spared (~40%), as evidenced by our analysis, might support this. However, the relation between sparing patients and saving time and trial costs is also unquestionable and indicates that there is also a market-driven intent. Our findings show that only a very small percentage of trials (~4%) were stopped early because of harm, i.e. serious adverse events, which is quite acceptable. Therefore, toxicity does not represent the main factor leading to early termination of trials.

Stopping a trial early does not guarantee that patients will receive the apparently beneficial treatment - assuming one believes they should - if study findings are not immediately publicly disseminated. We found long delays between study termination and published reports (~2 years), possibly because of confidentiality concerns in light of the current regulatory process. If the trials had continued for these further 2 years, more efficacy and safety data could have been gathered. In addition, such delays further lengthen the time needed for translating trial findings into general practice.

The study suffers one main limitation: since there is no 'standard' for reporting interim analysis methodology in scientific journals, there may have been some heterogeneity in this respect and some information might have been missed, affecting the sensitivity of the analysis. This could be overcome if study protocols were publicly available and details of interim analysis were reported better in peer-reviewed journals, e.g. by adoption of the Consolidated Standards of Reporting Trials statement.

In conclusion, a decision whether to stop a clinical trial before its completion requires a complex of ethical, statistical, and practical considerations, indicating that results of

RCTs stopped early for benefit should be viewed with criticism and need to be further confirmed. The main effect of such decisions is mainly to move forward to an earlier-than-ideal point along the drug approval path; this could jeopardise consumers' health, leading to unsafe and ineffective drugs being marketed and prescribed. Even if well designed, truncated studies should not become routine. We believe that only untruncated trials can provide a full level of evidence which can be translated into clinical practice without further confirmative trials.

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CHAPTER 3.2

A new anti-cancer drug in the market: Good news for investors or for patients?

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It is not infrequent to hear ethical appeals in order to shorten the validation process of a new health technology, but ethical considerations are difficult to reconcile with studies that have essentially a commercial aim. Pharmaceutical companies seek to maximise the profit of their product while users/buyers look for drugs that maximise health at an 'affordable' cost. It is hoped that drugs are rapidly released for patients who need them but the willingness to help patients should not be at the expense of adequate knowledge about the benefit of drugs.

Opinions on an earlier-than-ideal endpoint in the drug approval path vary from those who view it as an important step in improving public health by ensuring that beneficial drugs are made available as quickly as possible to those who see it as a dangerous shortcut that might jeopardise consumer health due to unsafe and ineffective drugs being marketed and prescribed. Research and development for a new drug is a long and complex process that has at least three critical steps: the passage from pre-clinical to clinical phases when first-time-to men studies are to be done, the evaluation of its clinical risk-benefit ratio at the end of the clinical phase before granting market approval, and the evaluation of its cost-effectiveness before deciding its market access and price. Decision-makers such as governmental regulatory agencies, purchasers of pharmaceuticals, physicians and patients need to have risk-benefit and cost-effectiveness indicators to judge its therapeutic value in the real world.

In an effort to obtain quick regulatory approval, pharmaceutical companies, under the pressure of the market, test their new anti-cancer drugs on human beings at the earliest possible point without fully knowing the true mechanism by which new drugs exert their clinical benefit. The testing process involves very specific sub-samples of progressing or refractory patients in an effort to obtain the status of 'accelerated approval' or 'under exceptional circumstances', using the simplest possible study design. Doubts about the added value of the new generation of drugs have indeed been raised in the framework of drug approvals either in the USA or Europe. In the past, the challenge was the use of non comparative studies and/or surrogate endpoints to document the efficacy of new products.[1–5] Other critics have suggested that the introduction of economic incentives to accelerate the drug review process, such as the Prescription Drug User Fee Act (PDUFA) in the USA, have actually reduced the time required for granting market approvals but have also increased the probability of discovering safety issues after the medications are in clinical use, either in terms of safety-based withdrawals or black-box warnings.[6]
New issues arise with the (inappropriate) utilisation of interim analyses to prematurely stop a clinical trial for benefit. Usually, interim analyses are planned to prematurely terminate a randomised clinical trial (RCT) for three reasons. First, for reasons of harm due to unacceptable toxicity; secondly, for ''futility'' as the efficacy of the new treatment is so

trivial that is unlikely that the continuation would detect a relevant difference; and finally, for apparent benefit. Previous research has documented that the number of RCTs stopped early for benefit has more than doubled since 1990.[7] Results of these trials should be interpreted with caution because statistical stopping rules are prone to stop a trial when a disproportionate number of events have occurred by chance thus exaggerating the estimated treatment effect.[8] In at least one third of trials stopped early for apparent benefit, it was not possible to confirm the statistical significance of preliminary results.[9,10] Recently, two independent teams of researchers carried out a secondary analysis of published papers to evaluate the use of interim analyses focussing on oncological clinical trials stopped early for benefit.[10,11] Wilcoxet al.[10] reviewed the study characteristics, features related to the decision to monitor and stop the study early, the number of events, and the estimated treatment effects reported in 29 RCTs evaluating the efficacy of health interventions in oncology. They estimated the correlation between the absolute number of events in each trial and the apparent treatment effect using the relative risk (RR), either reported or calculated. They found a median RR of 0.54, an effect that may be considered higher than expected in this setting, and an inverse association between RR and number of events (r 0.75; p-value=0.0001): the majority of RCTs (73%) that had an RR less than the median also evaluated fewer than the median number of events. This suggests that RCTs stopped after only a few events tend to report large treatment effects, while the risk of significantly overestimating the treatment effect diminishes when the number of events accrued is large. Trotta et al. identified 25 RCTs stopped early for benefit out of a total of 93 studies evaluating anti-cancer drugs. They found that evaluation of efficacy was protocol planned through time-related primary end points; >40% of them used overall survival as primary endpoint. In 95% of studies, at the interim analysis, efficacy was evaluated using the same end point as planned for the final analysis. As a consequence of early stopping after the interim analysis, 3300 patients/events across all studies were spared. Out of the 14 trials stopped and published between 2005–2007, 11 (79%) were used to support an application for marketing authorisation at the European Medicines Agency (EMEA) or at the Unites States Food and Drug Administration (FDA); before 2005, only 9% of the RCTs were used for registrative purposes. The most frequent consequences of the interim analysis were: stopping enrolment (48%), cross-over to the experimental group (24%) and disclosure of results (20%). The median time lag between the end of the enrolment and the study publication was indeed quite long: 22 months (range: 3 months–15 years), possibly because of confidentiality concerns.

According to this evidence, there is a high risk that drugs approved on the basis of preliminary and not fully validated evidence are utilised in a number of patients before other confirmative trials are carried out leading to an over-estimation of the impact of drugs in the cure/control of the cancer disease. This, in turn, leads to over-treatment, high costs,

safety problems and poor outcomes. In addition, when interim analysis makes the provision of commercial drugs to patients possible, this can interfere with patient accrual in confirmatory studies.[3] Finally, the publication delay may suggest a market-driven intent.

In most European countries, final users are neither the decision makers nor the direct payers (physicians choose a drug they will not eventually use, patients take a drug that they will not pay for and payers pay/reimburse for a drug they have not chosen at all). Supply and demand have little to no role to play in the pharmaceutical market. The price and the level of reimbursement are actually the result of a negotiation between producers (on behalf of share holders) and governments (on behalf of citizens and patients). Final decisions about market access, final price and reimbursement depend on the amount and completeness of data available on the proven efficacy (without information about its actual effectiveness)and future (predicted) cost of the system. In other words, the value of a drug reflects the quality of data and information and population health rather than the potential, but not fully demonstrated, attributes. In this context, the increasing use of interim analysis to prematurely stop clinical trials for benefit is a shortcut that puts decision-makers in a difficult situation with implications for consumers' health and for the economic balance of health systems. But, unfortunately, soft news about marketing approval and inclusion of drugs in lists of reimbursed health technologies have a much greater financial impact than validated clinical and economic yields. The pace of finance is more all-encompassing and dominant than the pace of clinical research, practice and even the 'real' economy.[12,13] Therefore, the arrival of a new anti-cancer drug, given a lack of complete and sound evidence, the controversies in the interpretation of results and ethical problems, may be considered better news for investors rather than for physicians and patients.

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CHAPTER 3.3

Therapeutic indications in oncology: Emerging features and regulatory dynamics

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ABSTRACT

The regulatory route leading to the definition of therapeutic indications of new compounds as well as extensions of indication (EoI) of already approved ones is a challenging process. If new anticancer drugs reach the market with a lack of complete evidence, this usually leads regulators to request additional data, post approval commitments or restrictions in therapeutic indications.

This study aims at quantifying the time needed for anticancer drugs approved by the EMEA to get an extension, the rates and characteristics of extensions approved, and at exploring the regulatory process leading to the definition of new indications.

A total of 103 therapeutic oncological indications, related to a cohort of 43 anticancer drugs, were retrieved between 1995 and 2008. The median time occurring between different indications for the same compound (defined as Time to New Extension, TtNE) significantly decrease from about 81 months in 1996 to 6 months in 2006. Twenty-four out of 43 approved anticancer medicines (about 56%) have only a single therapeutic indication, 12 of which were approved before 2005.

When considering two different cohorts of drugs in relation to the time of approval (1995–2004 versus 2005–2008), although not statistically significant, the older cohort tended to have a decreased probability of having EoI when compared to the new cohort (OR = 0.27; 95% confidence interval (CI): 0.07–1.04). With regard to the type of EoI (n = 60), our findings showed that in 48% of cases the initially approved indication was extended to treat a different tumour, in 37% of cases the extension consisted in a switch of line within the same therapeutic indication. The other two types of indication broadening refer to a different tumour stage (8%) and to the inclusion of a new patient population (7%).

The analysis of indication restrictions showed that in 20 cases out of 50 (40%) therapeutic indications were restricted by the Committee for Medicinal Products for Human Use (CHMP) during the assessment, with 60% of the restrictions occurring in 2006–2007.

This study adds three main pieces of information: (i) the majority of anticancer drugs still have a single indication regardless of the year of approval; (ii) the time needed to obtain an extension of indication has decreased significantly over the last decade and (iii) a highest rate of regulatory restrictions is matched to shorter clinical developments.

BACKGROUND

Once a medicinal product is on the market, companies usually perform new clinical studies to extend therapeutic indications.[1] Providing data from new trials is a requirement for expanding the indications, contrarily to the past, when case series or other less robust methods were considered sufficient evidence for this purpose. New indications may also include new patient settings or a switch in the treatment line (e.g. from second to first line). The regulatory route leading to the definition of therapeutic indications of new compounds and extensions of indication (EoI) of already approved ones are challenging processes. This is particularly the case for oncology, where there are many unmet medical needs, and where new therapeutic opportunities are often immediately translated into clinical practice. This process is per definition complicated by the fact that new anticancer drugs reach the market with a lack of complete and sound evidence.[2–5] An uncertain benefit/risk profile of a drug is hard to review for regulators, which usually leads to the requests for additional data, post approval commitments or restrictions in therapeutic indications.[6,7] A restriction of therapeutic indications is a tool with an immediate effect, which aims at identifying the specific patient's population that may benefit most from the medicine. Restrictions may also fuel off-label prescribing instantly, and on the long run, slow down the availability of formally approved indications and the investments in therapeutic innovation in general.

A critical factor is timing of a positive (or negative) decision about an additional and new indication of a medicinal product. When the decision is made (too) fast, patients maybe exposed to treatment on the basis of premature, weak or very uncertain data, asking for more and additional evidence to support a new indication. This study aims at quantifying the time needed for an anticancer drug to get an extension, the rates and characteristics of extensions approved, and at exploring the regulatory process leading to the definition of new indications.

METHODS

Information on regulatory steps leading to the definition of therapeutic indications for the cohort of anticancer drugs was extracted from the European Public Assessment Report (EPAR), publicly available on the EMEA website (http://www.emea.europa.eu/htms/human/epar/eparintro.htm).

Documents were surveyed for new applications as well as for later extensions between January 1995, when the EMEA was set up, and December 2008. The analysis includes all

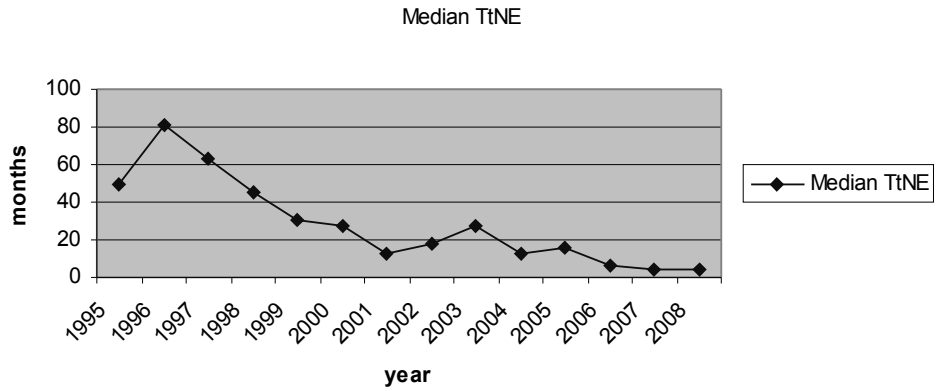
the anticancer drugs with a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) through the so-called Centralised Procedure. As the interferon a-2b (INFa-2b) application was aimed at obtaining a European Marketing Authorisation (MA) after earlier authorisations had been granted at the national level, there was not sufficient information for its oncology indications and the drug was therefore excluded from the analysis. Palliative or supportive therapies (such as bisphosphonates, immunoglobulins and anti-emetics), hormone treatments, colony-stimulating factors, chemoprevention treatments, vaccines and generics were also excluded from the analysis.

For the purpose of this analysis, the following parameters were extracted: active compound, date of issue of the European MA, number of therapeutic indications, study characteristics (design, number of patients and primary end-point), indication requested (IR) by the applicant and indication approved (IA) by the CHMP. Only indications for which the IR was clearly stated in the EPAR were considered eligible for the analysis. Then, a comparison between IR and IA was performed in order to find possible restrictions. The analysis of the types of extensions of indication was performed considering the following pre-specified categories: (i) new tumour, (ii) tumour stage, (iii) new population and (iv) switch in the treatment line. We defined a priori two common data acquisition forms to be completed. FT and GT independently evaluated all the EPARs and filled the respective forms. The results were then cross-checked, leading to a joint document. In the case of disagreement, the final decision was taken through a consensus process reached following further discussion.

RESULTS

A total of 103 therapeutic oncological indications, related to a cohort of 43 anticancer drugs, were retrieved between 1995 and 2008. Overall, 60 EoI were approved between 1995 and 2008. An increasing trend in EoI can be observed since 2002, with a median of 8 approved indications per year, while before 2002 only 5 out of 60 EoI (8.3%) were approved. In contrast, the rate of newly approved oncological products remains almost constant within the time frame 1995–2008 with an average of 3.3 per year. The median time occurring between different indications for the same compound (defined as Time to New Extension, TtNE) was also calculated, using the dates of European MA for each indication (Fig. 1).

Figure 1. Median Time to New Extension (TtNE) defined as the median time occurring between different indications for the same compound (n=103 indications).



A significant continuous decline of TtNE has been shown from 1995 up to 2008. For example, this means that for an anticancer medicine approved in 1996, about 81 months were necessary to have a new indication approved for the same drug. While for a product approved in 2006, the time needed was much shorter, i.e. 6 months.

Twenty-four out of 43 approved anticancer medicines (about 56%) have only a single therapeutic indication, 12 of which were approved before 2005 (Table 1). Only 7 products(about 16%) have at least five therapeutic indications (these include capecitabine, imatinib and docetaxel with 6, 9 and 11 indications, respectively). Except for bevacizumab, approved in 2005, the remaining 6 were approved between 1995 and 2001. Three products that, although recently approved present several indications, were identified: sunitinib approved in 2006 with three indications, cetuximab approved in 2004 with four and bevacizumab approved in 2005 with five.

When considering two different cohorts of drugs in relation to the time of approval (1995–2004 versus 2005–2008), although not statistically significant, the older cohort tended to have a decreased probability of having EoI when compared to the new cohort (OR = 0.27; 95% confidence interval (CI): 0.07–1.04).

With regard to the type of EoI, which usually aims at broadening the first indication, our findings showed that in 48% of cases the initially approved indication was extended to treat a different tumour (Fig. 2). For example, erlotinib, initially approved for non-small cell lung cancer, was then granted a new indication for pancreatic cancer. Moreover, in 22 out of 60 EoI (37%), the extension consisted in a switch of line within the same therapeutic indication (e.g. sunitinib, which was switched from second-line to first-line treatment of

Table 1: New anticancer drugs approved by the EMEA by number of therapeutic indications and year of approval

Number of indications	Number of new drugs	Name of compound firstly approved between 1995 and 2004	Name of compound firstly approved between 2005 and 2008
1	24	Imiquimod (2004); tasonermin (1999); cytarabine (2001); toremifene (1996); fulvestrant (2004); temoporfin (2001); cladribine (2004); mitotane (2004); doxorubicin (2000); alitretinoin (2000); bexarotene (2001); arsenic trioxide (2002)	Paclitaxel (as paclitaxel albumin) (2008); nelarabine (2007); clofarabine (2006); lenalidomide (2007); dasatinib (2006); nilotinib (2007); thalidomide (2008); temsirolimus (2007); lapatinib ditosylate monohydrate (2008); panitumumab (2007); azacitidine (2008); trabectedin (2007)
2	5	Busulfan (2003); alemtuzumab (2001); ibritumomab tiuxetan (2004)	Sorafenib (2006); erlotinib (2005)
3	5	Pemetrexed (2004); bortezomib (2004); topotecan (1996); temozolomide (1999)	Sunitinib (2006)
4	2	Doxorubicin hydrochloride (1996); cetuximab (2004)	-
5	4	Paclitaxel (1999); trastuzumab (2000); rituximab (1998)	Bevacizumab (2005)
6	1	Capecitabine (2001)	-
7	0	-	-
8	0	-	-
9	1	Imatinib mesilate (2001)	-
10	0	-	-
11	1	Docetaxel (1995)	-
Total	43	-	-

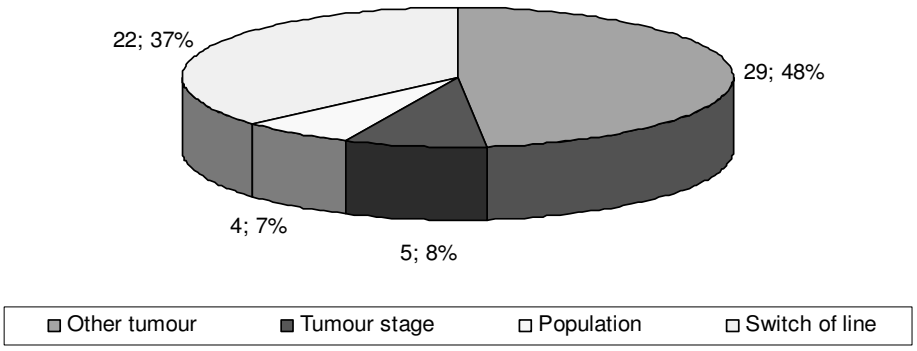


Figure 2: Types of broadening of therapeutic indication

Table 2: Number of indications restricted during the review process

Year of approval	Number of indications	Indication Requested (IR) available	Indications restricted
1995-2004	32	5	4
2005-2008	71	45	16
Total	103	50	20

renal cell carcinoma (RCC)). The other two types of indication broadening refer to a different tumour stage (8%) and to the inclusion of a new patient's population (7%) (e.g. busulfan indication extended to cover paediatric patients).

In order to investigate the regulatory dynamics occurring during the review process, a comparison was performed between the indications initially submitted by companies and those resulting at the end of the CHMP evaluation process. For this analysis, a clear information on the IR was retrieved in the EPARs for 50 out of the total sample of 103 indications (Table 2).

For example, sorafenib was granted the first indication in July 2006. The indication initially proposed by the applicant was the treatment of patients with advanced RCC as a first-line therapy. However, during the CHMP review process, it was acknowledged that the assessment of the full potential of sorafenib in terms of survival benefit in the treatment of advanced RCC was not possible due to the early unblinding of study results and subsequent cross-over. Therefore, due to the availability of other authorised treatments for the first-line treatment of advanced RCC, the indication was restricted to use in the second line.

A consistent retrieval on EPARs of the information about the IR was only possible since the year 2004. In fact, 45 out of 50 IR (90%) were available in the EPARs issued between2004 and 2008.

The analysis of indication restrictions occurring during the EMEA review showed that in 20 cases out of 50 (40%) therapeutic indications were restricted by the CHMP during the assessment, with 60% of the restrictions occurring in 2006–2007.

DISCUSSION

Our analysis confirms that, while the rate of newly approved drugs is constant over the years, there is an increase in the rate of EoI per year (91.7% of EoI occurred after 2002). Although this finding reflects the 'young age' of the EMEA (set up in 1995), it is also in line with the current awareness of the lack of original pharmaceutical products which leads drug companies to make the most out of already existing drugs.[8] The indicator (TtNE), considered to analyse how fast a new indication was developed and eventually approved during the last 13 years, showed a continuous decline. This reflects a shorter clinical development process and reduced regulatory delays. It also shows how quickly new treatments become available to patients. Furthermore, the shortened TtNE and the increased number of granted EoI suggest that companies set up wide clinical development plans, testing a compound in different oncological areas.

Contrary to common belief, most anticancer drugs (about 56%) present only a single therapeutic indication. It seems that drugs approved earlier do not have more EoI than newest compounds. There are very few examples of drugs having a large number of EoI and in most cases these are widely recognised as breakthrough drugs (e.g. imatinib, approved in 2001, holding nine indications; trastuzumab, approved in 2000, holding five indications). Other anticancer drugs with many indications are old cytotoxic compounds, such as paclitaxel, capecitabine and docetaxel, whose use is very well established and which still represent the basis of several therapeutic strategies. However, we identified three medicines, presenting multiple indications, with an uncommon accelerated development process: (i) sunitinib (approved in 2006 with three indications); (ii) cetuximab (approved in 2004 with four)and (iii) bevacizumab (approved in 2005 with five). On average, at least one indication per year was approved. Can this decrease of time between two subsequent indications ensure an adequate provision and assessment of clinical and safety data? Moreover, the two latter drugs, although examples of 'targeted drugs', were always approved in combination therapy with classical cytotoxic agents, showing their efficacy in this setting. This raises questions as to the real efficacy of such targeted compounds when used alone.

With regard to the broadening of indication, the practice of the switch of line is quite common and reflects companies' efforts to reach an earlier treatment line in an unidirectional way. This seems also to be the result of a precautionary regulatory approach, which often tends to restrict the indications proposed by the industry and then, as evidence is provided, relax these initial restrictions. About half of the EoI consist of the utilisation of the product for other tumours. This fulfils the industry expectations after the product reaches the market and it is generally favourable from a public health perspective. In

fact, stimulating further research on already approved drugs mainly contributes to limit the off-label use of drugs. Unfortunately, the broadening of indications including special populations such as children or the elderly is still highly neglected due to difficulties of generalising evidence in these special groups.
The analysis of restrictions of indications during the regulatory review process showed that, 50% of the indications could be included into our sample size due to a lack of sufficient information in part of the EPARs. A cut-off date for the improvement of EPARs quality could be traced in 2004, since before this year only 10% of reviewed EPARs explicitly reported the IR information. This improvement might be attributable to the effect of the EU Regulation (EC) No. 726/2004 (issued on 31 March 2004), which provided a clear and understandable information on medicinal products to be reported in the EPAR.[9] However, since useful information such as the IR is often still missing, more transparency on the regulatory dynamics leading to the conclusion of the assessment procedure is needed.

Our data highlighted that restricting the indications is quite a common and a recent 'practice', used by regulators. A graphical description of the regulatory dynamics over time for a general indication is provided in Fig. 3. In several cases, the indications requested at the time of the dossier submission tend to be wider than those eventually approved by regulators. Afterwards, the indications are widened again during subsequent extensions, in a time period that, as previously reported, is gradually declining (Δt_2).

Our findings show an interesting association between the time needed for an indication extension and the rate of indication restrictions: in fact during the time period 2006–2007,

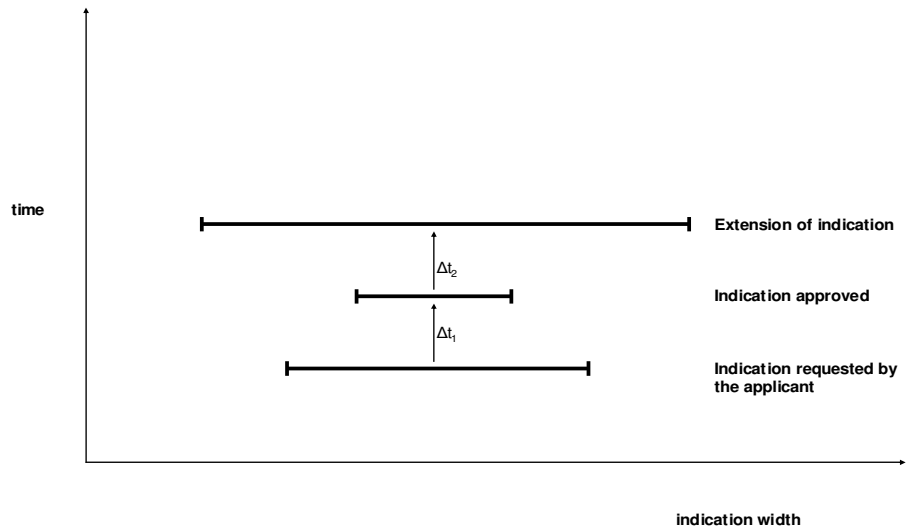


Figure 3: Graphical description of the regulatory dynamics over time for a general indication

when restrictions reach a peak, there is an evident decline in the time needed to obtain a new extension, TtNE. This leads to hypothesise a relationship between a faster clinical development and the chance of receiving an indication restriction from regulators. The fact that restrictions of indication occurred because of an incomplete clinical data package can then be easily assumed. It seems that in case of immature efficacy and safety data, regulators often tend to shift towards the terminal treatment lines in order to restrict the drug use only to patients with no alternatives. The consequence is a subsequent request by companies for getting earlier treatment lines approved, resulting in a *continuum* in terms of EoI for a single compound.

CONCLUSIONS

While companies can benefit from the extensions given the enlarged market and patent protection, extending therapeutic indications is also very positive from a public health perspective to better define drug benefit/risk profiles, to monitor safety issues and to reduce the off-label use.

From a regulatory point of view, the practice of restring or broadening indications is of pivotal interest given the challenge of finding the right balance between acquiring as much evidence as possible to support a new application of an existing product and risking widespread off-label use.

Submitting a drug dossier to regulatory authorities containing immature data could be risky for the industry itself as unexpected costs and delays could occur. The progressive shortening of the clinical development may result in an uncertain drug benefit/risk profile, which is hard to review for regulators and may result in harming the patient. As a consequence, the risk of restrictions in therapeutic indications, requests for additional data, and post approval commitments (such as further confirmatory trials) are increased, with a possibly negative impact on industry's resources.

In conclusion, this study adds three main pieces of information:(i) the majority of anticancer drugs still have a single indication regardless of the year of approval; (ii) the time needed to obtain an extension of indication has decreased significantly over the last decade and (iii) a highest rate of regulatory restrictions is matched to shorter clinical developments. Lots still remain to be done in terms of continuing broadening therapeutic indications. This would potentially determine a reduction of the off-label use of drugs, through an increase of labelled indications, with positive implications for therapeutic decision makers (e.g. clinical guideline committees and reimbursement authorities) and, most importantly, for patients, provided that the creation of new therapeutic indications is based on robust clinical evidence.

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CHAPTER 3.4

Evaluation of oncology drugs at the European Medicines Agency and US Food and Drug Administration: when differences have an impact on clinical practice

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ABSTRACT

Purpose The aims of this study were to compare the approaches of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in the evaluation and approval of new anticancer indications and to identify possible clinical implications associated with these differences.

Methods Information on the European Union therapeutic indications for the cohort of anticancer drugs was extracted from the European Public Assessment Reports and from the FDA review reports.

Results Overall, 42 anticancer drugs were approved by EMA between 1995 and 2008, corresponding to a total of 100 indications. In 47 of 100 indications, a difference was found. For 19 of these 47 indications, the difference was that one agency approved an indication, whereas the other agency did not. For the remaining 28 indications, the same indication was approved by both the agencies and differences were evaluated through an algorithm; in 10 cases, discrepancies in therapeutic indications between EMA and FDA were considered clinically relevant. We found an overall trend that the agency that was second to give a positive approval was usually more restrictive in terms of wording of the indication compared with the agency that provided approval first. Regarding the use and robustness of available clinical data for evaluation, no clear associations could be found.

Conclusion Clinically relevant differences in the outcome of the EMA and FDA approval process of oncology products were found. Neither of the agencies seems to have a prevailing restrictive behaviour over the other. Further efforts on harmonizing decision-making between regulatory systems are needed.

INTRODUCTION

In a globalised world, new information immediately reaches many people in all countries. This is especially the case for critical issues related to public health, both in terms of new therapies and potential health risks.[1-4] One regulatory action carried out in one country has unavoidably an impact on the others. Decisions taken by world's leading regulatory agencies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), are in the global public eye and are often considered as a reference by other health authorities in the world.[5-7] Different decisions about the same application for marketing approval between leading agencies may pose questions on the reasons why, often generating confusion both at the level of health professionals and in society at large.[8-10] Variable access to a drug that is available in one country but not in another country might be seen as unfair to the deprived patient populations. Paradoxically, patients who can use the new product are possibly more prone to risks because there are always unresolved uncertainties around the benefit-risk balance of new medicines, even when found to be positive at the moment of marketing approval.

The fact that similar drug dossiers are being submitted at virtually the same time to different regulatory authorities has paved the way for an increased need for cooperation between regulatory agencies. The FDA and EMA have agreed on projects regarding different topics (e.g. scientific advice, inspections, risk management), with the aim to harmonize decision making processes.[11-13] In addition, in the context of the International Conference on Harmonisation and other international regulatory platforms, alignment and dialogue between different regulatory systems have been strengthened over the last decades. The goals are to increase efficiency and consistency in the regulatory process, avoiding replication of the assessment of similar procedures, waste of time, and waste of financial and human resources, but also to learn from each other's experiences. A few decades ago, an identified drug lag between the United States and the United Kingdom caused great regulatory and political concern about the root cause of this lag and the implications for patients and public health.[14] The fact that some clinically important drugs were approved for marketing in one country but not in another one without obvious reasons was considered a failure of the regulatory systems in both countries. The definition of a therapeutic indication is a critical step in regulating medicinal products.[15] The wording of indications can have a huge impact on clinical practice by including or excluding certain patient populations.

The aim of this study was to compare the evaluation and approval of new products with an anticancer indication by the EMA and FDA and to identify possible clinical implications associated with any differences in the wording (e.g. whether one agency tends to be more restrictive in the definition of an indication, limiting drug use only to a specific patient

population). The factors that may influence restrictions (e.g. time of approval, use of the same pivotal trial, study design and characteristics) are also analyzed.

METHODS

The unit of analysis was the therapeutic indication related to an anticancer medicinal product. Information on the European Union (EU) therapeutic indications for a cohort of anticancer drugs with a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) through the Centralised Procedure between January 1995 and December 2008 was extracted from the European Public Assessment Reports, publicly available on the EMA Website.[16]

Information on therapeutic indications of the corresponding cohort of approved anticancer drugs in the United States was retrieved from FDA review reports and communications, available at the FDA website.[17] Palliative or supportive therapies (e.g. bisphosphonates, immunoglobulins, anti-emetics), hormone treatments, colony-stimulating factors, chemoprevention treatments, vaccines, and generics were excluded from the analysis. The analysis was carried out by designing a standard form, which was used to list and describe

Table 1: Selected Examples Demonstrating Overlap or Difference in Registration or Labeling Between EMA and FDA

Drug (INN)	EMA-Approved Indication	FDA-Approved Indication	Difference Between US and EU Indication	Comments
Cetuximab	In combination with irinotecan, cetuximab is indicated for the treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of irinotecan, including cytotoxic therapy	In combination with irinotecan, cetuximab is indicated for EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based	No difference	No restriction of indication applied by EMA or FDA
Imatinib mesylate	Treatment of adult patients with newly diagnosed Philadelphia chromosome–positive acute lymphoblastic leukemia integrated with chemotherapy	Indication not present in the United States	Indication not approved by one of the two agencies	-
Alemtuzumab	Treatment of patients with B-cell chronic lymphocytic leukemia for whom fludarabine combination chemotherapy is not appropriate	Indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia	Existing difference	EMA was more restrictive than FDA because it recommended the drug as second line

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; INN, International Nonproprietary Names; EU, European Union; EGFR, epidermal growth factor receptor.

selected items and each EU versus the corresponding US indication. The form included a semiquantitative grading of the key characteristics to judge whether the information in the corresponding EU and US documents was similar or different. F.T. and G.T. extracted this information and independently filled the form.A series of examples of how the comparisons were carried out and classified are listed in Table 1.

In cases when a difference between an EU and the corresponding US indication occurred, the type of such difference was identified as follows: a difference in cotherapy/prior treatment; a difference in schedule; a difference in the treatment line; or a difference in patient population. When a difference was found between corresponding indications, this meant that a restriction was applied by one of the two agencies. To establish clinical relevance of the differences, an algorithm was developed (Fig 1). For this step, the study benefitted from the expertise of a clinical oncologist (J.H.M.S). The occurrence of difference in therapeutic indication between the EMA and FDA and the clinical relevance of

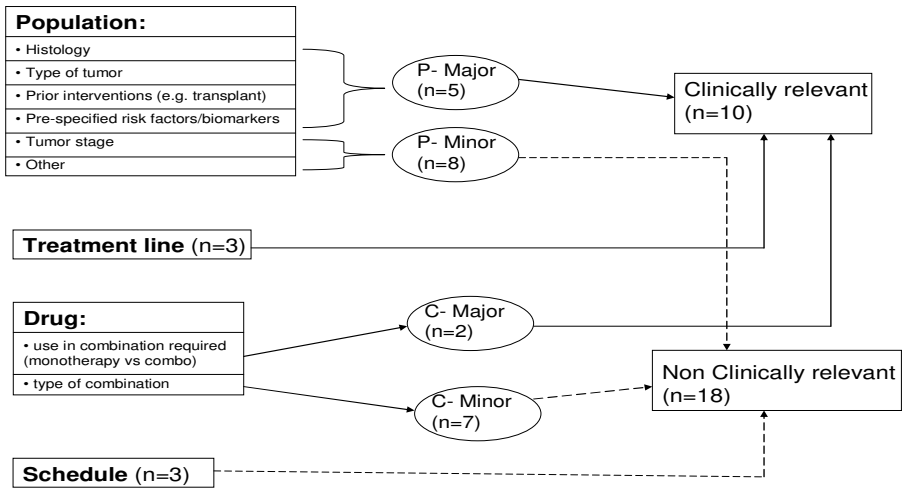

Figure 1: Algorithm to establish clinical relevance of the differences between registration of oncology indications by EMA and FDA

Algorithm to establish clinical relevance of the differences between registration of oncology indications by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). All 28 indications with differences in wording were analyzed through the algorithm to establish clinical relevance, based on the researchers' evaluation. Differences were divided into four main categories: population, treatment line, drug, and schedule. When differences involved the treatment line, these were always considered as clinically relevant. However, when differences involved the schedule, these were always considered as not clinically relevant. Within the main categories of population and drug, two subcategories were identified, major and minor, referring to clinically relevant and non–clinically relevant differences in the indication between the EMA and FDA, respectively. P, population; C, combination (ie, the new registered drug is used in combination with another agent or agents).

such difference were independently assessed in blind fashion by F.T., G.T., and J.H.M.S. The results were then cross-checked, leading to a joint document. In case of disagreement, the final decision was made through a consensus process after discussion. Dates of approval were used to analyze time lags occurring between the approvals of the same indication at both agencies. Time lags were classified into the following three categories: ≤ 6 months; 7 to 12 months; and ≥ 13 months. We classified the robustness of the submitted clinical package (i.e. excellent, good, medium, poor). A study was considered excellent when it was randomized, controlled, based on at least a time-related endpoint, and involved a minimum of 200 patients. The following associations with possible regulatory restrictions in indications were evaluated: the fact that one agency approved an indication first, before the other agency; the use of the same pivotal trial; and the robustness of the pivotal study design.

RESULTS

Overall, 42 anticancer drugs were approved by EMA between 1995 and 2008, corresponding to a total of 100 indications for the treatment of several tumours or malignancies (Fig 2). The primary analysis revealed that in 52 of 100 indications, there were no differences between the EMA and FDA. Comparison was not possible only in one case (i.e. cladribine), because of lack of public information on the US label. Therefore, 47 therapeutic indications showed a difference between the two agencies (Fig 3). In 19 of these 47 indications, one of the two agencies approved an anticancer indication, whereas the other did not. In three indications, an FDA indication was not approved by EMA, and in 16 indications,

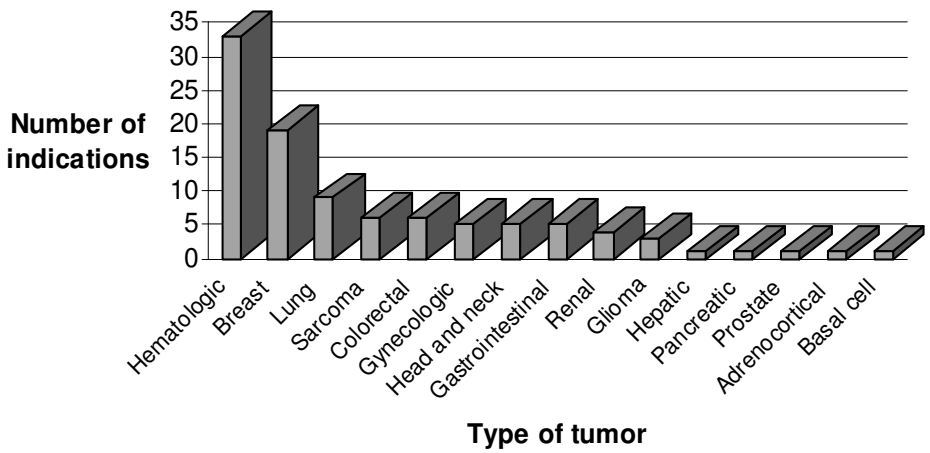

Figure 2: Types of tumors or malignancies

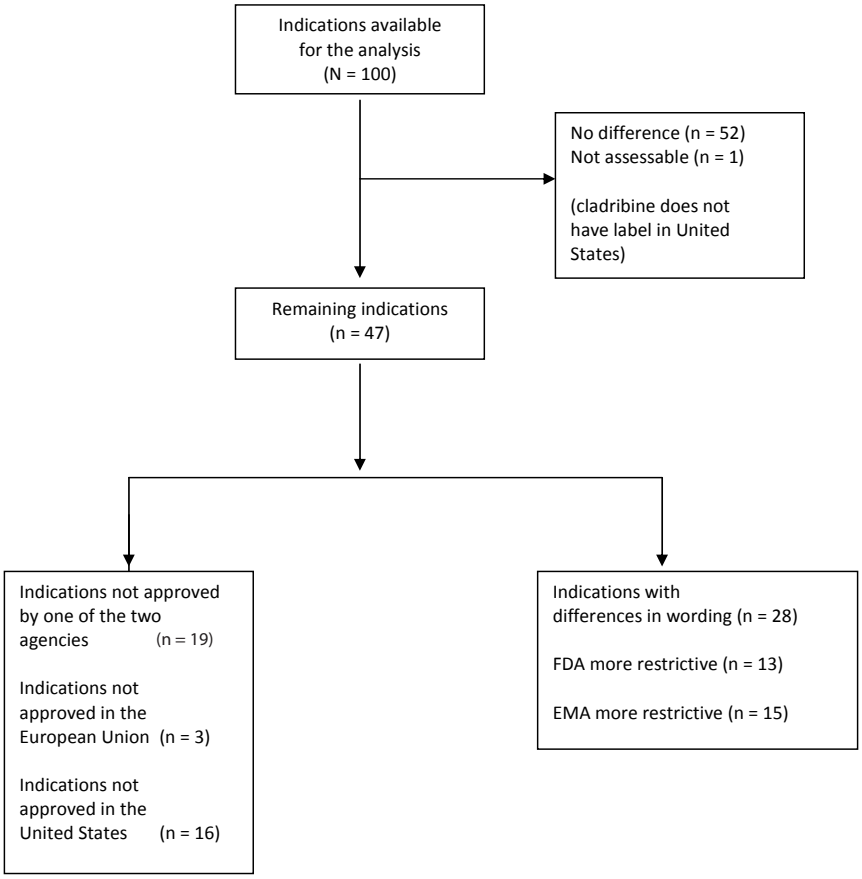

Figure 3: Flowchart

an EMA indication was not approved by the FDA. For the remaining 28 of 47 indications for which a difference between corresponding indications was found, further analysis showed that neither agency could be characterized as more restrictive compared with the other. The FDA was more restrictive in 13 (46%) of 28 indications, whereas the EMA was more restrictive in 15 (54%) of 28 indications. In 57 of the 100 analyzed indications, the EMA and FDA based the approval on the same pivotal study. In 22 of the 28 indications with a significant difference in the wording of the indication, the pivotal study was the same, whereas only in the remaining six indications, the pivotal study differed.

With regard to the type of difference, it was found that in nine cases, the indications differed in terms of the description of cotherapy/prior therapy requested. In three cases the

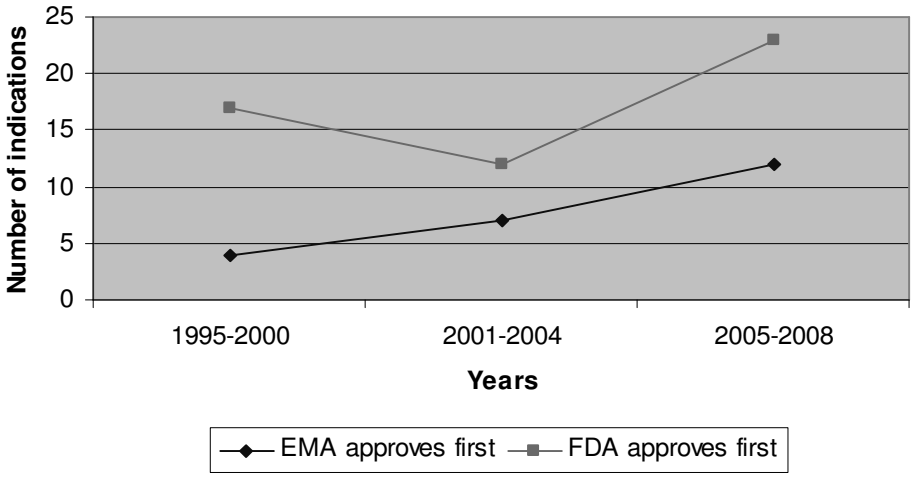

Figure 4: Rates of first approvals by agency and year.

difference concerned the schedule, and in three other cases, the difference concerned the line of treatment. In 13 other indications, discrepancies were found in the specification of the target population.

The 28 indications with a difference in the approved wording were further evaluated through the algorithm depicted in Figure 1, highlighting 10 clinically relevant indications (Table 2). The dates of approval by the EMA and FDA were used to determine which agency came first in the approval of a specific indication. The majority of indications (69%) were first approved by the FDA, although a trend shows that there is a continuous increase of first approvals by the EMA (Fig 4). Although limited numbers did not allow for formal statistical testing, we found an overall trend that the agency that positively approved an indication second was usually more restrictive in terms of wording of the indication compared with agency that approved the indication first.

A clear decrease in the time lags between the agencies' approval dates was observed. Between 2005 and 2008, 22 (59%) of 37 indications showed a time lag of ≤ 6 months, whereas during 1995 to 2000, only four of 21 approved indications showed a time lag ≤ 6 months. For 76% of approved indications, there was a time lag in that period of ≥13 months (Fig 5). Regarding the use and robustness of available clinical data for evaluation, no clear associations could be found.

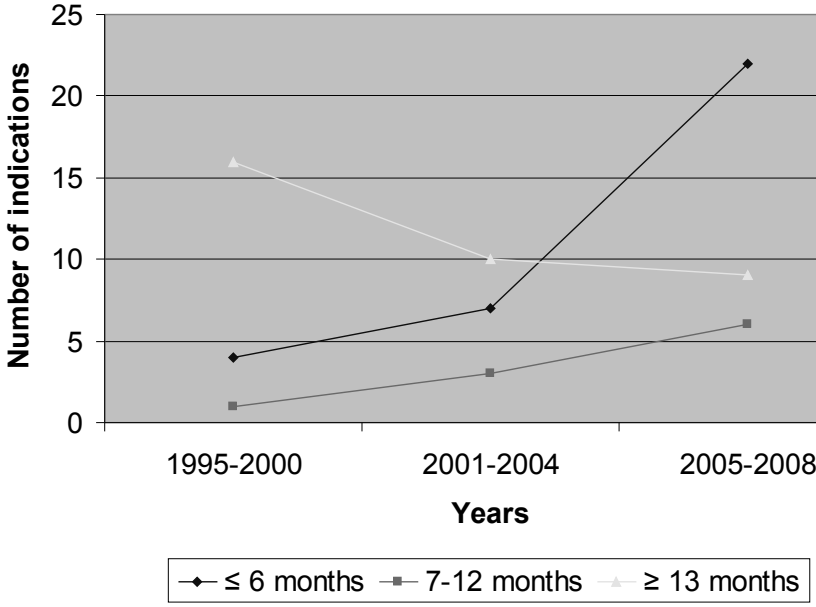

Figure 5: Time lag between EMA and FDA approval.

DISCUSSION

We found that in approximately only one out of two oncology indications (52 of 100 indications) evaluated by the EMA and FDA from 1995 to 2008, both agencies came virtually to the same conclusion. When a difference occurred, 19 of 100 indications were not approved by one of the two agencies, and 28 out of 100 indications had different wording of the label, including 10 cases in which these differences had significant clinical meaning for treating patients in need of anticancer drugs. Furthermore, time trends show an overall decrease in the time gap of when the two agencies come to an opinion. When there is a difference in timing on a positive opinion, the second agency to approve an indication tends to be more restrictive in wording of the indication.
A critical finding of this analysis lies in those indications approved only by one of the two agencies. This means that large patient populations may be deprived of treatments that are available in other countries or that patients who live in the countries where the drug is available could be exposed to drugs whose benefit-risk profile was not considered positive elsewhere.

Usually the rationale behind a negative opinion issued by a regulatory agency is not made publicly available. The fact that an indication is approved by one agency but receives a negative opinion by another agency represents a crucial issue from a public health

perspective. Lack of transparency on regulatory opinions is widely debated within the scientific community and deserves more action in the next future.[18,19]

Differences in access to treatments in such a globalised world may have several consequences. First, in the countries where the indication is not approved, a growing pressure on regulatory bodies, both from patients and health care professionals, can be expected. This may potentially influence the regulatory review process, possibly leading to a biased evaluation. Second, the off-label use of medicines is fuelled where the indication is not approved. However, if such an indication is approved in another country based on robust data, it can be considered as an off-label use only from a regulatory perspective.

When the indications are approved by both agencies, a problem occurs when corresponding indications differ in wording and/or meaning, as shown in this study. This means that the same indication is more restricted by one of the two agencies. Our analysis shows that such differences exist in about 60% of indications (28 of 47 indications). However, neither of the agencies seems to have a prevailing restrictive behaviour compared with the other agency. Despite differences in the US and European licensing systems, these do not result in a more or less frequent use of restrictions by one of the agencies.

Examining the details of the studied indications reveals ample opportunities for regulatory learning. For example, sorafenib is indicated in the EU as a second line treatment for renal cell carcinoma, whereas in the United States it is indicated as a first line treatment. The label of erlotinib in the EU indicates that there is no survival benefit or other clinically relevant effects of erlotinib in patients with non-small-cell lung cancer with epidermal growth factor receptor-negative tumors, whereas in the United States, the epidermal growth factor receptor status is not mentioned (more of such cases are listed in Table 2). These examples show that a different regulatory decision on the same indication can result in a different place in therapy for the same drug and/or may exclude a patient subgroup from a treatment. The fact that the decisions in those examples were made by the EMA and FDA based on the same pivotal trials makes these findings even more relevant. In this respect, the case of panitumumab is explanatory. The EMA reviewed this drug for metastatic colorectal cancer (CRC) based on a two-arm, randomized controlled trial, involving 463 patients. There was a statistically significant difference between the two treatment arms with regard to the primary end point of progression–free survival (PFS). However, the difference between median PFS in the two arms was only 5 days, and negative results were obtained for the secondary end point of overall survival. Therefore, the CHMP initially rejected it. Subsequently, the applicant identified a biomarker (*KRAS*) that allowed the selection of patients who did not benefit from panitumumab treatment and requested a re-examination. In this post hoc analysis, the median PFS in the wild-type

Table 2:Cases demonstrating clinically relevant differences in approved indications between the EMA and FDA

Case No.	Drug (INN)	EMA-Approved indication	FDA-Approved indication	Difference between US and EU indication	Difference category	Use of the same pivotal trial
1	Pemetrexed	Indicated as monotherapy for the treatment of patients with locally advanced or metastatic non–small-cell lung cancer after prior chemotherapy	Indicated as a single agent for the treatment of patients with locally advanced or metastatic non-squamous non–small-cell lung cancer after prior chemotherapy	Histology is restricted by FDA	Difference in the patient population	Yesv
2	Busulfan	Busulfan followed by cyclophosphamide is indicated as conditioning treatment before conventional hematopoietic progenitor cell transplantation in adult patients when the combination is considered the best available option	Indicated for use in combination with cyclophosphamide as a conditioning regimen before allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia	FDA restricts use to chronic myelogenous leukemia	Difference in the patient population	No
3	Cetuximab	Indicated for the treatment of patients with squamous cell cancer of the head and neck in combination with platinum-based chemotherapy for recurrent and/or metastatic disease	Indicated for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy	EMA recommends combination therapy	Difference in therapy (combination *v* monotherapy)	No
4	Trastuzumab	Indicated for the treatment of patients with HER2-positive, early breast cancer after surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy (if applicable)	Indicated as a single agent for the adjuvant treatment of HER2-overexpressing, node–negative (estrogen/progesterone receptor negative or with one high-risk feature) or node-positive breast cancer, after multimodality anthracycline-based therapy; indicated as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of HER2-overexpressing breast cancer	FDA specifies the patient population	Difference in the patient population	Yes
5	Alemtuzumab	Indicated for the treatment of patients with B-cell chronic lymphocytic leukemia for whom fludarabine combination chemotherapy is not appropriate	Indicated as a single agent for the treatment of B-cell chronic lymphocytic leukemia	EMA recommends second line	Difference in the treatment line	Yes

Table 2:Cases demonstrating clinically relevant differences in approved indications between the EMA and FDA (*continued*)

Case No.	Drug (INN)	EMA-Approved indication	FDA-Approved indication	Difference between US and EU indication	Difference category	Use of the same pivotal trial
6	Sorafenib	Indicated for the treatment of patients with advanced renal cell carcinoma who have experienced treatment failure with prior interferon alfa– or interleukin-2–based therapy or are considered unsuitable for such therapy	Indicated for the treatment of patients with advanced renal cell carcinoma	EMA recommends second line	Difference in the treatment line	Yes
7	Erlotinib	Indicated for the treatment of patients with locally advanced or metastatic non–small-cell lung cancer after failure of at least one prior chemotherapy regimen. When prescribing erlotinib, factors associated with prolonged survival should be taken into account. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumors	Erlotinib monotherapy is indicated for the treatment of patients with locally advanced or metastatic non–small-cell lung cancer after failure of at least one prior chemotherapy regimen. Results from two multicenter, placebo-controlled, randomized, phase III trials conducted in first-line patients with locally advanced or metastatic non–small-cell lung cancer showed no clinical benefit with the concurrent administration of erlotinib with platinum-based chemotherapy (carboplatin and paclitaxel or gemcitabine and cisplatin), and its use is not recommended in that setting	EMA specifies EGFR status and response likelihood	Difference in the patient population	Yes
8	Temsirolimus	Indicated for the first-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors	Indicated for the treatment of advanced renal cell carcinoma	EMA defines prognostic risk factors	Difference in the patient population	Yes

Table 2:Cases demonstrating clinically relevant differences in approved indications between the EMA and FDA (*continued*)

Case No.	Drug (INN)	EMA-Approved indication	FDA-Approved indication	Difference between US and EU indication	Difference category	Use of the same pivotal trial
9	Bortezomib	Indicated as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation	Indicated for the treatment of patients with multiple myeloma	EMA recommends second line	Difference in the treatment line	Yes
10	Bortezomib	In combination with melphalan and prednisone, bortezomib is indicated for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplantation	Indicated for the treatment of patients with multiple myeloma	EMA recommends combination therapy	Difference in therapy (combination *v* monotherapy)	Yes

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; INN, International Nonproprietary Names; EU, European Union; HER2,human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor.

KRAS population was found to be 12.3 weeks compared with 7.3 weeks in the mutant-type *KRAS* population, which is a difference of 5 weeks (hazard ratio, 0.45; 95% CI, 0.34-0.59). This was considered sufficient by the CHMP to grant the approval only in patients with CRC with non-mutated *KRAS* in December 2007. Conversely, the FDA approved the same drug for CRC in September 2006. Because at the time the *KRAS* biomarker was not identified, the US indication was broader, including all patients with CRC. The difference in the panitumumab indication can not be attributed to the restrictive behaviour of one of the two agencies, but only to the availability of new updated information at the time of regulatory review. This difference remained for almost 3 years, and only in July 2009 were the indications finally harmonized.

Because premarketing data are often incomplete, regulators tend to grant therapeutic indications that specifically reflect the characteristics of patients enrolled onto clinical trials.[15] This leads to the following unavoidable consequences: an increased use of restrictions; limited generalizability to the real world; increased risk of precautionary approvals, instead of regulatory approvals; and scientific societies sometimes issuing opinions conflicting with regulatory bodies. When indications become extremely specific, the risk of widening the gap between regulators and real clinical practice gets greater. For example, it was found that temsirolimus is indicated in the EU for the first-line treatment of advanced renal cell carcinoma only for patients who have at least three of six prognostic risk factors. Contrarily, in the United States, temsirolimus is indicated for all patients with advanced renal cell carcinoma. This difference between the EU and United States was evaluated as striking from a clinical point of view. More important questions arise. Is the EU indication really applicable in clinical practice? What is the influence of the wider US indication over the European one in the real setting?

Another case from which we can learn is represented by bevacizumab for the treatment of metastatic breast cancer. In December 2010, the FDA's assessment of bevacizumab contrasted with that of EMA regulators, who reaffirmed their approval of the drug for metastatic breast cancer the same day.[20] Although the EMA concluded that the balance of benefits and risks of bevacizumab in combination with docetaxel is negative and that this combination should no longer be used in the treatment of breast cancer, it also confirmed the benefits of the drug in combination with paclitaxel for patients suffering from metastatic breast cancer.[21] On the contrary, based on FDA decisions, breast cancer will be totally removed from bevacizumab label.

Our study results and the examples we discussed show that there is no evidence supporting a notion that one of the two regulatory communities might be a better or a worse performer. The FDA is still first in approving new oncologic indications over the last few

decades, but there is a trend for more convergence between the two agencies in regulatory decision making. Regulators' credibility could be negatively affected by precautionary approvals, which are understandable from the perspective of managing the uncertainties in the available evidence. Such precautionary approvals tend to be tailored to restricted patient populations and are potentially distant from the actual clinical needs, empowering third parties (e.g. scientific societies, reimbursement authorities) to define the real place in therapy of a new medicine. An effective decision on indications can only stem from an adequate balance between evidence-based decision making and consideration of the real needs of practice. A limitation in the regulatory system lies in the lack of robust and exhaustive information at the time of the approval, triggering the use of indication restrictions and thus identifying specific subpopulations. However, when a new option becomes available, there is a natural demand for it to be used by larger populations. Because post-approval commitments are not always met by the industry, the weighing of the product's benefit-risk remains a challenge for public health bodies.[22] For this purpose, public research should make more effort in conducting effectiveness studies, also supported by *ad hoc* official legislation.

In conclusion, clinically relevant differences in the outcome of the EMA and FDA approval process on oncology products were found. In some cases, such differences significantly affect patient's access to relevant therapeutic options. Although further efforts on harmonizing decision making between regulatory systems are needed, we see opportunities for variability-driven learning and regulatory science to get the best out of available data for the sake of patient benefit and public health.

Because no clear predictors of regulatory outcomes have been identified, there must be other driving forces causing such heterogeneity in the approval between the EMA and FDA. Economic, political, and sociocultural factors, possibly influencing regulatory decision making, need to be investigated.

Regulatory decision making should be driven by scientific data and strong logic. Despite all of the efforts regulators invest in regulatory science and better methods for robust benefit-risk assessment, clinically relevant differences between the EMA and FDA were identified.

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CHAPTER 3.5

How do the EMA and FDA decide which anticancer drugs make it to the market?

A comparative qualitative study

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ABSTRACT

Background The process leading to a regulatory outcome is guided by factors both related and unrelated to the data package, defined in this analysis as "formal and informal factors", respectively. The aim of this qualitative study is to analyse and to understand which formal and informal factors drive the decision-making process of the European Medicines Agency (EMA) and Food and Drug Administration (FDA) regulators with regard to anticancer drugs, using in-depth semi-structured interviews with regulators of the two agencies.

Methods In line with the theory and practice of qualitative research, no set sample size was defined a priori. Respondent selection continued until saturation and redundancy were reached. Data was collected through means of in-depth semi-structured interviews conducted either in a face-to-face setting or via Skype® with each regulator. The interviews were audio recorded and verbatim transcribed. The analysis was carried out manually on the transcribed text. Data was independently coded and categorized by two researchers. Interpretation of the findings emerged through a process of triangulation between the two.

Findings Thirteen EMA and FDA regulators, who had extensive experience with evaluating and making decisions about anticancer medicines, were interviewed between April and June 2012.
There is an open dialogue between the FDA and EMA, with the two moving closer and exchanging information, but not opinions. Differences in decision-making between the agencies may be due to a different evaluation of endpoints (e.g. Progression Free Survival seen as a clinical benefit per se by EMA, not by FDA; FDA more open to base approval on activity data). Different interaction modalities with both industry and patients represent an additional source of divergence with a potential impact on decision-making. The key message of our respondents was that the two agencies manage uncertainty in a different way: unlike the EMA, the FDA may have a prevailing attitude to take risks in order to guarantee quicker access to new anticancer treatments.

Conclusions This study has confirmed that although formal factors are the main drivers for regulatory decisions, the influence of informal factors plays an important role in the drug evaluation process.

INTRODUCTION

The decision-making process for the evaluation of drug applications is complex. Based on the assessment of non-clinical, clinical and quality data submitted by the pharmaceutical industry, regulators have to make sure that the benefits of a new drug outweigh the risks and that only products with a positive benefit/risk balance are brought to the public.
The importance of analysing and understanding the regulatory decision-making processes from a public health perspective has been recognised by both the two world leading agencies, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), who have set up projects to define a structured framework for regulatory decisions.[1-2]

A properly conducted benefit/risk assessment should be a rational and transparent process of combining objective elements, previous experiences, regulatory logic and, unavoidably subjective factors, leading to consistent decisions. Unfortunately the scientific evidence supporting the use of a new product is always incomplete and therefore decisions have to be made under conditions of uncertainty.[3] The less complete information available, the greater the uncertainty and, in turn, the risk of 'getting it wrong', which can

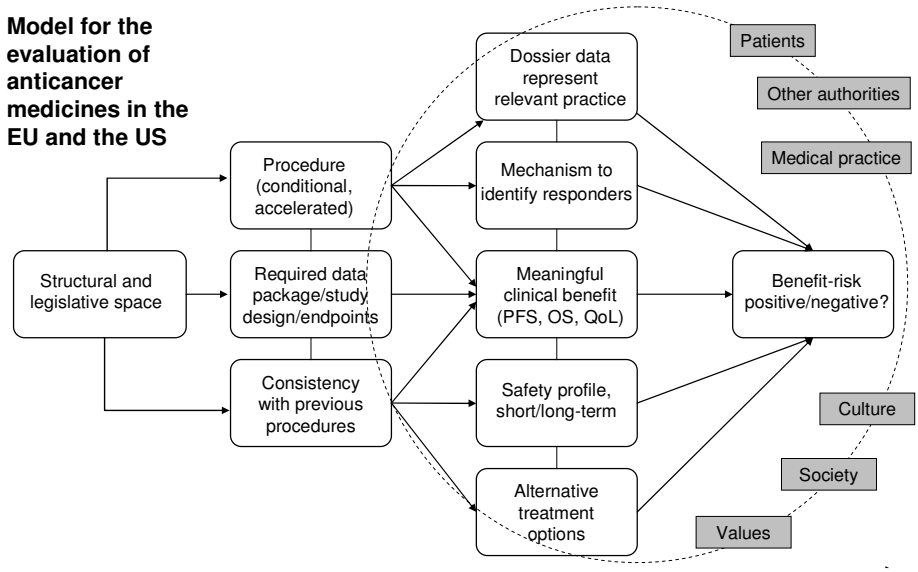

Figure 1: Model for the evaluation of anticancer medicines in the EU and the US

Legend: PFS: Progression-Free Survival; OS: Overall Survival; QoL: Quality of Life.The area encircled by the dashed line embodies the criteria in the assessment process that lead to the final regulatory decision on benefit/risk. This process is shaped by both formal and informal factors. The white boxes contained within the dashed line indicate the formal factors guiding the assessment of a new drug. The grey boxes on the dashed line itself represent informal factors mediating a regulator's assessment of the formal factors.

compromise the credibility of the decision making process. Furthermore, the problem of uncertainty is that a threshold of acceptability cannot be described by a single metric which can potentially give rise to variability among assessors and contribute to divergent opinions.[3-4]

Our previous analysis highlighted substantive differences between the EMA and the FDA in managing uncertainty when reaching decisions on anticancer drugs. Although such analysis showed clinically relevant differences in the EMA and FDA's decisions, it could not identify the causes of such heterogeneity.[5]

The present research is based on the assumption that the process leading to a regulatory outcome is guided by factors both related and unrelated to the data package, defined in this analysis as "formal and informal factors", respectively (see Figure 1). In fact we assumed that over the course of an application review, a regulator's assessment of the data package is likely to be mediated by informal factors such as the interaction with external stakeholders (e.g. pharmaceutical companies, patients or other regulatory agencies) and influenced by socio-cultural and behavioural aspects.

The aim of this qualitative study is to analyse and to understand which formal and informal factors drive the decision-making process of the EMA and FDA regulators with regard to anticancer drugs, using in-depth semi-structured interviews with regulators of the two agencies. The emphasis of the study is on acquiring insight into the dominant and critical features of the EMA and FDA when it comes to dealing with situations of uncertainty and to evaluating the robustness and credibility of the evidence regarding claims for anticancer medicines.

METHODS

Study population and sampling

The sampling process took into consideration the structural differences between the two agencies (see Box 1). Therefore, EMA respondents were purposely selected among the members of the Committee for Medicinal Products for Human Use (CHMP), of the Oncology Working Party (OWP) and of the Scientific Advisory Group on Oncology (SAG-O) as well as concerned staff. FDA respondents were selected on the basis of their seniority and longstanding experience with the assessment of drug applications for anticancer medicinal products to represent all levels of decision making from the FDA Center for Drug Evaluation and Research (CDER). No author of the present article was included among study respondents. Respondents were asked to speak on their own behalf, not aiming to represent the views of the respective Agencies.

In line with the theory and practice of qualitative research, no set sample size was defined a priori, although the research team expected to conduct between ten and fifteen interviews. Respondent selection continued until saturation and redundancy were reached.[6]

Data collection

Data was collected through means of in-depth semi-structured interviews conducted either in a face-to-face setting or via Skype® with each regulator. A letter of invitation was emailed to the selected regulators with an invitation for them to participate in the study. Once availability for the interview was communicated, the interview schedule and informed consent form were sent to the interviewee before the interview took place. The form contained information about confidentiality and interview methods. Once scheduled at a convenient time for the informant, the interviews were performed by GT, who acted as main interviewer, and PS, who acted as co-interviewer, according to a pre-defined interview guide.

The interview guide was developed by GT, RL and HGL with assistance from MDA and inputs from FT and PS and was piloted on four regulators. The interview guide reported questions on the formal factors, the informal factors and the possible causes of the differences between the FDA and the EMA regulatory decision making processes. The guide envisioned that questions should be asked in a set order, but the interviewers were allowed to divert from this order on a case to case basis if needed. Follow-up and probe questions were also adjusted to the informants' initial responses.

The names of the respondents were never mentioned during the interviews to guarantee anonymity. A code was assigned to each interview for this purpose.

All interviews were conducted in English, audio recorded and verbatim transcribed by independent transcribers. Each single audio file was audited by GT to make sure that the transcripts accurately reflected the interview contents.

Data analysis

The analysis was carried out manually on the transcribed text by two researchers, GT and MDA. First, the two coded and categorized the data independently from one another. The former relied on a deductive approach based on the themes addressed by the interview guide; the latter relied on an inductive approach, letting codes and categories emerge as the reading proceeded. Then, GT and MDA confronted the two analyses and returned to the material to resolve divergent interpretations. The interpretation of the findings emerged through this careful process of triangulation and was further discussed with the other authors, given their long standing experience as regulators.

RESULTS

Thirteen regulators of the EMA and of the FDA's Center for Drug Evaluation and Research (CDER), who had extensive experience with evaluating and making decisions about anticancer medicines (see Table 1), were interviewed between April and June 2012. Interviews lasted between 45 and 60 minutes.

Formal factors guiding the decision-making process

Based on our model for the evaluation of anticancer medicines in the EU and the US (see Figure 1), regulators were asked to describe the formal factors on which they base their own judgement on an anticancer drug application. Indeed, regulators' views were elicited on issues such as the relevance attributed to the long- and short-term safety data, the definition of a meaningful clinical benefit, and the lack of alternative treatment options. Most FDA and EMA respondents considered efficacy as a priority, with only two (one FDA and one EMA respondent) giving priority to safety.

"My concern is having products which have not proven adequate safety and efficacy. And giving inappropriate hopes to the patient population, because I could be at the receiving end some day. (...) I do enough research to know that they (the products) *would really not harm me, if they really* (do) *not give me the benefit I can live with that, but if they harm me then I am concerned about that"* (FDA respondent).

Most EMA and FDA respondents agreed that when no alternative drugs are available on the market, decisions to approve a product may be made even if clinical evidence is not complete or if toxicity is higher. FDA respondents, however, were concerned with the risk of deviating from regulatory requirements in cases when no alternative therapeutic option is available.

Table 1

EMA	FDA
– Three CHMP members – Two OWP members – One SAG-O member – One staff member with expertise in Regulatory Affairs.	Staff members of the "CDER Office of Hematology and Oncology Products" with specific expertise: – Two in Regulatory Affairs – One in Clinical Oncology – One in Clinical Pharmacology – One in Toxicology – One in Biometrics

Legend: CHMP: Committee for Medicinal Products for Human Use, OWP: Oncology Working Party, SAG-O: Scientific Advisory Group on Oncology , CDER: Center for Drug Evaluation and Research

"One thing I get concerned about, the unmet medical need situation is that I hope we do not use that pathway to promote development of drugs deviating from regulatory requirements" (FDA respondent).

Respondents from both agencies insisted on the need to ensure external validity, i.e. checking that study results are valid and applicable to the real world scenario. Respondents agreed on the importance of developing biomarkers, although they commented on how companies are not often interested in developing and validating new markers for commercial reasons.

"Well they say that we are all for recommending them (companies) *to have tumor biopsies for further analyses, investigators say patients are unwilling to undergo that. (...) They are not telling me: 'The upper management board wants us to go into confirmatory trials as fast as possible because they have other competitors with a similar compound'"* (EMA respondent).

Most respondents defined a clinical benefit in cancer as an improvement in the overall survival (OS), a substantial improvement in progression free survival (PFS), or in the quality of life.
A single EMA respondent held patients' perspective as central to the definition of clinical benefit, implying that there is a benefit only provided that this can be simply explained and understood by patients, such as a longer survival or symptom relief.

"I would say the most difficult thing is to understand what clinical benefit is. Which must be clinical benefit that could be understood by the patient, himself or herself. If I find something which is an interesting main drug I cannot explain to the patient that could convince him or her of taking the drug, I do not see the clinical benefit" (EMA respondent).

The influence of the informal factors on decision-making

In line with our model, respondents were asked about possible other factors, unrelated to the application documentation, that may influence their final opinion (see Figure 1), such as the interactions with pharmaceutical industry, with the clinical opinion leaders and with patient representatives. EMA respondents described the interactions with companies as regularly scheduled and structured during the entire review process, with the industry complaining about the limited contacts with the agency. The EMA wished to have more interactions with the companies in the early stages of clinical development.

"The industry should be accompanied as early as possible. What I think it is a big mistake(...) is that we leave them till the end (...) and we say "you know what? It is not good, there are

this, this and this". We could say this much earlier, we should accompany them and navigate together in the early phases" (EMA respondent).

FDA reported working in a *"mutual understanding environment"* with the companies and to have frequent dialogues with them especially given the short time lines for the application reviews. FDA respondents explained that their interactions with companies can be very useful, since sometimes these can bring to light aspects that had not been considered by the agency. FDA also described a mindset shift, since patients and not companies are now considered FDA most important *"customers".*

"In the past I think we thought that our customers were mainly pharmaceuticals. I think that mindset has really changed in the FDA over my twenty years of service here (...). We do believe that our customers are the American public first and second is the pharmaceuticals. So I think that has helped us to put ourselves in the shoe of a patient first, rather then a regulator first in making our decision" (FDA respondent).

FDA and EMA respondents were aligned on the value of the inputs from clinical opinion leaders. All respondents considered their influence as minimal on decision making. Respondents showed cautiousness towards them because they feared they may be influenced by pharmaceutical companies.

"They (clinical opinion leaders) *are just annoying. Having worked in the industry for a couple of years, I know how it works. What they* (clinical opinion leaders) *say is influenced a lot, but in fact since they are paid in part by the companies, it just means that they have a tendency to be biased. It doesn't mean everything they say is wrong. But you know, we often have key opinion leaders attending meetings with the companies. And sometimes I'm just embarrassed for them"* (FDA respondent).

Apart from potential conflict of interest, both EMA and FDA regulators felt that opinion leaders may have a different perspective in their own judgement of a new product: unlike regulators, they may focus more on the benefit for a single patient and may be keener to have a new therapeutic option, regardless of a robust benefit/risk balance in the overall population. Furthermore, most regulators said that opinion leaders involved in the development of a specific product may provide a biased opinion, tending to overestimate the clinical benefit and underestimate the risks of a new drug.

"You are an advisor to your company and you are married to this drug, this is your baby, you will have some bias. Into saying this is the best product you can ever think of" (FDA respondent).

Both EMA and FDA respondents appeared keen to disseminate the rationale of regulatory decisions, joining conferences and meetings with the oncology scientific community. However, during these interactions, EMA regulators felt that their agency is often the object of criticism for its decisions.

"When I go to conferences, and I talk about the affairs and approval of drugs in a broad audience of oncologists, I have the distinct impression that Europe is being more and more criticized for having the standards a little bit too low. (...) We are considered to be a little bit more lenient, more relaxed" (EMA respondent).

All the FDA respondents considered the inputs coming from patients as highly valuable although they still thought that FDA ought to make regulatory decisions based on independent scientific grounds. FDA respondents stressed that their agency has been increasing its transparency and interaction with the outside world over time, integrating the perspectives of patients, physicians, and health care system specialists at all levels. FDA respondents defined public hearings as an important instrument to guarantee transparency, especially in case of borderline applications or in case of rejected drug applications, because they give the opportunity to the agency to explain their position directly to the public. FDA respondents thought the inputs provided by the public hearings may be a factor leading to differences between EMA and FDA decision-making.

"Public hearing is actually essential for the things that we don't approve" (FDA respondent).

"Any advice we have, like that from the advisory committee, is open to the public, so people are pretty much put on the spot, when they are discussing this among their peers. I think it is a good system, that could be a major difference in the ultimate outcome of the decision making" (FDA respondent).

Most EMA respondents showed scepticism about the added value that patient advocacy groups could bring to the evaluation process and concern about their potential conflict of interest, and in general did not seem to agree about establishing public hearings in the EU.

"I have never seen that a patient organization came up with arguments or issues that we had not thought of ourselves already, or weighted these arguments in a different way. (...). In my view their contribution is really of limited value" (EMA respondent).

"If I would change a very complex dossier evaluation because of a public hearing? I am not sure" (EMA respondent).

In addition, they explained that an emotional involvement may "distract" the assessor from the data of the application and affect the objectivity of the review process, which should only be science and evidence-driven.

"Clearly, FDA is on a much more political pressure than the EMA. It's a major difference. That political or social pressure of the FDA forced them into, I would say, less wise decisions" (EMA respondent).

However, three EMA respondents thought that public hearings could be potentially useful for different reasons: they may bring a *"fresh eye"* to the process; they may introduce further transparency into the regulatory system; and they may be instrumental in explaining complicated situations to the patients, such as revoking or suspending a marketing authorisation. Even respondents who agreed in principle to the establishment of public hearings in Europe, however, were afraid that including additional steps into the decision-making process could further slow down the approval of new anticancer medicines.

"The nice thing of the public hearing would be to allow the public to voice their views and to therefore have the feeling of being closer to decision making process. This distance from the European institution is something which really does not help at all. (...) Something for the European public to have more confidence in the institution by seeing that it is open, by being able to observe how it takes its decisions, how it discusses, (...) by seeing who says what and how the committee acts" (EMA respondent).

The impact of a direct contact with patients is described by both an EU and a US respondent, who explained how this had a strong impact on their consideration and respect for patients inputs (see Box 2).

Why EMA and FDA reach different conclusions

Finally respondents were asked about the possible reasons why the final regulatory decision, representing the last step of our model (see Figure 1), can sometimes differ between the two agencies, even when they evaluate the same data. Respondents recognised the existence of an open dialogue between the FDA and EMA, with the two moving closer and exchanging information more frequently than in the past. Still, respondents unanimously reported that the two reach decisions independently, in spite of the monthly teleconferences between FDA and EMA. They revealed that the exchange is driven by the need

to check on the completeness of the documentation submitted by the pharmaceutical companies rather than by a wish to harmonize regulatory decisions across agencies.

"It is more an exchange of info but not an exchange of opinions" (EMA respondent).

"I haven't had a experience that they did something and that changed my mind. (...)" (FDA respondent).

Both FDA and EMA respondents were aware that the two Agencies may reach different decisions based on the same set of data. FDA respondents, however, were not concerned by this difference and expressed little interest in the decisions made by other agencies.

"But in terms of the judgment and the values, and so on, we are very happy to have different views. (...) We kind of agree to disagree" (EMA respondent).

"I don't usually have the time to read what their opinion was" (FDA respondent).

FDA respondents further reported that since FDA has capacity to analyse raw data of each application, other agencies rely on its analysis, but not on its decisions.

"I think, definitely the other countries look to what we have done. Simply because we have more in-depth analysis" (FDA respondent).

When discussing the independent statistical analysis of raw data submitted by companies, EMA respondents confirmed they rely on FDA for quality assurance of data analysis.

"We rely more or less on FDA for quality assurance that the data are correct" (EMA respondent).

When asked about the causes of the differences in decision-making between the EMA and the FDA, most EMA and FDA respondents attributed divergence to a different evaluation of clinical endpoints. EMA respondents tended to identify the endpoint of Progression Free Survival as a clinical benefit per se, while FDA respondents considered it as a surrogate endpoint that has to be confirmed by an Overall Survival (OS) benefit. Some EMA respondents pointed out that divergent opinions tend to occur with borderline applications, where it is difficult to reach consensus.
EMA and FDA agreed that unlike EMA regulators, FDA regulators are more open to base regulatory approval on activity data and phase II single arm trials. EMA and FDA respondents also reported that, through the use of accelerated approvals, the FDA has made

drugs available more quickly based on less mature data but at the same time has more easily withdrawn drugs from the market in the event of companies not complying with regulatory post-approval requirements. EMA and FDA respondents also agreed that the establishment of conditional approvals in the EU has increased the alignment of the two agencies.

"I think the EU uses the response rate less than what we do" (FDA respondent).

"In the US as soon as a drug established an activity, an effect, not a benefit, but an effect, which is promising and provided that the drug is not obviously dangerous, it could get marketing authorization. (...) In Europe we want to be sure that the benefit-risk ratio is positive which (...) must be based on the strong evidence of a direct benefit for the patient. Not on hopes, on facts" (EMA respondent).

"But overall I think that we approve a lot more than EU. Until recently EMA was not taking any single-arm studies at all, until they came up with this conditional approval process (introduced in the EU in 2006) *and even then I think they totally discourage having single-arm studies and they generally don't approve based on single-arm studies"* (FDA respondent).

"If you look at, for example, a conditional approval, the United States has more opportunities to withdraw a drug after conditional approval, compared with Europe" (EMA respondent).

Both EMA and FDA respondents noticed that another factor may be that the US regulatory system has traditionally been based on a close collaboration with the companies starting from the early stages of drug development. This was wished for by the EMA and only partly achieved in the EU through the increased use of scientific advice provided to the companies. The time lag between the EU and the US approvals was seen by both EMA and FDA as an additional factor, since more data may become available in the meantime and consequently have an impact on the decisions of the agency that comes second in the assessment of the new product. Only according to one FDA and one EMA respondent different regulatory guidelines and requirements may play a role. EMA respondents thought that regulatory divergence may also have cultural roots. They said that unlike the EU, the US has a prevailing attitude to take risks in order to guarantee quick access to new anticancer treatments and at the same time withdraw products from the market more easily than the EU.

"In Europe we build trust from zero to one hundred, in America we remove trust from one hundred to zero. (...) In Europe we want to be sure because we do not want to take the risks,

maybe we are more into "let's avoid risks" in Europe and in the United States they are more "let's take the benefits even if uncertain" (EMA respondent).

FDA respondents thought their agency tends to approve broader therapeutic indications than the EMA, while EMA respondents thought to be more restrictive, limiting the indication to very specific patient populations. Several FDA respondents thought that the assessment at the EMA level also takes costs into consideration with an impact on the different decisions between the two agencies.

"My impression is, at least from the EU point of view, costs are probably more of a factor, so that may impact in some of their decisions" (FDA respondent).

Most EMA respondents denied the impact of costs on the decision-making process, although they were concerned about the different access to new therapies across EU countries, depending on national resources and reimbursement systems. It also emerged that in the EU the more frequent use of therapeutic indications tailored on very specific patient populations may be related to country-specific reimbursement policies with only the selected patient population reported in the label being covered by the national health system.

FDA respondents also explained they feel distant from the EMA in terms of organization, since in the US both assessment teams and advisory committees are extremely specialized in specific therapeutic areas. The EU system based on rapporteurs, who vote for the approval of a drug in an area for which they do not necessarily hold an expertise, was seen by US colleagues as *"funny to watch"*.

"Here we have different advisory committees for each disease (...) So we're getting more specialized advise, versus there (at the EMA) *it is sort of everybody (...).* (At the EMA) *it's a whole different, another way, a preliminary word and then a final word and all of this kind of..., so it's funny for us to watch all that"* (FDA respondent).

The bureaucracy involved in the EU process and the different levels of participation to the decision-making process among the member states were reported as concerns for a system that, according to most EMA respondents, should be more open to change and innovation.

"You know, we have in Europe, 27 agencies, a system that is very bureaucratic. Very expensive, people do the same things, but don't go into the details. (...) I would personally prefer having a European FDA and not all these national agencies (...) Assessment reports are much too

lengthy (...) and one of the main problems with too lengthy reports is that they are not read, and if they are not read, it is a quality problem" (EMA respondent).

FDA regulators tended to appreciate their own agency for its transparency, for providing an international and stimulating environment, and for giving voice to all people involved in the evaluation of drug applications.

"We work as a multidisciplinary team. And we have something that is called "Equal Voice", so no matter where it's coming from, each person is free to provide their opinion and that opinion should be considered" (FDA respondent).

DISCUSSION

The analysis of the criteria guiding decision-making for the approval (or refusal) of medicines is of great importance from a public health perspective. Although the level of transparency has constantly been increasing, the regulatory "thought" process still remains a black box to many. There is still no agreed method to document how evidence, uncertainties and judgments result in a specific regulatory decision.[7]

This study represents the first systematic attempt to look into actual decision making at both EMA and FDA through a comparative qualitative study reporting directly the point of view of the regulators. The policy relevance of the findings has to be assessed in relation to the limited sample size, typical of qualitative studies seeking depth rather than breadth in coverage. This limited size, however, does by no means threaten the validity of the study.

Previous work has highlighted discrepancies between two agencies in terms of regulatory outcomes and speed to review drug applications [5,8-10] The study was based on information collected from the European Public Assessment Reports and detected a generalized belief among EMA and FDA regulators alike that different decisions are unavoidable and not necessarily negative. The ongoing harmonization process (e.g. parallel scientific advice) has increased cooperation and exchange of information between the two agencies,[11-13] still it has not fostered the exchange of opinions, leaving the two agencies feeling very distant from one another, mostly due to different core organisational structures.

The FDA is based on ad-hoc discipline specific working groups who base their judgments on re-analyses of the raw data provided by the company. The decision is then reached through a complex and inclusive process which involves all stakeholders. On the other hand regulatory decisions at the EU level are taken by the CHMP, whose members vote on the approval or refusal of a product, regardless of their expertise in a specific therapeutic

area or their actual contribution to the review process. This study showed that the contribution to the CHMP assessment is not equally distributed among the different EU member states. In line with our findings, recent research and strategy papers have highlighted the large variation among EU member states regarding their individual contributions to the EU regulatory system and have stressed the importance of a re-balance between member states in work-sharing and showing leadership in Centralised Procedures.[14-16]

Different interaction modalities with both industry and patients represent an additional source of divergence between the two agencies with a potential impact on decision-making. The FDA is characterised by both a closer collaboration with the industry from the early stages of drug development and by the establishment of public hearings within the FDA advisory committees, where patient representatives, who can be voting members, offer their experiences in an effort to provide a realistic look at a new product. A recent study has shown that FDA's approval decisions are broadly consistent with the recommendations of its advisory committees both for the approval and the non-approval of new applications.[17] In contrast EMA regulators do not seem to support patients' involvement in the decision-making process and generally dislike the idea of establishing public hearings in the EU. However, public hearings have recently been authorised (but not yet implemented) in the new EU pharmacovigilance legislation, applicable as of July 2012.[18] Interestingly in a time when a deeper patients involvement in decision-making seems to be "formally" advocated, there is no consensus among EMA regulators about what benefit patients may actually bring to the process. Is it going to change the perception of benefit and risk among regulators? Or rather, is it going to be a political instrument to show transparency towards the public and reduce distance between patients and institutions?

The key message of our respondents was that the EMA and the FDA manage uncertainty in a different way. According to the study respondents, the FDA is more open to take risks and base approval on less robust data in order to guarantee quicker access to anticancer medicines, although it allows product withdrawals from the market more easily than the EMA. It is noteworthy that the picture that emerged from the conclusions of a recent EMA project on benefit-risk methodology was that EU assessors are perceived as being risk averse.[1]

On the other hand, the FDA has adopted a new initiative for speeding up the approval of seemingly promising new drugs, officially known as the "Expedited Drug Development Pathway".[19] Although enabling new drugs with a favourable benefit-harm balance to become available to patients more rapidly is a laudable goal, the underlying question is what public health risks are taken when drugs are approved for widespread use while important safety questions remain unanswered.[20]

Another difference related to the organisational structures of the agencies emerging from this study is that EMA regulators are more exposed to the cost considerations for anticancer drugs. During the definition of therapeutic indication the issue of reimbursement (which is not an EMA task) seems to be taken into account by some EMA regulators, although not explicitly.

Respondents provided various explanations for regulatory divergent opinions but the different interpretation of the endpoints such as the PFS as a measure of the clinical benefit prevailed. Is a new treatment that improves PFS really an advance for patients? Or does it necessarily need to be confirmed by OS benefit? EMA regulators have moved away from the concept that PFS might be used for approval with expectation that relevant benefits in terms of OS would later materialise. Based on these opposite views on PFS between the two agencies, in December 2010 the FDA's assessment of bevacizumab contrasted with that of EMA regulators, who reaffirmed their approval of the drug for metastatic breast cancer the same day.[21] As a consequence such indication has been removed from bevacizumab label in the US and not in the EU.[22] It may be time for the oncology community and regulatory agencies to take a hard look at PFS and reflect on whether this can be used as a primary efficacy endpoint.

The harmonization process has certainly reduced the distance between the two agencies, favouring frequent communication and joint projects.[11-13] However, in a globalised world, the two still work and think as two separate entities, with an unavoidable impact on prescribers and patients access between the two sides of the Atlantic. It remains an open question whether further attempts to minimize regulatory divergence will or even should be made considering the number of contributory factors. [23] Future research in regulatory science should expand its scope focussing not only on differences in decision-making among different regulatory agencies, but also on investigating their actual impacts on the patients' health status. Only understanding which differences really count for patients will allow the development of harmonization polices that safeguard their interests. In conclusion, this study has confirmed that although formal factors are the main drivers for regulatory decisions, the influence of informal factors plays an important role in the drug evaluation process.

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BOX 1

Key features of the EU and US regulatory systems

At EMA, the final decision on the approval of oncology medicinal products is taken by the CHMP members supported by the EMA staff of the "Oncology, Haematology and Diagnostics Unit", the members of the Oncology Working Party (OWP) and the Scientific Advisory Group on Oncology (SAG-O). The CHMP, whose voting members are appointed by each EU Member State (two per Member State), makes decisions on the approval of anticancer drugs through the so-called "centralised procedure". If a drug is approved through such procedure, it is authorised for marketing authorisation across the EU member states. However, EMA does not make decisions on price and reimbursement. These decisions are made at a later stage at the national level.

At FDA, the regulators involved in the assessment of anticancer drugs are part of the agency's staff under the "CDER Office of Haematology and Oncology Products", and belong to discipline-specific groups. In cases where external input is needed, the FDA convenes an advisory committee meeting, which include patient representatives and an open public hearing session, during which interested persons may present relevant information or views orally or in writing.[24]

BOX 2

Two stories of interaction with patients

Two respondents, one from EMA and the other from FDA, described an experience of interaction with patients that changed their perspective in the assessment.

The EMA respondent recalled a very emotional experience of interaction with patients during the assessment of thalidomide for multiple myeloma, having to face the expectations of the multiple myeloma patients as well as the concerns of the "victims" of the drug, which had an impact on subsequent regulatory actions and decisions.

"The first opportunity I had to discuss with patients was a very tough one but very interesting, I will never forget. It was with thalidomide. (...)And I remember very well I had to face multiple myeloma patients and the victims of thalidomide. (...) And the patients were very positive because for them thalidomide was a very important drug in the treatment of multiple myeloma which is true. And for the victims it was impossible to accept any marketing authorization for such a product. And we had to discuss with them and I must say the ideas we had on the risk management program were modified significantly

by this interaction with the patients and with the victims. And the magic thing which was that at the end of the process we had a common letter coming from the victims and from the patients which was supposed to be sent to the doctors with the risk management program, saying: "This is the Risk Management Program we accepted in Europe, both victims and patients. And please observe this Risk Management Program: nothing more because it could limit the accessibility of the patients to the drug, nothing less because it could be dangerous and create new victims. So believe me I would never forget that, so since I listen very carefully to the patients".

The FDA respondent described how the inclusion of a former patient and cancer survivor in the FDA's work activities decided by the agency's management, eradicated any prejudices against patients contributions and reinforced the belief that patients' inputs are important and valuable for the assessment process.

"Well in my personal life the changes started to come in when a patient advocacy person was brought in as an employee of the FDA, she was a cancer survivor. And she participated in all of our meetings to give a patients perspective. And I learned a lot from her, she passed away subsequently to the disease ultimately, but I learned from her compassion and what it really means to a patient. And she was not any less tough on the regulatory issues as I would have thought about. So she balanced the toughness of following the regulatory pathway to develop the drug appropriately at the same time give a patients perspective and help us understand how we can look at it from other angles as well, beside being a regulator. (...)

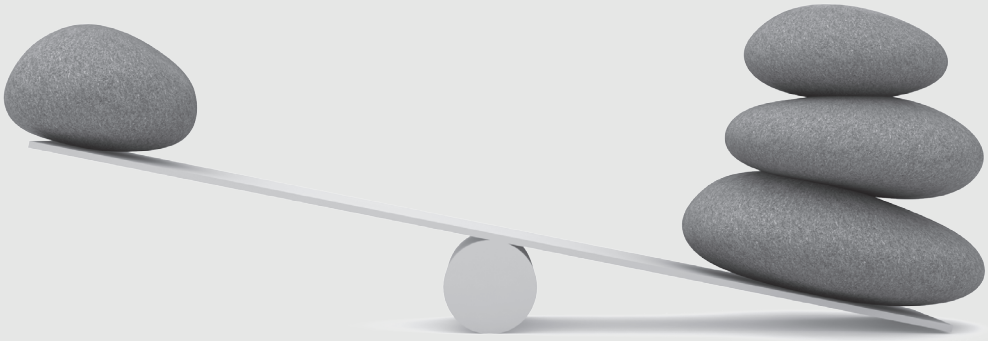
I remember in one of the meetings, after we finished the meeting with a company, in our internal discussion she was the strongest advocate for not allowing the pathway that the company was proposing us to go or to agree on. And I thought that was kind of like totally the opposite of what I would have expected from her, but at the same time she also described that disease and the population and what is the expectation of the population. Because she was an educator in her life, but she had the cancer and then she survived, she went through the treatment and she survived and then she decided to join the FDA. So she was not a pure scientist, so I was really surprised that how much she understood the regulatory needs at the same time balanced that with the patients perspective because she was saying that the patients will be getting a toxic agent and they won't get any benefit, it won't prolong her life at this time with the data that we know, rather that it would kill them faster... they need to be in that situation. So talking to her to understand and understanding the perspective that she was bringing in really

helped me personally to put in the patients perspective a lot more than the scientist and the regulatory perspective.

We do believe that our customers are the American public first and second is the pharmaceuticals. So I think that has helped us to put ourselves in the shoe of a patient first, rather then a regulator first in making our decision".

CHAPTER 4

General discussion



This concluding chapter critically discusses key findings of each study, placing them in a broader perspective and considers the current scenario of medicines development and regulation. Finally, key lessons learned and areas for future research in regulatory science are identified.

The challenges of the current regulatory scenario

Drug regulatory authorities, particularly in North America and Europe, have made essential and unique contributions to public health. It is likely that tragedies such as the sulphanilamide or thalidomide disasters have been confined to history.[1] However, questions and concerns are still raised by various stakeholders: how well does the current regulatory system serve the European public and how close is it to the actual patients' needs and clinical practice? And what information is really needed from a medicines development and regulatory perspective so that patients, prescribers and payers can make the best informed decisions?

The overall context in which regulators, industry and patients are moving must be considered. While the number of new therapies authorised has declined, the cost of bringing them to the market has soared.[2] Various analysts attribute this to the "ever-increasing burden of regulation". They suggest that drug regulation could hinder public health by setting unnecessary hurdles for drugs entering the market through ineffective and costly regulatory requirements.[3] The "cautious regulator" problem, based on a progressive lowering of risk tolerance of regulatory agencies, has been named as one of the main causes of increasing R&D costs and declining R&D efficiency.[4]

In addition, the high proportion of non-approved marketing authorisation applications for new medicinal products in the EU is of serious concern and has raised questions about the efficiency of drug development and the regulatory system.[5] The high costs of these "failures" must be paid for and are eventually borne by those paying for the fewer products that do make it to the market.[2]

Another important aspect of the current regulatory system is the evolution of the role of patients. Patient organisations have become increasingly visible and vocal actors in medicines policy in recent years. A gradual shift from "paternalism" to "consumerism" in the health care sectors of many societies has resulted in wide-spread recognition that patients should no longer be regarded simply as "passive recipients" of healthcare, but need to be actively engaged in making decisions about their treatment. Medicines policy-making institutions have therefore sought to increase the legitimacy of their activities by seeking heightened levels of input from representative groups of patients.[6] For example, the EMA has a Working Party with Patients' and Consumers' Organisations, whose members monitor patient participation in the varied activities within the Agency, such as the

review of information for the general public and participation in scientific advisory group meetings.[7]

Under this scenario the regulatory decision-making process has become very difficult. Regulators are not only expected to "protect" public health by keeping "bad" medicines off the market, but also to "promote" public health by facilitating "good" medicines getting to those who need them as quickly as possible. Regulators are obliged to take timely decisions on the availability of drugs for patients, even under conditions of uncertainty.

Novel forms of clinical trials, such as the use of adaptive designs, are increasingly encouraged by regulators with the aim to align drug approval more closely with patient needs for timely access to new technologies. Over the past five years, a wave of proposals for prospectively planned adaptive approaches to drug licensing has emerged under various labels, including "staggered approval", "managed entry", "adaptive approval", and "progressive authorisation". All are based on the premise that knowledge of drugs is not binary but continues to evolve over time. The dichotomy of pre- versus post-licensing stages is replaced with progressive management and reduction of uncertainty. Indeed adaptive licensing is designed to manage the entire life span of a drug, during which data continue to be generated on the product through various modalities, including active surveillance and additional studies after initial licensing. There are considerable challenges and benefits to implement adaptive licensing as the common pathway for drug approval. Pilot projects will try to generate the data to determine whether adaptive licensing offers a more favourable alternative to the current licensing paradigm that maximises the benefits of drug development and science-based regulation for patients and public health.[8]

The public and the scientific communities also require the regulatory decision-making process to be transparent. Requests directed to drug regulatory authorities such as the EMA and the FDA for full disclosure of information on internal discussions, minutes and assessment reports related to regulatory decision-making are becoming increasingly pertinent. In particular both public, clinical and scientific communities seem to be interested in i) agenda and minutes of scientific committees' meetings held, ii) discussions held with the pharmaceutical industry, iii) internal reports on safety and/or efficacy issues of approved and yet to be approved drugs.[9-11] It has also been argued that the full clinical trial reports of authorised drugs should be made publicly available to enable independent re-analyses of drugs' benefits and risks.[12]

However, although the level of transparency has constantly been increasing through public advisory committees and online availability of regulatory documents, the regulatory "thought" process still remains a black box to many. There is still no consensus on how to document how evidence, uncertainties and judgments result in a specific regulatory decision.[2] In certain circumstances this can generate criticisms towards regulators. In general as long as "bad" outcomes do not occur, most in the larger community are less interested in regulatory decisions. However, when "bad" outcomes do occur, regulators come under

attack. It may also occasionally happen that different regulatory agencies make different decisions when assessing the same data. When this occurs populations and parliaments are understandably confused, the credibility of regulators may be questioned and their strategies for risk assessment, communication and management can become suspect to the public. The immediate consequence is that the distance between the people and the regulatory agencies widens and the credibility of regulators declines.
To bridge the gap between public health policy and public expectation, the regulator has a responsibility to accessibly communicate to the public the risks of medicines, as well as the concept of a benefit/risk balance. Experience indicates that the public may have problems understanding this balance and may have the unrealistic expectation that marketed medicines should demonstrate absolute safety. The histories of rofecoxib and rosiglitazone also illustrate the importance of transparent and comprehensible regulatory communication as new risks emerge.[13]

The research questions addressed in this thesis stemmed from this general context. It is well known that when regulators determine the benefit/risk profile of a new application, the system requires a yes or a no dichotomy. We have tried to describe the dynamics involved over the course of an application review and the factors guiding regulators in their decision-making process before the final outcome is presented to the world.

Regulation and transparency (Chapter 2)

As previously reported, various stakeholders have raised concerns about the level of evidence required for regulatory decision-making and the need to avoid unnecessary studies whenever this is possible.[1,3] A systematic consideration of the available evidence for safety and efficacy represents a valuable approach to avoid unnecessary studies in the target population for ethical reasons, for efficiency and to allocate resources to areas where studies are the most needed. This approach is particularly relevant to deal with the off-label use of medicines in the paediatric population.
The need for more studies to obtain paediatric information for medicines used in children is a matter of consensus on a global basis.[14,15] A recent 2010 EU survey explored unlicensed and off-label use of medicines in children based on data from 20 EU and 2 non-EU countries covering 50% of the total population in Europe.[16] Overall the analysis revealed that 45-60% of all medicines in children were used outside their marketing authorisation. In particular one of the most frequently used off-label medicines belong to the class of proton pump inhibitors (PPIs). This raises new questions. Which line of action should be followed to better protect paediatric patients? And are clinical trials always necessary to extend therapeutic indications?
In **Chapter 2.1** we used the case of PPIs for the treatment of gastroesophageal reflux in children to verify whether drugs not formally approved for use in a specific population

may nonetheless have sufficient evidence supporting their off-label use. We found several trials testing PPIs in children although these medicines do not have a formal paediatric indication. Interestingly, EU and US regulators made different decisions with regard to the inclusion of children or specific age-ranges in the labels of PPIs.
Performing additional clinical studies in children may not always be necessary, and translating clinical evidence into regulatory decision-making can be a useful strategy to minimise regulatory hurdles, avoid unethical replication of trials and fill the gap between regulatory authorities and specific patient groups, thereby ensuring an equal and quicker access to medicines.
This model could also help regulatory decision-making. In fact in some cases regulators could simply identify research priorities for a specific compound (e.g. a further pharmacokinetics study) and require specific mandatory studies only for those efficacy and safety issues that remain uncertain. Furthermore, similar analyses could be helpful for the decision-making of prescribers. This would at least allow a more evidence-based approach to off-label prescribing.
The evaluation we carried out on the appropriateness of off-label use of PPIs in children could be easily extended to other classes of drugs or other special populations, considering that requiring separate trials for each patient sub-group – in paediatrics as well as in other populations – may not be always feasible. For instance, in the case of the elderly, the combination of different age strata, co-morbidities, and concomitant use of different drugs may create an enormous number of potential different groups.

After addressing the issue of what level of evidence may be considered necessary for regulatory decisions, we investigated the cases where evidence is considered insufficient by regulatory agencies **(Chapter 2.3)**. Our analyses of the grounds of failed drug applications revealed that (lack of) efficacy is the main predictor for success or failure of an application. Withdrawn or refused applications provide an important look at what may go wrong in bringing a product from bench to the clinic, and what could be improved in future applications.
A clear propensity of a positive opinion of the Committee for Medicinal Products for Human Use (CHMP) seems to be a good and robust clinical trial program, with a good rationale, and a targeted and efficient trial performance. In fact, this analysis showed that statistical significance alone is not sufficient for an approval for a marketing authorization, but most importantly clinical relevance must be demonstrated. Interestingly, in none of the withdrawal cases was non-clinical data the main driver. This finding also fuels further reflection on how to bridge and integrate better non-clinical and clinical data. Non-clinical data with little to no link to what this means for clinical practice, seems to be rather useless. On the other hand, non-clinical, mechanistic insight is indispensable for a

better understanding of variance in drug response, also in the post-approval period of a drug's lifecycle.

Information on withdrawals and refusals can be considered an important transparency indicator in the interest of public health and innovation. Indeed a negative opinion on a drug application may generate huge disappointment in the deprived patients who may feel the need to understand why they cannot access a therapeutic option.

Analysing the factors influencing non-approval is also important to identify which deficits in drug development plans are associated with failure to be approved. A recent analysis based on 68 applications evaluated by the EMA showed that the clinical development plan is extremely important to increase the likelihood that a medicinal product is approved.[17] In particular, deficits in the learning phase studies (early stage trials focussing on mode of action, proof of concept, pharmacokinetics, dose findings and safety pharmacology) were more strongly associated with non-approval than deficits in any of the confirmatory studies.

This suggests the importance for companies to invest in adequate early phase I and II studies to reduce the number of failed dossiers and speed up pharmaceutical innovation. On the other hand, regulators will have to increase the predictability of their decision-making process, through more formal and structured approaches to benefit/risk assessment.[5,18]

Regulatory dynamics in oncology (Chapter 3)

The difficult task of regulatory decision-making consists in reconciling the tension between strict evidence-based standards and being responsive to rapid innovation of emerging technologies.

Analysis of past regulatory decisions supports the notion that the level of acceptable uncertainty is not constant across all therapeutic indications. Regulators are generally willing to accept a higher level of uncertainty around the benefit/risk assessment for life-threatening or otherwise severe conditions for which there is a high unmet medical need such as cancer, as opposed to less severe conditions.[19] Regulating the emerging changes in cancer management, such as targeted therapies, requires flexible, iterative, product-focused, science-based approaches. Nowadays, a more holistic approach is being taken where new molecular biomarkers and bioinformatic patient data are integrated to improve the accuracy of predicting prognosis and treatment efficacy. Huge advances have already been made, which can be exemplified by recent progress in the management of metastatic colorectal cancer, particularly the discovery and implementation of KRAS as a predictive biomarker.[20] With the advent of these newer technologies and therapeutic approaches regulators are expected to facilitate the process of translating scientific discoveries into therapies. Therefore the evaluation of anticancer medicines poses additional challenges to regulators.

In oncology a very controversial issue for regulatory decision-making is the interpretation of results based on early stopped randomised clinical trials (RCTs) following interim analyses. In general the prevalence of RCTs stopped early for benefit is increasing [21], and in particular our analysis highlighted a consistent increase in the field of oncology (**Chapter 3.1**).

Multiple reasons exist to consider the premature termination of a clinical trial: excessive toxicity, changes in standard of care, poor accrual and stopping for "futility" because the trial is highly unlikely to ever attain a statistically significant result.[22] The reason for early stopping within an ongoing trial that generates the greatest controversy, however, is terminating a trial early due to the apparent efficacy of the experimental arm versus the control.

Interim analyses pose the ethical dilemma of safeguarding the interests of patients enrolled in clinical trials while also protecting society from overzealous premature claims of treatment benefit. Trials stopped early because of harm (toxicity) or futility tend to result in prompt discontinuation of useless or potentially harmful interventions. In contrast, trials stopped early for benefit may result in the quick identification, approval, and dissemination of promising new treatments. However, the premature termination of a clinical trial can have highly problematic consequences. Conclusions based on immature data may change with further follow-up or provide inadequate evidence to convince the broader scientific community. In addition data from the initial patients enrolled in a trial may not be representative of data that would be obtained from the remainder of the trial, as the early patients may not be representative of the general population. Release of early data may also prohibit the collection of meaningful data on long-term benefits or adverse events from therapy if the data release results in a change in care for patients currently on the clinical trial, for example, with cross-over treatment.[23]

Finally there are some statistical considerations that should be taken into account. Results of trials stopped early from benefit should be interpreted with caution because statistical stopping rules used by investigators to justify termination of the study are prone to exaggerate the estimated treatment effect. Bias arises because random fluctuations towards greater treatment effects may result in early termination.[24] If the decision to stop the trial did result from observing the apparent benefit of treatment at a "random high", the resulting estimate of the treatment effect will be misleading.[25] The other problem has to do with multiple testing: repeated analyses on the same data pool often lead to statistically significant results only by chance.[26,27] The potential overestimation of the magnitude of the treatment effect is of particular concern in oncology, in which the more subjective endpoint of progression-free survival has increasingly been adopted as the primary endpoint in pivotal phase III trials.[28]

There are several examples of trials in the literature whereby a statistically significant improvement in the primary endpoint early on in a study, subsequently disappeared at the

final analysis.[29,30] On the other hand there are also situations where an interim analysis shows no statistically significant benefit in the primary outcome. These studies tend to be terminated early and in many cases, no further information on long-term outcomes is available following study closure.[31,32]
In contrast, some recent literature suggests that some trials are appropriately stopped early and that this strategy may be reasonable in situations where the trial is well planned and a sufficient number of events have occurred.[33]
Interim monitoring of clinical trials performed by independent monitoring committees and guided by appropriate statistical stopping rules can certainly reduce the risks of drawing the wrong conclusions. However, there are still unresolved issues that raise questions with regard to the correct interpretation of interim results which put regulators in a difficult situation with implications for patients' health. The STOPIT-2, an international methodological study funded by the British Medical Research Council, promises in the future to provide some answers to remaining questions.[34]

The uncertainty surrounding the benefit/risk profile of new drugs at the time of marketing entry has led to a gradual evolution of the regulatory model from a one-off marketing authorisation to a product life cycle approach.[19] Indeed when faced with uncertainty regulators tend to request additional data and post-approval commitments. Therefore the development of medicines is a continuous and dynamic process in which new knowledge has consequences for the conditions of marketing authorisation. Extensions of indications as well as new safety information lead to a continuous evaluation of the benefit/risk profile. **Chapter 3.3** investigates the extensions of oncology indications approved by the EMA, analysing the time needed for anticancer drugs to get an extension, the rates and characteristics of extensions approved, and the regulatory process leading to the definition of new indications. This analysis confirms that, while the rate of newly approved drugs is constant over the years, there is an increase in the rate of extensions of indication per year. This is also in line with the current awareness of the lack of original pharmaceutical products which leads drug companies to make the most out of already existing drugs.[35] Furthermore the fact that the median time occurring between different indications for the same compound has shown a continuous decline reflects a shorter clinical development process and reduced delays in regulatory decision-making. However, contrary to common belief, most anticancer drugs (about 56%) present only a single therapeutic indication.
With regard to the broadening of indication, the practice of the switch of line is quite common and reflects companies' efforts to reach an earlier treatment line in an unidirectional way. This seems also to be the result of a "precautionary" regulatory approach, which often tends to restrict the indications proposed by the industry and then, as evidence is provided, relax these initial restrictions. Indeed, since premarketing data are often incomplete, regulators tend to grant therapeutic indications that specifically reflect the

characteristics of patients enrolled onto clinical trials. Such precautionary approvals are potentially distant from the actual clinical needs, empowering third parties (eg, scientific societies, reimbursement authorities) to define the real place in therapy of a new medicine. An effective decision on indications can only stem from an adequate balance between evidence-based decision making and consideration of the real needs of practice.
Our findings also show a relationship between a faster clinical development and the chance of receiving an indication restriction from regulators. The fact that restrictions of indication
occurred because of an incomplete clinical data package can then be easily assumed. It seems that in case of immature efficacy and safety data, regulators often tend to shift towards the terminal treatment lines in order to restrict the drug use only to patients with no alternatives. The consequence is a subsequent request by companies for getting earlier treatment lines approved, resulting in a continuum in terms of extensions of indication for a single compound.
While companies can benefit from the extensions given the enlarged market and patent protection, extending therapeutic indications is also very positive from a public health perspective to better define drug benefit/risk profiles, to monitor safety issues and to reduce the off-label use.
However, in certain cases post approval studies prioritise more on studies searching for new indications than on deepening comparative knowledge about optimal use of approved indications, thus leaving important demands of clinical practice unanswered.
Etanercept, a tumour necrosis factor whose first approved indication was the treatment of rheumatoid arthritis, is a pivotal learning case illustrating the dynamics of post approval knowledge gain. Although the scientific community urged to have comparative efficacy and safety data on this compound, at ten years after its market entry nearly two-thirds of the post approval trials with etanercept focused on new applications based on the request for an extension of the indication.[36] The analysis of how etanercept evolved over time is a clear example of the needed development of continuous evaluation of new and existing medicines in terms of new applications, safety profile, improving optimal use, building comparative evidence and ensuring benefit/risk throughout the whole life cycle of medicinal products. For this purpose, public research should make more effort in conducting effectiveness studies, also supported by ad hoc official legislation.
In general, the definition of a therapeutic indication is a critical step in regulating medicinal products. The wording of indications can have a huge impact on clinical practice by including or excluding certain patient populations. In **chapter 3.4** our research has shown that major agencies like the EMA and the FDA, based on the review of the same applications, can differ when taking decisions on the wording of indications, e.g. when one agency tends to be more restrictive in the definition of an indication, limiting drug use only to a specific patient population. In 10% of the oncology indications analysed,

these differences had significant clinical meaning for treating patients in need of anti-cancer drugs. In fact a different regulatory decision on the same indication can result in a different place in therapy for the same drug and/or may exclude a patient subgroup from a treatment. The fact that the decisions in those examples were made by the EMA and FDA based on the same pivotal trials makes these findings even more relevant. However, neither of the agencies seem to have a prevailing restrictive behaviour compared with the other agency. Despite differences in the US and European licensing systems, these do not result in a more or less frequent use of restrictions by one of the agencies.

A critical finding of this analysis lies in those indications approved only by one of the two agencies. This means that large patient populations may be deprived of treatments that are available in other countries or that patients who live in the countries where the drug is available could be exposed to drugs whose benefit/risk profile was not considered positive elsewhere. Differences in access to treatments in such a globalised world may have several consequences. First, in the countries where the indication is not approved, a growing pressure on regulatory bodies, both from patients and health care professionals, can be expected. This may potentially influence the regulatory review process, possibly leading to a biased evaluation. Second, the off label use of medicines is fuelled in the country where the indication is not approved. However, if such an indication is approved in another country based on robust data, it can be considered as an off-label use only from a regulatory perspective.

An interesting case of regulatory divergence which reflects the different approval systems among regulatory agencies is the case of gemtuzumab ozagomycin (GO), a humanized monoclonal antibody conjugated to a cytotoxic agent, to be used for the treatment of acute myeloid leukemia (AML). GO was first approved by FDA in 2000, under the accelerated approval program, on the basis of surrogate marker endpoints but then following serious safety issues, at the request of FDA, the drug was withdrawn by the manufacturer from the US market in 2010. In the EU, a marketing application for GO was made to EMA in 2005; considerable debate ensued as to its benefit/risk balance and in 2008 marketing authorization was refused on the grounds that there were no randomised clinical trials. Interestingly, GO was approved as an orphan drug in Japan in 2005, and the Japanese regulatory authority decided to continue with the approval in 2010 on the condition that post-marketing surveillance be strengthened. In 2011 new results of RCTs appeared and the role of GO in AML was refocused worldwide.[37]

Another case from which we can learn is represented by crizotinib, conditionally approved by the FDA in August 2011 for anaplastic lymphoma kinase mutated patients with non small cell lung carcinoma, based on a single phase 2 non-randomized trial showing compelling efficacy benefit. While the US patients were benefiting from this treatment, the EMA demanded that the sponsor complete a randomized phase III trial for the EU

registration and marketing approval, which delayed getting this treatment to patients by over 14 months (EU marketing authorization was obtained in October 2012).[7,38]

The ongoing harmonization process has increased cooperation and exchange of information among agencies.[39-41] However, each regulatory agency has its own rules and requirements for the approval of new drugs, which have an impact on the regulatory review time and consequently on time needed for market entry. A recent analysis based on novel therapeutic agents approved between 2001 and 2010 showed that the FDA reviewed applications more quickly, on average, than the EMA or Health Canada did, and the vast majority of these new therapeutic agents were first approved for use in the United States.[42] This finding is in line with our analysis which shows that the FDA is still first in approving new oncologic indications over the last few decades, although there is a trend for more convergence between EMA and FDA.

Overall, the importance of these differences is not which agency is correct and which is wrong in its decisions but rather why the differences exist.

Because no clear predictors of regulatory outcomes were identified by our research, we hypothesised the involvement of other driving forces causing such heterogeneity in the approval between the EMA and FDA. This led us to investigate the decision-making processes for anticancer drugs at the two agencies through a comparative qualitative study using semi-structured in-depth interviews (**chapter 3.5**).

The analysis of the criteria guiding decision-making for the approval (or refusal) of medicines is of great importance from a public health perspective. This is confirmed by the fact that FDA is currently working on the definition of a structured framework for the regulatory decision-making process.[43] Similarly in 2006 the EMA set up a working group to provide recommendations on ways to improve the methodology, transparency and consistency of decision-making, which included an analysis of the different risk perception among regulators in the EU.[18]

Our research was based on the assumption that the process leading to a regulatory outcome is guided by factors both related and unrelated to the application data package, defined as "formal" and "informal" factors, respectively. In fact we assumed that over the course of an application review, a regulator's assessment of the data package is likely to be mediated by informal factors such as the interaction with external stakeholders (e.g. pharmaceutical companies, patients or other regulatory agencies) and influenced by socio-cultural and behavioural aspects. Our findings showed that the ongoing harmonization has fostered the exchange of information but still not the exchange of opinions, leaving the two agencies to feel very distant from one another, mostly due to different core organisational structures. The FDA is based on ad-hoc discipline specific working groups who base their judgments on re-analyses of the raw data provided by the company. The decision is then reached through a complex and inclusive process which involves all stakeholders. Unlike the EMA, the FDA decision-making process is, in fact, characterised

by a close collaboration with the industry from the early stages of drug development and by the establishment of public hearings where patient representatives, who can be voting members, offer their experience. On the other hand regulatory decisions at the EU level are taken by the CHMP, whose nationally representative members vote on the approval or refusal of a product, regardless of their expertise in a specific therapeutic area or their actual contribution to the review process. Of note, the EMA regulators did not seem to support patient's involvement in the decision-making process and generally disliked the idea of establishing public hearings in the EU (although public hearings have recently been authorised - but not yet implemented - in the new EU pharmacovigilance legislation).[44] This leads to a reflection on what exactly a patient brings to the table in decision-making processes and how it can be defined and secured. A deeper understanding of the nature and value of patient involvement is still needed. In the literature, examples are given of how meaningful involvement of patients and citizens is complicated by the inequality of power in the decision-making process between the expert community of scientists on the one hand and the patient representatives on the other.[45] Therefore participation can only be successful if patient's organisations are at a proper level of empowerment.

The key message of our respondents was that the EMA and the FDA manage uncertainty in a different way. According to the study respondents, the FDA is more open to take risks and base approval on less robust data in order to guarantee quicker access to cancer medicines, although it allows product withdrawals from the market more easily than the EMA. It is noteworthy that the picture that emerged from the conclusions of a recent EMA project on benefit/risk methodology was that EU assessors are perceived as being risk averse.[46]

Another difference related to the organisational structures of the agencies emerging from this study is that EMA regulators are more exposed to cost considerations for anticancer drugs. During the definition of therapeutic indication the issue of reimbursement seems to be taken into account by some EMA regulators, although not explicitly. They also expressed concern that decisions made are not necessarily applicable to all member states at the same time, due to different resources and heterogeneous pricing/reimbursement policies at the national level, which may create unequal access to new therapies across EU countries. This leads to important considerations on the growing importance of Health Technology Assessment (HTA) in Europe, due to a large extent to increased pressure on healthcare budgets. Harmonising requirements for HTA across Europe has become a political priority at the EU level, in which the European Commission is investing substantial resources.[47]

As part of the objectives set out in its Road Map to 2015, the EMA continues to increase its engagement with HTA bodies. For instance, the agency is now engaging with HTA bodies through its provision of scientific advice early in medicine development and throughout

the medicinal product's lifecycle. The aim is to harmonise advice given to companies on the development of a medicine by regulators and HTA bodies wherever possible.
In our interview study, a different interpretation of Progression Free Survival (PFS), viewed as a clinical benefit per se by the EMA but not by the FDA, was considered the prevailing reason for regulatory divergence. Of note, the scientific community has still not found consensus on this issue and it is divided in those who believe that a new treatment that improves PFS is really an advance for patients and those who think that a PFS improvement, in the absence of an OS (Overall Survival) improvement, only lowers the bar to declare active some of the new molecular targeted therapies.[48] Based on these opposite views on PFS between EMA and FDA, in December 2010, the FDA's assessment of bevacizumab contrasted with that of EMA regulators, who reaffirmed their approval of the drug for metastatic breast cancer the same day. Although the EMA concluded that the balance of benefits and risks of bevacizumab in combination with docetaxel was negative and that this combination should no longer be used in the treatment of breast cancer, it also confirmed the benefits of the drug in combination with paclitaxel for patients suffering from metastatic breast cancer.[49] On the contrary, based on FDA decisions, breast cancer was totally removed from the bevacizumab label in November 2011.[50]
Considering the number of contributing factors, it remains an open question whether further attempts to minimise regulatory divergence will or even should be made.[51] Although the mandate of the International Conference on Harmonisation is to harmonise regulatory requirements for data by tripartite-agreed guidelines, harmonisation is not intended to extend any deeper into domestic assessment of the data submitted, risk/benefit evaluation of medicinal products and their labelling. Even between the EU Member States, achieving harmonisation has often proved to be an onerous process, requiring legally set out referral and arbitration procedures for resolving disharmony. On the other hand, the fact that in a globalised world the EMA and the FDA still work and think as two separate entities has an unavoidable impact on prescribers and patients access between the two sides of the Atlantic. A better communication of processes and opinions (e.g. through the attendance of EMA regulators at FDA public hearings or of FDA staff at CHMP meetings) would certainly help mutual understanding of different regulatory systems. Nevertheless only understanding which differences really count for patients will allow the development of harmonisation policies that safeguard their interests.

Lessons learned and future avenues for regulatory science

In conclusion, this thesis provides an insight into the regulatory decision-making process when it comes to dealing with situations of uncertainty and to evaluating the robustness and credibility of the evidence of medicines. Regulatory decision-making follows a process that requires flexibility. Under certain circumstances the evidence already available may be enough and conducting additional clinical trials may be unnecessary. In other

cases, when data are based on trials prematurely stopped for apparent benefit, evidence should be viewed with caution. When evidence is considered insufficient this obviously leads to a non-approval, and this is especially due to lack of clinical relevance of the data submitted by the companies. However, even when a drug makes it to the market, an uncertain benefit/risk profile often leads regulators to what we call "precautionary approvals", which tend to be tailored to restricted patient populations and are potentially distant from the actual clinical needs. Uncertainty may also be interpreted differently across regulatory authorities and this may significantly affect patients' access to relevant therapeutic options. These divergences are due to "formal factors", such as a different interpretation of clinical endpoints, as well as to "informal factors", such as a different perception of risk and differences in the core organisational structures of regulatory agencies.

The task of regulatory science is to evaluate and study regulatory systems in terms of their ability to ensure patient safety, enhance public health, and stimulate innovation.[19,52,53] New and emerging science (personalised medicine, nanotechnologies, regenerative medicine, synthetic biology as well as advances to streamline non-clinical and clinical development) bring along new challenges for regulators and new potential avenues for regulatory science. Analysing regulatory decision-making and actions will provide a measure of how the new science is translated into regulatory requirements and how the regulatory system promotes innovation and creativity at various points throughout the development process. Future research in regulatory science should also expand its scope focussing not only on regulatory actions within a single agency or differences in decision-making among different regulatory agencies, but also on their actual impacts on the patient's health status. What are the actual consequences of regulatory dynamics or regulatory divergence on patients? Does the restriction of a therapeutic indication fuel off-label prescribing? These questions deserve to be addressed by further research in regulatory science and developments in electronic medical records may provide important tools to gain information on the effects of regulatory decisions.

The growing importance of HTA bodies on the access to market of novel medicines offers another interesting opportunity for research in this field, especially at the EU level where harmonisation of licensing and reimbursement requirements is being attempted to overcome disparities of access across Europe. It will be interesting to investigate the effects of these initiatives (such as parallel HTA-EMA scientific advice) and their actual impact on access to medicines.

Finally regulatory science should focus on the evolving role of the patient in the regulatory scenario. The involvement and participation of civil society representatives is formally recognised as an element of growing importance for regulatory authorities. However whether patients will actually represent an added value in benefit/risk considerations

and how their view will be complemented with regulatory outcomes remain open questions for future research.

In general, research in regulatory science in the next years will be facilitated by the increasing level of transparency and openness in the field of medicines regulation, fuelling better access to information on the decision-making process for the evaluation of medicinal products

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Summary

The role of drug regulatory authorities is to protect public health while facilitating availability of efficacious medicines to meet clinical needs. The basis of regulatory decisions is the benefit/risk assessment, a complex process that requires the evaluation of quality, non-clinical and clinical data submitted by the pharmaceutical company. It is the core task of drug regulatory agencies to make sure that the benefits of a new medicine outweigh the risks and that only products with a positive benefit/risk balance are authorised for release to the public. A properly conducted benefit/risk assessment should be a rational process of combining objective elements (data and uncertainties) with subjective elements, leading to consistent decisions and should occur in a transparent process, communicable to the various stakeholders. Although the level of transparency has been increasing through the online availability of regulatory documents, the regulatory "thought" process still remains a "black box" to many. There is still no consensus as how best to document how evidence, uncertainties and judgments result in a specific regulatory decision. In certain circumstances this can generate criticisms towards regulators. In general as long as "bad" outcomes do not occur, most in the larger community are less interested in regulatory decisions. However, when "bad" outcomes do occur, regulators come under attack. It may also occasionally happen that different regulatory agencies make different decisions when assessing the same data. When this occurs populations and parliaments are understandably confused, the credibility of regulators may be questioned and their strategies for risk assessment, communication and management can become suspect to the public. The immediate consequence is that the distance between the people and the regulatory agencies widens and the credibility of regulators declines.

In addition, with the current decline in the number of new therapies and increasing costs of bringing new products to the market, regulators are not only expected to "protect" public health by keeping "bad" medicines off the market, but also to "promote" public health by facilitating "good" medicines getting to those who need them as quickly as possible. Regulators are obliged to make timely decisions on the availability of drugs for patients, even under conditions of uncertainty.
The research questions addressed in this thesis stemmed from this general context. It is well known that when regulators determine the benefit/risk profile of a new application, the system requires a yes or a no dichotomy. We have tried to describe the dynamics involved over the course of an application review and the factors guiding regulators in their decision-making process before the final outcome is presented to the world.

Chapter 2 focuses on the level of evidence needed by regulators to make their decisions and the importance of transparency in communicating their decisions to the public. In **Chapter 2.1** we used the case of proton pump inhibitors (PPIs) for the treatment of gastroesophageal reflux in children to verify whether drugs not formally approved for

use in a specific population may nonetheless have sufficient evidence supporting their off-label use. Nineteen clinical trials testing omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole, were retrieved. At the time of the analysis, of these five PPIs only omeprazole had a paediatric indication in the EU (i.e. children aged ≥2 years). The scenario in the United States appeared to be different: three out of five compounds (omeprazole, esomeprazole and lansoprazole) were authorised for children. Given the consistent available evidence retrieved in literature, we evaluated the off-label use of omeprazole, esomeprazole and lansoprazole in children as highly appropriate. Moderate appropriateness was attributed to pantoprazole, due to a lack of pharmacokinetics data and insufficient efficacy trials. Since no adequate evidence was available for rabeprazole, its off-label use was considered to be scarcely appropriate in children.

We concluded that performing additional clinical studies in children may not always be necessary and that translating clinical evidence into regulatory decision-making can be a useful strategy to minimise regulatory hurdles, avoid unethical replication of trials and fill the gap between regulatory authorities and specific patient groups, thereby ensuring an equal and quicker access to medicines.

After addressing the issue of what level of evidence may be considered necessary for regulatory decisions, we investigated the cases where evidence is considered insufficient by regulatory agencies **(Chapter 2.3)**. The analysis of drug applications withdrawn by the company prior to the conclusion of the evaluation process or refused at the end of it, provides an important look at what may go wrong in bringing a product from bench to the clinic, and what could be improved in future applications. Based on the analysis of EMA public assessment reports, we identified a total of 86 drug applications with either a withdrawal (70 out of 86) or a refusal (16 out of 86). The reasons leading to a withdrawal or refusal could be related to all of the three critical criteria for approval, i.e. quality, safety and efficacy issues; sometimes a combination of the three. Overall, 156 quality, safety and efficacy major objections were raised by the Committee for Medicinal Products for Human Use (CHMP): 106 objections were due to efficacy deficiencies, while 27 to safety and 23 to quality, respectively. Within the scope of efficacy-related major objections, five main categories could be identified: i) lack of clinical relevance (44 out of 106, 41.5%), ii) methodological issues (23 out of 106, 21.6%), iii) Pharmacokinetic issues, including bioequivalence (20 out of 106, 18.8%), iv) lack of statistical significance (13 cases, 12.2%), and v) major Good Clinical Practice issues (5 out of 106, 4.7%). The lack of clinical relevance was the most frequent objection in all failed applications, accounting for approximately 50% of all efficacy objections. We also queried several other regulatory authorities in a sample of countries across the world in order to check whether they have similar transparency measures in place on failed drug applications. Apart from Europe, only Australia seems to have such a disclosure system.

In conclusion, our analyses of the grounds of failed drug applications revealed that (lack

of) efficacy is the main predictor for success or failure of an application. A clear propensity of a positive CHMP opinion seems to be a good and robust clinical trial program, with a good rationale, and a targeted and efficient trial performance.

All the analyses presented in **Chapter 3** focus on oncology. New anticancer drugs reach the market with a lack of complete and sound evidence and this has complicated the decision-making process for oncology medicines. Analysis of past regulatory decisions supports the notion that the level of acceptable uncertainty is not constant across all therapeutic indications. Regulators are generally willing to accept a higher level of uncertainty around the benefit/risk assessment for life-threatening or otherwise severe conditions for which there is a high unmet medical need such as cancer, as opposed to less severe conditions or where an effective treatment already exists.
In oncology a very controversial issue for regulatory decision-makers is the interpretation of results based on early stopped randomised clinical trials (RCTs) following interim analyses. Interim analyses pose the ethical dilemma of safeguarding the interests of patients enrolled in clinical trials while also protecting society from overzealous premature claims of treatment benefit. Trials stopped early because of harm (toxicity) or futility tend to result in prompt discontinuation of useless or potentially harmful interventions. In contrast, trials stopped early for benefit may result in the quick identification, approval, and dissemination of promising new treatments. In general the prevalence of RCTs stopped early for benefit is increasing, and in particular our analysis highlighted a consistent increase in the field of oncology (**Chapters 3.1-3.2**). Based on the analysis of 25 published RCTs, selected as having been stopped early for benefit after an interim analysis, we found a consistent increase (56%) in prematurely stopped trials in oncology between 2005-2007 in comparison to the whole period analysed (1997-2007). Of note, 79% of the RCTs published between 2005-2007 with an interim analysis ending the trial were used for registration purposes. This suggests that there may be a commercial component in stopping trials prematurely.
In the studies that were stopped prematurely the evaluation of efficacy was protocol planned through time-related primary end points, >40% of them overall survival. In general, the studies analysed were formally well designed; all were randomised, controlled, based on robust endpoints and with a large sample size. In 95% of studies, at the interim analysis, efficacy was evaluated using the same end point as planned for the final analysis. There was no Data and Safety Monitoring Committee in 24% of the studies. In 15 RCTs, interim analysis was done when ≥50% of the planned sample size for final efficacy analysis was reached. Five, however, reported an interim analysis conducted on a sample ≤43% of that planned for the final analysis. The full sample size initially planned was ~8000 patients/ events across all trials retrieved. As a consequence of early stopping after the interim analysis, ~3300 patients/events across all studies were spared.

In conclusion, though criticism of the poor quality of oncological trials seems out of place, early termination raises new concerns. There are still unresolved issues that raise questions with regard to the correct interpretation of interim results which put regulators in a difficult situation with implications for patients' health.

The uncertainty surrounding the benefit/risk profile of new drugs at the time of marketing entry has led to a gradual evolution of the regulatory model from a one-off marketing authorisation to a product life cycle approach. Indeed when faced with uncertainty regulators tend to request additional data and post-approval commitments. Therefore the development of medicines is a continuous and dynamic process in which new knowledge has consequences for the conditions of marketing authorisation. Extensions of indications (EoI) as well as new safety information lead to a continuous evaluation of the benefit/risk profile. **Chapter 3.3** investigates the extensions of oncology indications approved by the European Medicines Agency (EMA), analysing the time needed for anticancer drugs to get an extension, the rates and characteristics of extensions approved, and the regulatory process leading to the definition of new indications.

A total of 103 therapeutic oncological indications, related to a cohort of 43 anticancer drugs, were retrieved between 1995 and 2008. The median time occurring between different indications for the same compound significantly decreased from about 81 months in 1996 to 6 months in 2006. This reflects a shorter clinical development process, reduced regulatory delays and quicker availability of new treatments to patients. Of note, at the time of the analysis, 24 out of 43 approved anticancer medicines (about 56%) had only a single therapeutic indication.

When considering two different cohorts of drugs in relation to the time of approval (1995–2004 versus 2005–2008), although not statistically significant, the older cohort tended to have a decreased probability of having EoI when compared to the new cohort (OR = 0.27; 95% confidence interval: 0.07–1.04). With regard to the type of EoI (n = 60), our findings showed that in 48% of cases the initially approved indication was extended to treat a different tumour, in 37% of cases the extension consisted in a switch of line within the same therapeutic indication. The other two types of indication broadening refer to a different tumour stage (8%) and to the inclusion of a new patient population (7%).

In order to investigate the regulatory dynamics occurring during the review process, a comparison was performed between the indications initially submitted by companies and those resulting at the end of the CHMP evaluation process. For this analysis, clear information on the indication requested by the company was retrieved for 50 out of the total sample of 103 indications. The analysis showed that in 20 cases out of the 50 (40%) therapeutic indications were restricted by the CHMP during the assessment, with 60% of the restrictions occurring in 2006–2007. During the time period 2006-2007, when restrictions reached a peak, there is an evident decline in the time needed to obtain a

new extension. This leads to the hypothesis of a relationship between a faster clinical development and the chance of receiving an indication restriction from regulators.
This study added three main pieces of information: (i) the majority of anticancer drugs still have a single indication regardless of the year of approval; (ii) the time needed to obtain an extension of indication has decreased significantly over the last decade and (iii) a highest rate of regulatory restrictions is matched to shorter clinical developments.

In general, the definition of a therapeutic indication is a critical step in regulating medicinal products. The wording of indications can have a huge impact on clinical practice by including or excluding certain patient populations. In **chapter 3.4** our research has shown that major agencies like the EMA and the FDA, based on the review of the same applications, can differ when taking decisions on the wording of indications, e.g. when one agency tends to be more restrictive in the definition of an indication, limiting drug use only to a specific patient population. Overall, 42 anticancer drugs were approved by the EMA between 1995 and 2008, corresponding to a total of 100 indications. In 47 of 100 indications, a difference was found. For 19 of these 47 indications, the difference was that one agency approved an indication, whereas the other agency did not. In three indications, an FDA indication was not approved by EMA, and in 16 indications, an EMA indication was not approved by the FDA. For the remaining 28 of 47 indications for which a difference between corresponding indications was found, further analysis showed that neither agency could be characterized as more restrictive compared with the other (out of 28 indications, FDA was more restrictive in 13, whereas EMA in 15). The 28 indications with a difference in the approved wording were further evaluated through an algorithm, highlighting 10 cases where discrepancies were considered clinically relevant. The majority of indications (69%) were first approved by the FDA, although a trend shows that there is a continuous increase of first approvals by the EMA. Although limited numbers did not allow for formal statistical testing, we found an overall trend that the agency that positively approved an indication second was usually more restrictive in terms of wording of the indication compared with agency that approved the indication first.
Of note, in 57 out of the 100 analysed indications, the EMA and the FDA based the approval on the same pivotal study.
In conclusion, our study results showed clinically relevant differences in the outcome of the EMA and FDA approval process of oncology products, although there is no evidence supporting that one of the two regulatory communities might be a better or a worse performer, and neither of the agencies seems to have a prevailing restrictive behaviour over the other. The FDA is still first in approving new oncologic indications over the last few decades, but there is a trend for more convergence between the two agencies in regulatory decision making. Because no clear predictors of regulatory outcomes were identified by this research, we hypothesised the involvement of other driving forces causing such

heterogeneity in the approval between the EMA and FDA. This led us to investigate the decision-making processes for anticancer drugs at the two agencies through a comparative qualitative study using semi-structured in-depth interviews (**chapter 3.5**). Such research was based on the assumption that the process leading to a regulatory outcome is guided by factors both related and unrelated to the application data package, defined as "formal" and "informal" factors, respectively. In fact we assumed that over the course of an application review, a regulator's assessment of the data package is likely to be mediated by informal factors such as the interaction with external stakeholders (e.g. pharmaceutical companies, patients or other regulatory agencies) and influenced by socio-cultural and behavioural aspects. Our findings showed that the ongoing harmonization between EMA and FDA has fostered the exchange of information but still not the exchange of opinions, leaving the two agencies to feel very distant from one another, mostly due to different core organisational structures. The key message of our respondents was that the EMA and the FDA manage uncertainty in a different way. According to the study respondents, the FDA is more open to take risks and base approval on less robust data in order to guarantee quicker access to cancer medicines, although it allows product withdrawals from the market more easily than the EMA. Furthermore, a different interpretation of Progression Free Survival (PFS), viewed as a clinical benefit per se by the EMA but not by the FDA, was considered the prevailing reason for regulatory divergence.
Considering the number of contributing factors, it remains an open question whether further attempts to minimise regulatory divergence will or even should be made. Nevertheless only understanding which differences really count for patients will allow the development of harmonisation policies that safeguard their interests.

In **Chapter 4** we placed our findings from this thesis in a broader context and identified new potential avenues for regulatory science. Analysing regulatory decision-making and actions will provide a measure of how the new and emerging science is translated into regulatory requirements and how the regulatory system promotes innovation and creativity at various points throughout the development process. Future research in regulatory science should also expand its scope focussing not only on regulatory actions within a single agency or differences in decision-making among different regulatory agencies, but also on their actual impacts on the patient's health status.
The growing importance of HTA bodies on the access to market of novel medicines offers another interesting opportunity for research in this field, especially at the EU level where harmonisation of licensing and reimbursement requirements is being attempted to overcome disparities of access across Europe. It will be interesting to investigate the effects of these initiatives (such as parallel HTA-EMA scientific advice) and their actual impact on access to medicines.

Finally regulatory science should focus on the evolving role of the patient in the regulatory scenario. The involvement and participation of civil society representatives is formally recognised as an element of growing importance for regulatory authorities. However whether patients will actually represent an added value in benefit/risk considerations and how their view will be complemented with regulatory outcomes remain open questions for future research.

In general, research in regulatory science in the next years will be facilitated by the increasing level of transparency and openness in the field of medicines regulation, fuelling better access to information on the decision-making process for the evaluation of medicinal products

Samenvatting

Registratieautoriteiten moeten de volksgezondheid beschermen door het waarborgen van de veiligheid van geneesmiddelen, terwijl ze tegelijkertijd zorg moeten dragen voor het tijdig op de markt komen van effectieve, klinisch relevante geneesmiddelen. De beoordeling van de balans tussen werkzaamheid en veiligheid vormt de basis van het besluitvormingsproces rondom de toelating van geneesmiddelen. Dit is een complex proces waarbij de gegevens over kwaliteit, preklinisch en klinisch onderzoek zoals ingediend door een farmaceutisch bedrijf worden beoordeeld. Het is de taak van de registratieautoriteiten om er zorg voor te dragen dat de voordelen van een nieuw geneesmiddel opwegen tegen de nadelen en dat alleen geneesmiddelen waarvoor deze balans positief uitvalt tot de markt worden toegelaten. Een weloverwogen besluitvorming zou het resultaat moeten zijn van een rationeel proces waarin objectieve elementen (onderzoeksgegevens en gedocumenteerde onzekerheden) worden gecombineerd met subjectieve elementen. Dit leidt dan tot consistente beslissingen die op een transparante wijze tot stand komen en helder kunnen worden uitgelegd aan belanghebbenden. Hoewel de mate van transparantie in de afgelopen jaren is toegenomen door het elektronisch beschikbaar komen van regulatoire documenten, blijft het besluitvormingsproces voor velen een "zwarte doos". Er is nog steeds geen overeenstemming hoe de totstandkoming van een oordeel en de weging van feiten en onzekerheden het beste kan worden vastgelegd. Dit kan in bepaalde situaties tot kritiek op registratieautoriteiten leiden. Zolang zich geen "problemen" voordoen, zal de samenleving over het algemeen weinig belangstelling hebben voor beslissingen rondom de toelating van geneesmiddelen. Maar registratieautoriteiten komen onder vuur te liggen, zodra dergelijke "problemen" zich wel voordoen. Verschillende registratieautoriteiten kunnen ook tot verschillende besluiten komen op basis van dezelfde onderliggende gegevens. Dit kan tot verwarring leiden bij het publiek en de politiek, waardoor er vraagtekens worden gezet bij de geloofwaardigheid van de autoriteiten en de manier waarop zij risico's beoordelen en hierover communiceren. Het resultaat is dat de afstand tussen het publiek en de registratieautoriteiten toeneemt en het vertrouwen afneemt.

Het aantal nieuwe geneesmiddelen dat op de markt komt neemt af en de kosten voor het op de markt brengen stijgen. Hierdoor wordt van registratieautoriteiten niet alleen verwacht dat zij de volksgezondheid beschermen door "slechte" geneesmiddelen niet tot de markt toe te laten, maar ook dat zij de volksgezondheid bevorderen door toegang tot "goede" geneesmiddelen zo snel mogelijk te bewerkstelligen. Registratieautoriteiten zijn dus genoodzaakt beslissingen rondom de beschikbaarheid van geneesmiddelen tijdig te nemen, ook bij aanhoudende onzekerheid over de ingediende gegevens.

Binnen deze algemene context komen verschillende onderzoeksvragen in dit proefschrift aan bod. Het is bekend dat van beoordelaars wordt verwacht dat zij een dichotoom besluit nemen (wel of geen toelating tot de markt), nadat zij de baten en risico's van een nieuwe

aanvraag hebben afgewogen. In dit proefschrift wordt de dynamiek tijdens dit proces beschreven en worden de factoren die hierbij een rol spelen bestudeerd.

Hoofdstuk 2 richt zich op de hoeveelheid gegevens die nodig zijn voor beoordelaars om een weloverwogen besluit te kunnen nemen en op het belang van transparantie bij het uitleggen van deze besluiten aan het publiek. In **hoofdstuk 2.1** is onderzocht of er voor een geneesmiddel dat niet formeel voor gebruik door een specifieke patiëntengroep is geregistreerd toch voldoende klinische gegevens beschikbaar zijn om het "off-label" gebruik te kunnen ondersteunen. Het gebruik van protonpompremmers (PPIs) voor de behandeling van gastro-oesofageale refluxklachten bij kinderen is hierbij als casus gekozen. Negentien klinische onderzoeken met omeprazol, esomeprazol, lansoprazol, rabeprazol of pantoprazol werden bestudeerd. Ten tijde van de analyse was in de Europese Unie (EU) alleen omeprazol geregistreerd voor gebruik bij kinderen van 2 jaar of ouder. In de Verenigde Staten (VS) waren daarentegen drie van de vijf PPIs (omeprazol, esomeprazol en lansoprazol) geregistreerd voor gebruik bij kinderen. Op basis van de beschikbare gegevens in de literatuur die een consistent beeld lieten zien voor omeprazol, esomeprazol en lansoprazol concludeerden we dat het "off-label" gebruik van deze middelen bij kinderen gerechtvaardigd is. Dit was in mindere mate het geval voor pantoprazol, waarvoor farmacokinetische gegevens ontbraken en klinisch onderzoek naar de effectiviteit niet voldoende was. Omdat er geen goede gegevens beschikbaar waren voor rabeprazol, werd het gebruik van dit middel bij kinderen als nauwelijks gerechtvaardigd beoordeeld.
We concludeerden dat het uitvoeren van aanvullend klinisch onderzoek bij kinderen niet altijd noodzakelijk is; het vertalen van beschikbare klinische gegevens naar gebruik voor toelating tot de markt kan regulatoire barrières verminderen en het herhalen van klinisch onderzoek bij specifieke patiëntengroepen, wat onethisch is, voorkomen. Zo kan de toegang tot geneesmiddelen ook voor dergelijke groepen sneller worden gewaarborgd.
Na dit onderzoek naar de hoeveelheid gegevens die nodig zijn voor toelating tot de markt hebben we vervolgens onderzoek gedaan naar gevallen waarbij de onderliggende gegevens niet voldoende waren volgens de registratieautoriteiten (**hoofdstuk 2.3**). Het analyseren van registratieaanvragen die door de indieners zijn teruggetrokken voordat er een definitief besluit werd genomen of die aan het eind van de procedure zijn afgekeurd kan inzicht verschaffen in wat er fout kan gaan bij de ontwikkeling van nieuwe geneesmiddelen en wat er in bij toekomstige aanvragen zou kunnen worden verbeterd. Op basis van Europese beoordelingsrapporten selecteerden we 86 aanvragen voor registratie die waren teruggetrokken (70 van de 86) of waren afgekeurd (16 van de 86). De redenen voor terugtrekking of afkeuring konden allen worden teruggevoerd op (een combinatie van) de drie belangrijkste criteria voor markttoelating, namelijk kwaliteit, effectiviteit en veiligheid. Er werden totaal 156 bewaren geuit met betrekking tot deze drie criteria door het Committee for Medicinal Products for Human Use (CHMP): 106 met betrekking tot

effectiviteit, 27 met betrekking tot veiligheid en 23 met betrekking tot kwaliteit. Binnen de bezwaren met betrekking tot de effectiviteit konden 5 categorieën worden onderscheiden: i) gebrek aan klinische relevantie (44 van de 106, 41.5%), ii) methodologische problemen (23 van de 106, 21.6%), iii) farmacokinetische problemen, waaronder bioequivalentie (20 van de 106, 18.8%), iv) gebrek aan statistische significantie (13 bezwaren, 12.2%) en v) belangrijke problemen met betrekking tot Good Clinical Practice (5 van de 106, 4.7%). Het gebrek aan klinische relevantie was het meest voorkomende bezwaar met bijna de helft van alle bezwaren. We benaderden wereldwijd ook een aantal andere registratieautoriteiten om te vragen of zij vergelijkbare systemen voor het bekendmaken van gegevens over teruggetrokken of afgewezen registratieaanvragen hadden. Het bleek dat dit naast in Europa alleen in Australië het geval is.
Concluderend kan worden gesteld dat (het gebrek aan) effectiviteit de belangrijkste voorspeller voor de goedkeuring of afkeuring van een registratieaanvraag is. Een goed en robuust opgezet en uitgevoerd klinisch onderzoeksprogramma met een duidelijke rationale lijkt tot de beste kans op een positief oordeel van de CHMP het meeste te leiden.

Alle onderzoeken in **hoofdstuk 3** richten zich op de oncologie. Nieuwe geneesmiddelen tegen kanker komen vaak op de markt zonder een complete en eenduidige hoeveelheid gegevens en dit bemoeilijkt het besluitvormingsproces rondom de toelating van deze geneesmiddelen. Onderzoek naar eerdere besluiten laat zien dat de mate waarin onzekerheid acceptabel gevonden wordt niet constant is voor alle indicaties. Beoordelaars zijn over het algemeen bereid een hogere mate van onzekerheid te accepteren voor levensbedreigende ziektes of andere ernstige aandoeningen waarvoor een urgente behoefte voor geneesmiddelen bestaat dan voor minder ernstige aandoeningen of aandoeningen waarvoor reeds een effectieve behandeling beschikbaar is.
Een zeer controversieel onderwerp binnen de oncologie is de interpretatie van onderzoeksgegevens na interim-analyses bij het vroegtijdig stoppen van klinisch onderzoek. Interim-analyses werpen het ethische dilemma op van het waarborgen van de belangen van deelnemers aan klinisch onderzoek, terwijl de samenleving tegelijkertijd moet worden beschermd tegen voorbarige claims ten aanzien van gunstige effecten. Het stoppen van onderzoeken vanwege veiligheidsproblemen of ineffectiviteit lijkt te resulteren in het tijdig stoppen van interventies die risicovol of onnodig zijn. Het vroegtijdig stoppen van klinisch onderzoek vanwege gunstige effecten kan resulteren in een snelle identificatie, toelating en disseminatie van veelbelovende nieuwe behandelingen. Klinische onderzoeken worden in toenemende mate vroegtijdig gestopt en onze onderzoeken laten vooral een consistente toename binnen de oncologie zien (**hoofdstukken 3.1-3.2**). In een analyse van 25 gepubliceerde klinische studies, die waren geselecteerd omdat ze vroegtijdig waren gestopt vanwege gunstige effecten, vonden we een toename (56%) van vroegtijdig gestopte klinische onderzoeken binnen de oncologie tussen 2005-2007

ten opzichte van de gehele onderzoeksperiode (1997-2007). Een opvallende bevinding was dat 79% van de klinische studies die tussen 2005-2007 werden gepubliceerd uiteindelijk gebruikt werd voor een registratieaanvraag. Dit duidt erop dat het vroegtijdig stoppen van klinisch onderzoek wellicht ook een commerciële reden heeft.
In de vroegtijdig gestopte studies werd het primaire eindpunt, in > 40% van de gevallen de totale overleving, volgens het protocol op vooraf vastgestelde tijdstippen geëvalueerd. In het algemeen betrof het goed opgezette onderzoeken; alle studies waren gerandomiseerd, gecontroleerd, gebaseerd op robuuste eindpunten en met een grote onderzoekspopulatie. In 95% van de studies werd de effectiviteit tijdens de interim-analyse voor hetzelfde eindpunt vastgesteld als gepland voor de eindanalyse. Er was geen Data and Safety Monitoring Committee in 24% van de studies. De interim-analyse werd voor 15 klinische studies uitgevoerd op een moment waarbij inclusie van ≥50% van de geplande onderzoekspopulatie was bereikt. Vijf studies rapporteerden echter een interim-analyse op een moment waarop ≤ 43% van de vooraf geplande onderzoekspopulatie was bereikt. De geplande onderzoekspopulatie in alle studies gezamenlijk bedroeg oorspronkelijk ~ 8000 patiënten / uitkomsten, maar door het vroegtijdig stoppen werd uiteindelijk de inclusie van ~ 3300 patiënten / uitkomsten bespaard.
We concludeerden dat de kritiek op de lage kwaliteit van klinisch onderzoek binnen de oncologie niet terecht is, maar dat het vroegtijdig stoppen van dergelijk onderzoek wel tot nieuwe vraagstukken leidt. Er zijn onopgeloste vragen met betrekking tot de correcte interpretatie van interim-resultaten en dit kan beoordelaars in een lastige situatie brengen met mogelijke gevolgen voor de gezondheid van patiënten.

De onzekerheid rondom de balans tussen effectiviteit en veiligheid op het moment van markttoelating heeft bijgedragen aan een geleidelijke evolutie van het model van markttoelating, van een eenmalig besluit tot een benadering waarin de levenscyclus van een geneesmiddel wordt gevolgd. Wanneer zij met onzekerheden worden geconfronteerd, vragen beoordelaars aanvullende klinische gegevens of de toezegging om deze gegevens na markttoelating aan te leveren. Het ontwikkelen van geneesmiddelen wordt zo een continu en dynamisch proces waarin het ontstaan van nieuwe kennis consequenties heeft voor de voorwaarden voor markttoelating. Uitbreidingen van de indicatie en nieuwe veiligheidsinformatie leiden tot een continue afweging van gunstige en ongunstige effecten.
Hoofdstuk 3.3 onderzoekt uitbreidingen van oncologische indicaties die door de European Medicines Agency (EMA) zijn goedgekeurd, waarbij is gekeken naar de tijd die nodig is voor een eerste uitbreiding, de hoeveelheid en karakteristieken van de goedgekeurde uitbreidingen en het besluitvormingsproces dat leidt tot het vaststellen van nieuwe indicaties. In totaal werden 103 oncologische indicaties, afkomstig van een cohort van 43 oncolytica, gevonden in de periode 1995-2008. De mediane tijd tussen het toekennen

van verschillende indicaties voor één geneesmiddel nam significant af van 81 maanden in 1996 tot 6 maanden in 2006. Dit betekent een korter ontwikkelingsproces, minder vertraging tijdens het registratieproces en eerdere beschikbaarheid van nieuwe behandelingen voor patiënten. Een interessante bevinding was dat 24 van de 43 oncolytica (ongeveer 56%) slechts één indicatie had.
Wanneer we de oncolytica indeelden in twee cohorten op basis van het moment van markttoelating (1995-2004 versus 2005-2008), bleek het oudere cohort een niet-significant verlaagd risico op een uitbreiding van de indicatie te hebben ten opzichte van het nieuwere cohort (OR=0.27, 95% betrouwbaarheidsinterval 0.07-1.04). Wanneer naar de karakteristieken van de uitbreidingen (n=60) werd gekeken, bleek dat de oorspronkelijke indicatie in 48% werd uitgebreid met de behandeling van een andere tumor en in 37% vond er een verschuiving binnen de behandeling van dezelfde indicatie plaats. De andere twee vormen van uitbreiding betroffen uitbreiding naar een andere fase waarin de tumor wordt behandeld (8%) en inclusie van een nieuwe patiëntenpopulatie (7%).
Om de dynamiek van het beoordelingsproces verder te bestuderen zijn de door de farmaceutische bedrijven aangevraagde indicaties vergeleken met de uiteindelijk goedgekeurde indicaties. Voor deze analyse was duidelijk informatie over de aangevraagde indicatie nodig en deze was beschikbaar voor 50 van de 103 indicaties. Hieruit bleek dat de CHMP in 20 van de 50 gevallen (40%) de indicatie tijdens de beoordeling beperkte. In 60% gebeurde dat in de periode 2006-2007, een piek in het aantal beperkingen, waarin ook een duidelijke afname van de tijd tot het verkrijgen van een nieuwe uitbreiding werd gezien. Deze bevinding leidt tot de hypothese dat er een relatie bestaat tussen een sneller ontwikkeltraject en de kans op het opgelegd krijgen van een indicatiebeperking door registratieautoriteiten.
Dit onderzoek leverde drie nieuwe inzichten op: (i) de meerderheid van de oncolytica heeft nog steeds slechts één indicatie, ongeacht wanneer het middel tot de markt is toegelaten; (ii) de tijd die nodig is om een uitbreiding van de indicatie te verkrijgen is aanzienlijk afgenomen gedurende de afgelopen periode; en (iii) meer beperkingen van de indicatie door beoordelaars valt samen met een korter ontwikkeltraject.

Het vaststellen van de exacte bewoording van een indicatie is een cruciale stap in het besluitvormingsproces. De uiteindelijke bewoording kan van invloed zijn op de klinische praktijk en het wel of niet behandelen van patiëntengroepen. Ons onderzoek in **hoofdstuk 3.4** laat zien dat de belangrijkste autoriteiten zoals de EMA en de Food and Drug Administration (FDA) in de VS kunnen verschillen in hun besluiten ten aanzien van de bewoordingen, ook als deze besluiten genomen zijn op basis van dezelfde gegevens in de registratieaanvraag. Eén van de autoriteiten kan bijvoorbeeld strenger zijn in de gekozen bewoording en gebruik van het geneesmiddel alleen toestaan bij een specifieke groep van patiënten. In totaal werden 42 oncolytica voor 100 indicaties door de EMA goedge-

keurd tussen 1995 en 2008. Voor 47 van de 100 indicaties werd een verschil gevonden tussen de EMA en de FDA. In 19 gevallen was de indicatie slechts door één van beide autoriteiten goedgekeurd (3 keer alleen door de FDA en 16 keer alleen door de EMA). Voor de overige 28 van de 47 indicaties waarin een verschil werd gevonden kon verder onderzoek niet bevestigen dat één van beide autoriteiten strenger was; in 13 van de 28 indicaties was de FDA strenger dan de EMA en in 15 indicaties was het tegenovergestelde het geval. De 28 indicaties met een verschil in bewoording werden verder onderzocht met behulp van een algoritme waaruit bleek dat 10 verschillen klinisch relevant waren.
De meerderheid van de indicaties (69%) was eerst goedgekeurd door de FDA, hoewel er een trend gaande is richting meer eerste goedkeuringen door de EMA. We vonden ook een trend dat de autoriteit die als tweede een indicatie goedkeurde deze meer inperkte dan de autoriteit die de indicatie als eerste goedkeurde. Door de kleine aantallen kon deze bevinding echter niet verder statistisch worden onderbouwd. Een andere interessante bevinding was dat in 57 van de 100 indicaties de EMA en de FDA hun goedkeuring op hetzelfde onderzoek baseerden.
Concluderend liet dit onderzoek zien dat er klinisch relevante verschillen zijn in het besluitvormingsproces rondom oncolytica tussen de EMA en de FDA, hoewel er geen bewijs is dat de ene autoriteit beter of slechter werk verricht dan de andere en geen van beide lijkt restrictiever dan de andere. De FDA is vaak nog de eerste die nieuwe indicatie als eerste goedkeurt, maar er lijkt een trend gaande te zijn naar meer convergentie in het besluitvormingsproces van beide autoriteiten. Omdat er uit dit onderzoek geen duidelijke voorspellende factoren naar voren kwamen, vermoedden we dat er andere drijvende krachten achter de verschillen in besluitvorming tussen de EMA en de FDA een rol spelen. Dit heeft ertoe geleid dat we het besluitvormingsproces voor oncolytica bij deze registratieautoriteiten verder hebben onderzocht door middel van een vergelijkende kwalitatieve studie, waarbij gebruik gemaakt is van semi-gestructureerde interviews (**hoofdstuk 3.5**). Dit onderzoek was gebaseerd op de aanname dat het proces dat tot een besluit leidt wordt beïnvloed door factoren die wel en niet samenhangen met de gegevens die onderdeel zijn van de registratieaanvraag, de zogenoemde "formele" en "informele" factoren. We namen ook aan dat de beoordeling van de gegevens tijdens het proces mede vorm krijgt door informele factoren zoals de interactie met externe belanghebbenden (bijvoorbeeld de farmaceutische industrie, patiënten of andere registratieautoriteiten) en wordt beïnvloed door sociaal-culturele en gedragsmatige aspecten. Onze resultaten laten zien dat initiatieven voor harmonisatie tussen de EMA en FDA het uitwisselen van informatie heeft vergemakkelijkt, maar niet het uitwisselen van besluiten. De twee agentschappen voelen zich niet verwant wat voornamelijk wordt veroorzaakt door aanzienlijke verschillen in de organisatiestructuur. De belangrijkste boodschap van de geïnterviewden was dat de EMA en de FDA verschillend omgaan met onzekerheden. De FDA zou meer bereid zijn om risico's te nemen en de toelating te baseren op minder

robuuste gegevens om zo snellere toegang tot oncolytica te bewerkstelligen, hoewel de FDA geneesmiddelen ook makkelijker van de markt terugtrekt dan de EMA. Daarnaast werd een verschillende interpretatie van de progressievrije overlevingskans - wel erkend als klinisch waardevol door de EMA, maar niet door de FDA - als belangrijke reden voor de uiteenlopende besluitvorming gezien.
Met het oog op het aantal factoren dat bijdraagt aan verschillen in besluitvorming, blijft ht de vraag of verder pogingen om diversiteit in besluitvorming te voorkomen zullen of moeten worden ondernomen. Alleen inzicht in welke verschillen echt van belang zijn voor patiënten zal kunnen bijdragen aan het ontwikkelen van verder beleid op het gebied van harmonisatie, zodat uiteindelijk de belangen van patiënten kunnen worden gewaarborgd.

In **hoofdstuk 4** worden de bevindingen van dit proefschrift in een bredere context geplaatst en worden nieuwe mogelijkheden voor wetenschappelijk onderzoek op het gebied van toelating van geneesmiddelen verkend. Het analyseren van het besluitvormingsproces en bijbehorende acties zal een richtlijn kunnen geven hoe deze nieuwe tak van wetenschap leidt tot regulatoire eisen en hoe het regulatoire systeem innovatie en creativiteit tijdens het ontwikkeltraject bevordert. Toekomstig onderzoek op dit gebied zal zich niet alleen moeten richten op besluiten van een enkele autoriteit of verschillen in besluitvorming tussen autoriteiten, maar ook op de daadwerkelijk impact op de gezondheid van de patiënt.
Het toenemende belang van autoriteiten die beslissingen nemen over de vergoeding van geneesmiddelen in relatie tot de toegang van nieuwe geneesmiddelen tot de markt biedt een andere interessante mogelijkheid voor verder onderzoek. Dit geldt vooral voor Europa waar naar een toenemende mate van harmonisatie tussen eisen voor toelating en vergoeding wordt gestreefd om zo ongelijkheid in toegang tot geneesmiddelen in Europa te voorkomen. Onderzoek zou zich kunnen richten op de effecten van dergelijke initiatieven (zoals parallel wetenschappelijk advies) en de daadwerkelijke impact op toegang tot geneesmiddelen.
Tenslotte zou wetenschappelijk onderzoek zich moeten richten op de toenemende rol van patiënten in het besluitvormingsproces. De betrokkenheid en deelname van vertegenwoordigers van patiënten en consumenten is formeel erkend door registratieautoriteiten als een onderwerp dat in toenemende mate van belang is. Of patiënten echter daadwerkelijk een toegevoegde waarde hebben in het besluitvormingsproces en in hoeverre hun gezichtspunten een aanvulling zijn op de uitkomsten van dat proces moet verder worden onderzocht.
In zijn algemeenheid zal het onderzoek naar het regulatoire systeem in de komende tijd worden vergemakkelijkt door de toenemende mate van transparantie en openheid op het gebied van toelating van geneesmiddelen en zal dit het besluitvormingsproces rondom de toelating van geneesmiddelen verder kunnen voeden.

Riassunto

Le agenzie regolatorie hanno il ruolo di proteggere la salute pubblica, facilitando al tempo stesso la disponibilità di farmaci efficaci che rispondano alle esigenze cliniche. La base delle decisioni a livello regolatorio è la valutazione del rapporto rischio/beneficio, un processo complesso che richiede la valutazione dei dati clinici, pre-clinici e relativi alla qualità, presentati dalle aziende farmaceutiche nel dossier registrativo. Le agenzie regolatorie devono quindi assicurarsi che i benefici di un nuovo farmaco superino i rischi e che solo i prodotti con un rapporto rischio/beneficio positivo siano autorizzati all'uso.
Una corretta valutazione del rapporto rischio/beneficio consiste in un processo che combina elementi oggettivi (dati e incertezze) ed elementi soggettivi, che porta a decisioni riproducibili, che sia trasparente e comunicabile ai diversi *stakeholders*. Sebbene il grado di trasparenza sia aumentato con la disponibilità di documenti online da parte delle agenzie, il processo decisionale a livello regolatorio resta ancora un "mistero" per molti. Non vi è ancora un consenso rispetto a come documentare il processo attraverso il quale le evidenze, le incertezze ed il giudizio individuale risultano in una decisione finale. In determinate circostanze ciò può anche generare critiche verso le agenzie regolatorie. Infatti, nonostante il pubblico sia generalmente poco attento alle decisioni prese in ambito regolatorio, l'atteggiamento diventa ostile e le autorità regolatorie vengono messe sotto accusa quando queste decisioni producono effetti negativi.
A volte accade, per esempio, che diverse agenzie regolatorie prendano decisioni differenti sulla base degli stessi dati. Quando ciò si verifica, il pubblico e le istituzioni ne restano comprensibilmente confusi, la credibilità delle autorità regolatorie viene messa in discussione e le loro strategie di valutazione, comunicazione e gestione del rischio vengono guardate con sospetto. La conseguenza è che la distanza tra il pubblico e le agenzie regolatorie aumenta e che la credibilità di queste istituzioni ne risulta inevitabilmente intaccata. Inoltre, l'attuale diminuzione del numero di nuove terapie e l'aumento del costo che implica portare nuovi farmaci sul mercato richiede che le autorità regolatorie non solo "proteggano" la salute pubblica, evitando l'utilizzo di farmaci potenzialmente nocivi, ma che anzi la "promuovano" facilitando il processo attraverso il quale i nuovi farmaci raggiungono i pazienti nel più breve tempo possibile. I *regulators*, ossia gli addetti ai lavori all'interno delle agenzie, sono tenuti a prendere decisioni secondo tempistiche prestabilite, anche in situazioni di incertezza, perché ciò condiziona la disponibilità dei farmaci per i pazienti.
I quesiti ai quali questa tesi cerca di dare una risposta nascono da questo contesto. E' ben noto che quando i *regulators* determinano il profilo rischio-beneficio di un nuovo farmaco, il sistema richiede un giudizio dicotomico, ossia un si o un no. Abbiamo cercato, nei vari lavori che compongono questa tesi, di descrivere le dinamiche coinvolte nel corso della valutazione di un dossier ed i fattori che guidano il processo decisionale a livello regolatorio prima che venga elaborato un parere definitivo.

Il **Capitolo 2** descrive il livello di evidenza necessario per prendere decisioni a livello regolatorio e dell'importanza di comunicare in modo trasparente tali decisioni al pubblico. Nel **Capitolo 2.1** abbiamo utilizzato il caso degli inibitori di pompa protonica (IPP) per il trattamento del reflusso gastroesofageo nei bambini per verificare se farmaci non formalmente approvati per l'uso in una specifica popolazione di pazienti possano tuttavia presentare un livello di evidenza sufficiente a supportarne l'uso *off-label*. In letteratura abbiamo trovato diciannove studi clinici che testavano omeprazolo, esomeprazolo, lansoprazolo, rabeprazolo e pantoprazolo nei bambini. Al tempo della nostra analisi, di questi cinque IPP solo l'omeprazolo aveva un'indicazione pediatrica nell'Unione Europea (in particolare, per bambini di età uguale o superiore ai 2 anni). Lo scenario negli Stati Uniti era differente: tre dei cinque principi attivi (omeprazolo, esomeprazolo e lansoprazolo) erano autorizzati per uso pediatrico. Sulla base del consistente livello di evidenza trovato in letteratura, abbiamo valutato l'utilizzo *off-label* di omeprazolo, esomeprazolo e lansoprazolo nei bambini come "molto appropriato". Abbiamo invece assegnato un livello di appropriatezza "moderato" all'utilizzo *off-label* del pantoprazolo nei bambini, per la mancanza di dati sulla farmacocinetica e lo scarso numero di studi clinici disponibili. Sulla base della mancanza di un'adeguata evidenza scientifica a supporto dell'utilizzo di rabeprazolo nella popolazione pediatrica, abbiamo invece giudicato il suo uso *off-label* come scarsamente appropriato nei bambini. Abbiamo pertanto concluso che condurre studi clinici aggiuntivi nei bambini può non essere sempre necessario e che tradurre l'evidenza clinica in decisioni regolatorie può essere un'utile strategia per minimizzare il peso dei requisiti regolatori, evitare la replicazione degli studi clinici e ridurre la distanza tra i requisiti regolatori e le esigenze cliniche, favorendo un più rapido accesso ai farmaci da parte dei pazienti.

Dopo aver affrontato la questione del livello di evidenza necessario per le decisioni a livello regolatorio, abbiamo analizzato i casi in cui l'evidenza è, al contrario, considerata insufficiente (**Capitolo 2.3**). L'analisi delle domande di autorizzazione in commercio ritirate dalle aziende farmaceutiche stesse prima della conclusione del processo valutativo o che avevano ricevuto parere negativo dall'autorità regolatoria è importante proprio per chiarire quali possono essere i problemi nel passaggio dal banco di laboratorio al letto del malato e cosa può essere fatto per ridurre il rischio di un decisioni negativa. Sulla base delle relazioni pubblicate dall'Agenzia Europea per i Farmaci (European Medicines Agency, EMA) sui dossier valutati, abbiamo identificato un totale di 86 domande che erano state ritirate dalle aziende (70 di 86) o che avevano ricevuto parere negativo dall'EMA (16 di 86). Le ragioni che avevano portato ad un ritiro o ad una opinione negativa erano legate a problemi relativi alla qualità, alla sicurezza e all'efficacia, a volte ad una combinazione dei tre. In totale, sono state sollevate dal "Comitato per i Medicinali per Uso Umano" (Committee for Medicinal Products for Human Use, CHMP) 156 obiezioni relative alle qualità, alla sicurezza ed all'efficacia: in particolare, 106 obiezioni erano dovute a problematiche relative all'efficacia, 27 alla sicurezza e 23 a problemi di qualità. Nell'ambito delle obiezioni maggiori relative all'ef-

ficacia, abbiamo identificato cinque categorie: i) mancanza di rilevanza clinica (44 di 106, 41.5%), ii) problemi legati alla metodologia clinica (23 di 106, 21.6%), iii) problemi legati alla farmacocinetica, inclusi quelli di bioequivalenza (20 di 106, 18.8%), iv) mancanza di significatività statistica (13 casi, 12.2%), v) problemi relativi alle Norme di Buona Pratica Clinica (5 di 106, 4.7%). La mancanza di rilevanza clinica è stata la più frequente tra tutte le obiezioni sollevate dall'EMA e rappresentava circa il 50% di tutte le obiezioni relative all'efficacia. Abbiamo, inoltre, interrogato altre autorità regolatorie nel mondo per verificare se avessero applicato misure di trasparenza simili a quelle dell'EMA. Il risultato è stato che oltre all'Europa, solo l'Australia sembra avere un sistema simile.
In conclusione, la nostra analisi sui motivi per i quali le domande delle aziende falliscono l'obiettivo dell'autorizzazione al commercio ha rivelato che l'efficacia rappresenta il principale elemento predittivo per il successo o il fallimento di una domanda. I fattori determinanti di un'opinione positiva da parte del CHMP sembrano essere studi clinici ben strutturati, con un programma clinico che includa una popolazione di pazienti consistente con l'indicazione terapeutica richiesta.

Tutte le analisi presentate nel **Capitolo 3** sono relative all'area dell'oncologia. I nuovi farmaci antitumorali raggiungono il mercato con un livello di evidenza ancora incompleto e ciò ha inevitabilmente complicato il processo decisionale a livello regolatorio. L'analisi di passate decisioni regolatorie dimostra che il livello di incertezza ritenuto accettabile varia a seconda delle indicazioni terapeutiche. I *regulators* sono generalmente più disposti ad accettare un maggiore livello di incertezza nel valutare il rapporto rischio/beneficio di farmaci per patologie gravi o prive di alternative terapeutiche come il cancro, rispetto a condizioni patologiche meno gravi o per le quali esistono già trattamenti efficaci.
In oncologia un problema estremamente controverso è quello dell'interpretazione dei risultati derivanti da studi clinici randomizzati precocemente interrotti a seguito di analisi ad interim. Le analisi ad interim pongono un dilemma etico, quello cioè di salvaguardare da un lato l'interesse del paziente arruolato negli studi e dall'altro di proteggere la società dall'attribuzione ancora prematura di un beneficio clinico. Gli studi clinici interrotti precocemente per tossicità o per futilità (cioè per mancanza di efficacia) risultano in una immediata sospensione di trattamenti dannosi o inutili. Al contrario, studi clinici interrotti precocemente per un apparente beneficio clinico possono risultare nella rapida approvazione e diffusione di nuove e promettenti terapie. La prevalenza degli studi precocemente interrotti per apparente beneficio sono in aumento, in particolare in oncologia **(Capitoli 3.1-3.2)**. Sulla base dell'analisi di 25 studi clinici oncologici, randomizzati e precocemente interrotti per beneficio apparente, abbiamo rilevato un consistente aumento (56%) di questo tipo di studi tra il 2005 ed il 2007 rispetto all'intero periodo analizzato (1997-2007). Inoltre il 79% degli studi clinici interrotti e pubblicati tra il 2005 e il 2007 erano stati usati ai fini registrativi. Ciò suggerisce la presenza di una componente com-

merciale nell'interruzione precoce degli studi clinici. Nel campione degli studi analizzati, la valutazione dell'efficacia era pianificata nel protocollo attraverso *end point* correlati al tempo, che nel 40% dei casi erano rappresentati dalla sopravvivenza globale. Complessivamente gli studi erano ben disegnati: tutti erano randomizzati, controllati, basati su *end point* robusti e con un'ampia popolazione di pazienti arruolata. Nel 95% degli studi, al momento dell'analisi ad interim, l'efficacia veniva valutata usando gli stessi *end point* che erano stati previsti per l'analisi finale. Nel 24% degli studi non era presente un Comitato di Monitoraggio dei Dati e della Sicurezza. Inoltre in 15 studi clinici randomizzati, l'analisi ad interim era stata effettuata al raggiungimento di un numero pari o maggiore del 50% del numero dei pazienti pianificato per l'analisi finale di efficacia. In cinque studi, tuttavia, l'analisi ad interim era stata condotta su un campione ≤43% del campione pianificato per l'analisi finale. Il totale del campione pianificato per tutti gli studi era pari a circa 8000 pazienti/eventi. Come conseguenza delle analisi ad interim, il numero di pazienti/eventi risparmiati era pari a circa 3300.
In conclusione, sebbene la qualità degli studi oncologici appaia migliorata rispetto al passato, il fenomeno dell'interruzione precoce solleva nuove preoccupazioni. Vi sono ancora quesiti irrisolti riguardo alla corretta interpretazione dei risultati ad interim che mettono in difficoltà i *regulators* e che hanno implicazioni per la salute del paziente.

L'incertezza relativa al profilo rischio-beneficio di nuovi farmaci al momento dell'immissione in commercio ha portato ad una graduale evoluzione del modello regolatorio verso un approccio basato sul "ciclo vitale" del prodotto. Infatti, nei casi di maggiore incertezza i *regulators* tendono a richiedere alle aziende dati aggiuntivi da produrre in una fase successiva all'autorizzazione in commercio. Pertanto lo sviluppo dei farmaci è un processo dinamico in cui la produzione di nuovi dati e di nuove conoscenze ha un impatto sull'autorizzazione alla commercializzazione. Le estensioni di indicazione terapeutica così come l'aggiornamento delle informazioni sulla sicurezza generano un *continuum* nella valutazione del rapporto rischio/beneficio. Il **Capitolo 3.3** analizza le estensioni di indicazione oncologiche approvate dall'EMA, analizzando il tempo necessario affinché i farmaci antitumorali ottengano una estensione, i tassi e le caratteristiche delle estensioni approvate ed il processo regolatorio che porta alla definizione delle nuove indicazioni.
Sono stati estratti dati relativi ad un totale di 103 indicazioni terapeutiche oncologiche, approvate nel periodo tra il 1995 ed il 2008, da una coorte di 43 farmaci antitumorali. Il tempo mediano che intercorreva tra diverse indicazioni per lo stesso principio attivo è risultato diminuito da circa 81 mesi nel 1996 a 6 mesi nel 2006. Ciò riflette uno sviluppo clinico più breve, ridotti ritardi a livello regolatorio ed una disponibilità dei nuovi trattamenti più rapida per i pazienti.
E' interessante notare che al tempo dell'analisi, 24 dei 43 antitumorali approvati (circa il 56%) avevano un'unica indicazione terapeutica. Mettendo a confronto due differenti

coorti di farmaci in relazione al tempo di approvazione (1995-2004 rispetto a 2005-2008) la coorte più vecchia tendeva ad avere una probabilità minore di avere estensioni rispetto alla coorte più recente (OR=0.27; Intervallo di Confidenza 95%: 0.07-1.04), sebbene in modo non statisticamente significativo. Relativamente al tipo di estensione, su un totale di 60 estensioni, nel 48% dei casi l'indicazione inizialmente approvata era stata estesa per coprire il trattamento di un tumore di tipo differente, mentre nel 37% dei casi l'estensione consisteva in un passaggio di linea all'interno della stessa indicazione terapeutica. Gli altri due casi di estensione riguardavano un diverso stadio del tumore (8%) e l'inclusione di una nuova popolazione di pazienti (7%).
Al fine di analizzare le dinamiche che si verificano durante il processo di valutazione di una richiesta di estensione, abbiamo confrontato le indicazioni inizialmente richieste dalle ditte rispetto a quelle approvate dal CHMP dell'EMA al termine del processo valutativo. Solo per 50 delle 103 indicazioni che costituivano il nostro campione abbiamo ricavato un'informazione chiara sull' indicazione inizialmente richiesta dalla ditta farmaceutica. L'analisi delle restrizioni delle indicazioni terapeutiche ha mostrato che in 20 casi su 50 (40%) le indicazioni erano state ristrette dal CHMP durante la fase di valutazione, con il verificarsi del 60% delle restrizioni tra il 2006 e il 2007. Si fa presente che nel periodo 2006-2007, quando le restrizioni raggiungevano un picco, vi era un evidente declino del tempo necessario ad ottenere una nuova estensione. Questo fa ipotizzare una relazione tra un più rapido sviluppo clinico e la possibilità di ricevere una restrizione da parte dell'autorità regolatoria.
Questo studio aggiunge pertanto tre principali informazioni: (i) la maggioranza degli antitumorali presenta ancora un'unica indicazione terapeutica indipendentemente dall'anno dell'iniziale approvazione del farmaco; (ii) il tempo necessario ad ottenere una estensione di indicazione è diminuito significativamente negli ultimi dieci anni e (iii) un più alto tasso di restrizioni delle indicazioni da parte dell'EMA è associato ad un più rapido sviluppo clinico.

Generalmente, la definizione di una nuova indicazione terapeutica è un passaggio critico in ambito regolatorio. La scelta delle parole contenute nelle indicazioni può avere un enorme impatto sulla pratica clinica, determinando l'inclusione o l'esclusione di determinate popolazioni di pazienti. Nel **Capitolo 3.4** la nostra ricerca ha dimostrato che agenzie come l'EMA e l'FDA, sulla base degli stessi dati, possono prendere decisioni diverse riguardo alla definizione dell'indicazione terapeutica. Ad esempio, un'agenzia può essere maggiormente restrittiva rispetto all'altra nell'elaborazione di una nuova indicazione, limitando l'uso del farmaco unicamente ad una specifica popolazione di pazienti. Complessivamente, i farmaci antitumorali approvati dall'EMA tra il 1995 e il 2008 erano 42, corrispondenti ad un totale di 100 indicazioni. In 47 di queste 100 indicazioni, è stata rilevata una differenza tra EMA ed FDA. Per 19 di tali 47 indicazioni, la differenza

consisteva nel fatto che solo una delle due agenzie aveva approvato una determinata indicazione. In particolare, tre indicazioni approvate dall'FDA non erano state approvate dall'EMA, mentre 16 indicazioni approvate dall'EMA non erano state approvate dall'FDA. Per le restanti 28 delle 47 indicazioni per le quali era stata trovata una differenza tra corrispondenti indicazioni EMA-FDA, ulteriori analisi hanno dimostrato che nessuna delle due agenzie aveva un comportamento più restrittivo rispetto all'altra (di 28 indicazioni, FDA era risultata più restrittiva in 13 mentre l'EMA in 15).

Le 28 indicazioni per le quali vi era una differenza nella scelta delle parole contenute nell'indicazione terapeutica sono state valutate mediante un algoritmo. Ciò ha evidenziato la presenza di 10 casi in cui la differenza tra le indicazioni EMA-FDA è clinicamente rilevante. Si fa inoltre notare che la maggioranza delle indicazioni (69%) erano state approvate prima dall'FDA, nonostante vi sia una tendenza dell'EMA ad approvare sempre più per prima le indicazioni. Nonostante numeri limitati non consentano elaborazioni statistiche, abbiamo rilevato che l'agenzia che approva per seconda un'indicazione, lo fa in modo più restrittivo rispetto all'agenzia che l'ha approvata per prima. E' inoltre importante sottolineare che in 57 delle 100 indicazioni analizzate, l'EMA e l'FDA hanno basato l'approvazione sugli stessi studi clinici principali.

In conclusione, il nostro studio ha dimostrato differenze clinicamente rilevanti nel risultato finale del processo di approvazione di farmaci oncologici tra EMA ed FDA, nonostante non si possa concludere che una delle due agenzie produca risultati migliori dell'altra, né che una delle due abbia un atteggiamento maggiormente restrittivo rispetto all'altra. L'FDA approva per prima le nuove indicazioni oncologiche, ma le due agenzie tendono a convergere sempre più nelle tempistiche.

Non avendo questa ricerca individuato chiari fattori predittivi delle decisioni a livello regolatorio che spiegassero questa eterogeneità, abbiamo analizzato il processo decisionale per i farmaci antitumorali nelle due agenzie tramite uno studio qualitativo che utilizzava interviste semi-strutturate con *regulators* dell'EMA e dell'FDA **(Capitolo 3.5)**. Tale ricerca era basata sull'ipotesi che il processo che porta ad una decisione in ambito regolatorio è guidato sia da fattori correlati ai dati presenti nel dossier registrativo, i cosiddetti fattori "formali", che da fattori da essi indipendenti, definiti fattori "informali". Infatti, abbiamo assunto che nel corso della valutazione di un dossier, la valutazione dei dati sia mediata anche da fattori informali come l'interazione con attori esterni (quali, per esempio, l'industria farmaceutica, i pazienti o altre agenzie regolatorie) e influenzata da aspetti socio-culturali e comportamentali propri del valutatore e dell'agenzia di appartenenza. I nostri risultati hanno dimostrato che l'armonizzazione in atto tra EMA ed FDA ha sicuramente incoraggiato uno scambio di informazioni tra le due agenzie ma non uno scambio di opinioni, lasciandole pertanto molto distanti l'una dall'altra, soprattutto a causa di differenze organizzative.

Il messaggio principale dei valutatori intervistati è stato che l'EMA e l'FDA gestiscono l'incertezza in modo diverso. Secondo gli intervistati, infatti, l'FDA è più aperta al rischio e tende a basare l'approvazione di nuovi farmaci antitumorali su dati meno robusti pur di garantire un accesso più rapido da parte dei pazienti, sebbene però il sistema regolatorio americano consenta il ritiro dei farmaci dal mercato più facilmente rispetto a quello europeo. Inoltre, una differente interpretazione dell'*end point* della Sopravvivenza Libera da Progressione (Progression Free Survival, PFS), vista come un beneficio clinico in quanto tale dall'EMA ma non dall'FDA, era considerata la ragione prevalente della divergenza di opinione tra le due agenzie.
Considerando il numero di fattori che contribuiscono a determinare l'eterogeneità tra EMA ed FDA, ci si chiede se è necessario tentare di minimizzare queste differenze. Tuttavia è necessario capire quali differenze contino per i pazienti perché ciò consentirà l'elaborazione di politiche di armonizzazione che ne salvaguardino realmente gli interessi.

Nel **Capitolo 4** abbiamo inserito i risultati della tesi in un contesto più ampio e abbiamo identificato potenziali spunti di ricerca in campo regolatorio. L'analisi del processo decisionale e delle politiche intraprese delle agenzie regolatorie può rappresentare una misura di come le nuove conoscenze scientifiche vengano tradotte in requisiti regolatori e di quanto l'attuale sistema regolatorio promuova realmente l'innovazione scientifica nei diversi stadi dello sviluppo dei farmaci. Ricerche future nel campo delle scienze regolatorie non dovranno però limitarsi ad analizzare le azioni di una singola agenzia o al confronto tra diverse agenzie. Esse dovranno infatti analizzare il reale impatto delle politiche regolatorie sulla salute del paziente.
Inoltre, la crescente importanza dell'Health Technology Assessment (HTA) sull'accesso al mercato di nuovi farmaci offre interessanti spunti di ricerca, specialmente a livello dell'Unione Europea, dove è in atto un tentativo di allineare i requisiti dell'EMA con quelli delle autorità responsabili della decisioni sulla rimborsabilità negli Stati Membri. Sarà interessante analizzare gli effetti di iniziative di questo tipo (come le procedure di *scientific advice* effettuate in parallelo tra EMA e le autorità di HTA) ed il loro reale impatto sull'accesso ai farmaci.
Infine, le scienze regolatorie dovranno concentrarsi sul ruolo del paziente in costante evoluzione.
Se da un lato il coinvolgimento e la partecipazione di rappresentanti della società civile è formalmente riconosciuto come un elemento di crescente importanza per le autorità regolatorie, dall'altro resta da capire se i pazienti rappresenteranno realmente un valore aggiunto nelle considerazioni sul rapporto rischio/beneficio e come il loro punto di vista verrà integrato nelle decisioni regolatorie.
In generale, nei prossimi anni la ricerca in campo regolatorio sarà facilitata dal crescente livello di trasparenza e apertura, che stimolerà un migliore accesso alle informazioni sul processo decisionale per la valutazione dei farmaci.

Acknowledgments
List of co-authors
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