GLOBALLY APPLICABLE FACILITATED REGULATORY PATHWAYS TO IMPROVE EQUITABLE ACCESS TO MEDICINES

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The research presented in this PhD thesis was conducted under the umbrella of the Utrecht-World Health Organization (WHO) Collaborating Centre for Pharmaceutical Policy and Regulation (http://www.pharmaceuticalpolicy.nl/), which is based at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, The Netherlands and in collaboration with the Centre for Innovation in Regulatory Science (CIRS)(www.cirsci.org), London, UK. The WHO Collaborating Centre aims to develop new methods for independent pharmaceutical policy research, evidence-based policy analysis and conceptual innovation in the area of policy making and evaluation in general. CIRS is a neutral, independent organisation conducting novel research, convening international forums for healthcare stakeholders and providing science-based insights to advance global regulatory and HTA policies and enhance patient access to medicines.

Globally applicable facilitated regulatory pathways to improve equitable access to medicines
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Breed toepasbare en gefaciliteerde regulatoire routes om de rechtvaardige toegang tot geneesmiddelen te verbeteren (met een samenvatting in het Nederlands)

Proefschrift

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chapter 1

GENERAL INTRODUCTION

Equitable access to medicines is a right of all patients. Patients may have great expectations of rapid and efficient regulatory processes and in response, regulators have sought ways to accelerate access to safe and effective innovative new medicines. However, the use of expedited regulatory reviews and authorisations should not be limited to those jurisdictions where the initial assessments can benefit from a formalised accelerated pathway. Rather, even countries with limited regulatory infrastructure should be able to benefit from the implementation of an accelerated regulatory pathway designed to maximise the efficient use of the health agency's resources; these pathways must ensure that a benefit-risk decision appropriate to the local population supports the timely availability of quality safe and effective medicines.

We characterise these various expedited pathways as facilitated regulatory pathways (FRPs): regulatory pathways designed to accelerate product development, the submission of market authorisation applications and regulatory reviews. The goal of FRPs is to speed the assessment of new medicines with a positive benefit-risk balance, often for serious diseases or where there is an unmet medical need. But FRPs may be applicable to a broader group of products, including the assessment of generics, biologics and vaccines among others. FRPs may increase the level of communication and commitment between the sponsor and the regulatory agency, can give a larger role to medicines' effects on surrogate endpoints and may move some of the burden of clinical benefit and safety evidence generation from the pre- to the post-authorisation phase. Importantly, some FRPs are designed to encourage reliance on or recognition of prior decisions made by reference authorities, thereby reducing regulatory duplication and the burden of review.

In spite of the on-going trend towards global regulatory convergence, no internationally relevant guidelines or best practices have been promulgated that describe the elements or conditions needed to implement an accelerated regulatory review pathway. The diversity of FRPs found across high-, middle- and low-income countries creates confusion across stakeholders, with uncertainty about the accelerated review requirements and processes across jurisdictions; this results in patients questioning the timing or divergences in access to important medicines. No single FRP can address the most appropriate route for the accelerated review of all medicines.

Therefore, we conducted this research to identify and characterise the key building blocks that provide context and support for the efficient use of FRPs. We hypothesised that through the methodical assessment of four key themes (stakeholder support and the regulatory environment; processes that contribute to predictability in regulatory decision making; use and interpretation of evidence associated with regulatory outcomes; post-authorisation assessments) we would be able to characterise a globally applicable pragmatic framework for the use of a diverse set of currently

available FRPs. Herein we present our observations, based on these building blocks, that support our proposal for a globally applicable approach to using FRPs.

This thesis, which is focused on the constituent elements required to develop a pragmatic approach to implementing FRPs, builds on a body of prior work that has laid the groundwork for our research. Investigations into the effective use of FRPs such as conditional marketing authorisations by the EMA [1] and the breakthrough therapy designation at FDA [2] indicated that there was a steady move towards stakeholder support for these processes and the likely appropriate regulatory environment for FRPs. However, the benefits of accelerated approvals were questioned by some [3] and opened expedited approaches to further scrutiny about the predictability of the safety and efficacy of products approved by these routes [4,5]. But others observed that FRPs, such as those used by the FDA, provided flexible pathways for the accelerated assessment of medicines while assuring the quality, safety and efficacy of the products even through the post-authorisation period [6]. Therefore, we sought to further investigate the environment that can best promote the use of FRPs.

As the use of priority approval pathways in the US and EU increased, there was a growing concern that a lack of aligned requirements and processes might contribute to divergent decisions across jurisdictions [7]. We agree that having processes that contribute to predictability in regulatory decision making are key to the success of FRPs. Therefore, we investigated the ways in which good review practices and decision frameworks prepare an agency to undertake a review, including those undertaken through an FRP.

How medicine regulators interpret scientific evidence to arrive at their outcomes is a key facet of regulatory predictability and an important building block for FRPs. Factors influencing approvals and non-approvals of new drugs by the EMA were investigated by Putzeist et al [8] and provided the seed for work we conducted to identify factors that have been associated with positive and negative regulatory outcomes. Because a variety of non-data-dependent factors had been found to influence regulatory outcomes [9,10] we explored these in more detail, paying particular attention not only to the data-dependent factors that regulators must weigh, but also to the less studied compensatory "social factors" that can influence a regulatory decision. We postulated that these factors play key roles in decisions made about products using FRPs.

Questions were also being raised about whether there were adequate post-authorisation assessment processes in place to better define the benefits and risk of products that had been approved by expedited pathways [11,12]. We recognised that as a fourth building block toward an FRP framework we would need to better understand how post-authorisation activities contributed to the profiles of products approved by FRPs.

We believe that the work conducted by earlier investigators have helped to lay the groundwork for our building blocks, allowing us to consolidate early findings with our new observations into the proposed pragmatic framework for the use of FRPs. We trust that our work can serve as the basis for internationally aligned recommendations or policies to streamline medicines reviews and improve equitable access to medicines.

WHY IS THERE A NEED FOR SPEEDIER REGULATORY ROUTES?

Global initiatives are supporting a growing portfolio of products for neglected diseases at a time when emerging national regulatory agencies (NRAs) and the World Health Organization (WHO) are expanding their commitment to ensure new treatments will be widely and readily available. All NRAs have come under pressure because of a growing workload complicated by the advent of new, complex therapeutic options. Nevertheless, opportunities exist for improving public health and stimulating innovation in medicines development through the availability of a common accelerated approach to medicine regulation.

Implementing an accelerated review and authorisation pathway that is fit-for-purpose and aligned with the mission and capabilities of an NRA can benefit the country's healthcare system in several ways. Regulators can implement time- and cost-efficient systems that address only the elements that ensure a defensible decision about the quality, safety and efficacy of a product without duplicating assessments previously conducted by others. Pharmaceutical sponsors can provide the data required for the relevant form of review based on transparent guidelines and clear expectations. Importantly, patients can be assured of timely assessments of quality medicines. These incentives have resulted in the development of numerous country- and region-specific pathways to expedite regulatory reviews.

When considered holistically, these approaches provide numerous options for FRP routes to be pursued by a sponsor and agency. Deciding which route is best suited for a particular agency requires guidance offered through a framework process. The WHO Good Regulatory Practice guidance [13] recognises that transparent guidelines facilitate formal and informal work sharing and cooperation among agencies. While not FRP-specific, groups such as the ICH Global Cooperation Group (GCG) and the International Conference of Drug Regulatory Authorities (ICDRA) provide opportunities for sharing regulatory best practices and serve as a platform for aligning activities, such as the use of FRPs.

ACCELERATED REVIEW PATHWAYS IN SRAS

Formalised FRPs have been in place in stringent regulatory authorities (SRAs) for many years (*SRA* is a term used by the World Health Organization, but these agencies are

alternatively referred to as a *Well-Resourced Authority*, S*trong Regulatory Authority*, *Mature Regulatory Authority*, or C*ompetent Regulatory Authority*, among others).

At the US FDA, following the introduction of the Fast Track (FT) designation in 1997, three additional FRP programme options were implemented: the Accelerated Approval pathway (AA) and Priority Review designation (PR) and most recently the Breakthrough Therapy designation (BTD). FT and BTD were designed to encourage early interactions between the sponsor and the agency while PR and AA were applied to accelerate the review process. The use of these FRPs has been expanding in SRAs; in 2016, 73% of products approved by the FDA benefitted from the use of at least one FRP [14].

Similarly, the European Medicines Agency (EMA) implemented the Marketing Authorisation under Exceptional Circumstances and Conditional Marketing Authorisation programmes to accelerate assessments. More recently (2016), the Priority Medicines (PRIME) programme was created to enhance interactions between the sponsor and agency with the goal of making the development process more efficient and reducing regulatory burden during the review. Other SRAs have also introduced or implemented FRPs, including Priority Review and the Sakigake route at the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and Priority Reviews at Health Canada. To provide its regulatory agency with more flexibility to conduct accelerated reviews, recent legislative initiatives in Australia have resulted in the development of novel Priority Review and Provisional Approval pathways [15]. The use of FRPs is not limited to SRAs but as we explored, are being used in approximately 30 countries.

ACCELERATED REVIEW PATHWAYS ACROSS JURISDICTIONS

FRPs fall into two distinct categories. *Primary* FRPs are those used by an SRA to speed the development, review and initial approval of a product; these are often described by terms such as *expedited*, *accelerated authorisation*, *priority review*, and *conditional authorisation*, among others [16]. *Secondary* FRPs (those used by NRAs or regional regulatory initiatives [RRIs]) are those wherein regulatory decisions can be expedited by the reliance on or recognition of prior reviews.

Even those agencies that offer some form of primary FRP could benefit from the availability of multiple flexible pathways. Reliance- or recognition-based secondary FRP approaches are now being considered by many authorities to minimise duplicative effort and optimise resource use. The benefit of international cooperation, in all its forms, has long been recognized [13]. Secondary FRPs benefit from their ability to rely on or recognise a SRA or regional reference agency decision. Therefore, the importance of reliance and recognition-based FRPs has increased especially for emerging NRAs. *Reliance* is the act whereby the NRA in one jurisdiction may take into account and give significant weight to (i.e., totally or partially rely upon) evaluations

performed by another NRA in reaching its own decision. Work sharing involving joint assessments of marketing applications could be considered a form of reliance where the assessments of the components assigned to each party are combined into a single assessment report. A reliance arrangement could be either unilateral or bilateral, and it could be used as a stepping stone to greater reliance on, or recognition of, the other NRA [13].

Recognition of another agency's decisions is a more complex and advanced cooperative arrangement. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. It allows the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition may be unilateral or multilateral, and may be the subject of a mutual recognition agreement. Recognition examples include inspections reports, evaluation reports and lot release certificates. At its most advanced, an NRA or RRI may recognise the approved marketing authorisation of another agency without additional assessment [13].

As the goal of this thesis, we have developed a 4-step pragmatic approach to a framework designed to help agencies determine how best to address the use of FRPs. Each of the four steps in our proposed framework is based on characteristics identified through research, surveys, literature assessments, regulatory capacity categorisation analyses and practical experience, documented within the chapters of this thesis. Step 1 assesses four domains of the environment preparedness, Step 2 offers process criteria that should be in place to effectively use an FRP, Step 3 tiers agencies through a self-assessment of readiness and capacity, and Step 4 provides a pathway for agencies to determine the most relevant FRP for their use. This framework represents the first endeavour to holistically address the multifaceted aspects that should be considered for the effective use of an FRP.

Our proposed framework builds on reliance on prior regulatory decisions to inform a local recommendation through the use of a risk-stratification process. When considering the review of a dossier, an agency must clearly define how its activity adds value, especially when prior reviews have been conducted with positive recommendations by SRAs or reference agencies. To address this issue, a risk-stratification approach has been implemented by many agencies. However, there is no common or single approach to this stratification process. More appropriately referred to as *benefit-harms-uncertainty stratification,* a product can be risk-stratified by a variety of factors: the risk to the population by not making the product available while an unmet medical need exists; its expected benefit-risk profile; the uncertainty around the nature and results of the supportive evidence; the trust level in agencies that have conducted prior assessments, and the strengths and limitations of relying on that decision.

Where the agency has the capability and capacity, it can undertake a full independent dossier review; it can conduct a standard review or an accelerated review

using a primary FRP. Based on the assessment of the risks noted above, an agency can determine the best use of two categories of secondary FRP routes: *verification* or *abridged*. These routes are characterised by the extent to which the agency relies on prior decisions, the details available for the review, and timing of the review process. By using verification or abridged FRPs, an agency can ensure the quality, safety and efficacy of their products while relying on reviews and assessments previously conducted by reference authorities. Our framework proposes guidelines for appropriate conditions for the use of primary and secondary FRPs. This approach provides regulatory flexibility, the ability to allocate resources to key dossier reviews, the jurisdictional sovereignty to reach a locally relevant benefit-risk decision and the ability to speed the review of important new medicines.

By addressing reliance and recognition in the context of tiered capabilities and processes, the research presented herein provides agencies with a pragmatic framework for the efficient use of reviewer resources while addressing their legal mandates to ensure quality, safe and effective medicines in a timely manner for their constituents. The framework offers process transparency to address the needs of sponsors and suggests timelines that address the practical considerations of sponsors and agencies and the expectations of patients.

THESIS OUTLINE AND PREVIEW

This thesis contains eight studies organised into four sections that reflect the four blocks upon which the proposed FRP framework described in **Chapter 6.1** is constructed (Figure 1). Each of the chapters represents a building block used to support the development of the proposed pragmatic framework for FRPs.

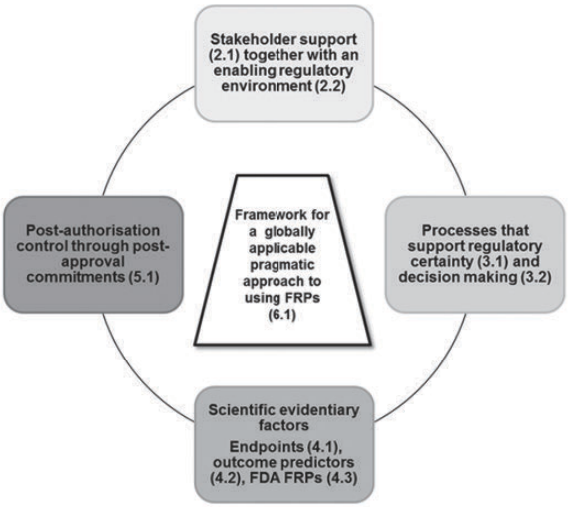

Figure 1. How the thesis chapters form the building blocks of the proposed FRP framework

Chapter 2 focuses on describing the stakeholder support and regulatory environment needed to be in place for FRPs to be used effectively. Despite the growing interest in accelerated pathways, no research had assessed stakeholder perceptions of currently available FRPs and for the potentially transformative *adaptive licensing* pathways (these latter are not addressed in this thesis). Therefore, we conducted a study to characterise stakeholder impressions of these pathways, to understand opinions about the key elements, to recognise the barriers to implementing these pathways and to seek recommendations for overcoming these challenges (Chapter 2.1). Unlike FRPs being used or piloted by SRAs, no one had systematically reviewed and assessed formal FRPs implemented by emerging NRAs. Therefore, to understand the diversities and similarities, we undertook a descriptive study of FRPs used by more than two dozen emerging NRAs (Chapter 2.2). Characteristics of FRPs used around the world were compared. We felt that this research would help inform our development of characteristics for a globally applicable approach to FRPs; could help standardise approaches to accelerated medicine reviews; and would provide international organisations with evidence to help focus their regulatory strategies to increase capacity within emerging NRAs.

In order to use a regulatory pathway efficiently, companies must address the requirements in the context of a global development programme and this is the focus of Chapter 3. In Chapter 3.1 we assess approaches to global development and simultaneous submissions, including the use of enhanced clinical design and the use of tools such as biomarkers and appropriate endpoints. These concepts are evolving rapidly and may result in greater predictability in the pharmaceutical development process and improved targeted therapies with better benefit-risk profiles resulting in the minimisation of divergent regulatory outcomes. The use of standardised benefit-risk assessment tools, the use of validated endpoints and patient-focused outcomes, and the mitigation of cultural differences in the development and review process are approaches companies can take to implement best practices that support efficient and transparent regulatory decision making, especially when using an FRP. In Chapter 3.2, we explored these concepts further to make recommendations as to how good review practices can facilitate transparent, timely, procedurally predictable and good-quality evaluations of new medicines. Training in the use of decision tools was found to be key and quality decisions were best made with the input of diverse stakeholders (e.g., the sponsor, healthcare professionals, patients and regulators).

FRPs are often used to assess important medicines where there is an unmet medical need. In these cases, the experiential data set may be smaller or more time-limited than observed with a product undergoing a standard review. Consequently, in Chapter 4 we sought to understand how the use and interpretation of evidence was associated with regulatory outcomes in these special cases and to extrapolate these observations to decision making in support of FRPs. In Chapter 4.1 we explored the association of three key endpoint properties (type of endpoint [hard/

surrogate], magnitude of an endpoint outcome and its statistical significance) with oncology product authorisation outcomes to determine the extent to which these were associated with a positive or negative regulatory outcome at the EMA. These observations led to the broader question of whether there were specific factors that were associated with positive or negative regulatory outcomes. Based on a comprehensive literature survey, in **Chapter 4.2** we identified four "Factor Clusters": evidentiary support; product or indication characteristics; company experience or strategy; social and regulatory factors. We observed a heterogeneous mix of technical factors (e.g., study designs, clinical evidence of efficacy) and less studied "social" factors (e.g., company-regulator interactions); we confirmed factors known to be of relevance to drug approval decisions (imperative) and a cohort of less understood (compensatory) social factors. Our observations illustrated the multifactorial nature of regulatory decision making and that factors need to be considered holistically while having varying, context-dependent importance for both development and regulatory outcomes. Tied to whether understanding such factors could add predictability to the development and regulatory review processes was the question of the extent to which FRPs actually influenced these activities. Therefore, in **Chapter 4.3** we focused on a cohort of products that had been approved by the FDA through specific FRPs and compared their development and regulatory review times to products that used the standard route. Our findings not only confirmed shortened development and review times for certain FRPs and combinations but also provided the information needed to create a novel "metro map" approach to illustrating FRP pathways.

Because a more rapid decision made using an FRP may seek to more fully understand the product's benefit-risk profile by shifting the burden of evidence collection to the post-authorisation period, in **Chapter 5** we present a preliminary assessment of the types of post-approval commitments sought by the FDA for products that have recently been approved through an FRP.

As regulatory agencies are coming under increased pressure to rapidly review medicines of critical importance to facilitate equitable access, the benefits of using expedited review pathways as alternatives to standard dossier reviews are being explored by many countries around the world. Despite availability of several FRP options, there is no formal guideline or consensus for the definition, basic elements or best practices associated with FRPs. Therefore, in **Chapter 6** we integrate the findings from the previous chapters and present a 4-step pragmatic framework approach designed to help agencies of all maturity levels determine how best to address the use of FRPs. Step 1 assesses four domains of the environment preparedness, Step 2 offers process criteria that should be in place to effectively use an FRP, Step 3 tiers agencies through a self-assessment of readiness and capacity, and Step 4 provides a pathway for agencies to determine the most relevant FRP for their use.

This framework represents the first endeavour to holistically address the multifaceted aspects that should be considered for the effective use of an FRP through the integration of all of the elements explored in this thesis.

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chapter 2

CREATING THE SUPPORTIVE REGULATORY ENVIRONMENT

chapter 2.1

ADAPTIVE LICENSING AND FACILITATED REGULATORY PATHWAYS: A SURVEY OF STAKEHOLDER PERCEPTIONS

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BACKGROUND

Timely access to safe and effective new medicines of societal value is a goal of medicine developers, regulators and payers. However, medicine development remains a costly and time-consuming activity with median development times of 9.9 years for new molecular entities in 2013 [1].

Flexible approaches have been formalised in several mature jurisdictions, providing options to accelerate the regulatory review process, particularly in response to unmet medical needs. Baird and colleagues [2] described 13 accelerated access pathways being adopted or investigated by key agencies. We characterise these approaches as Facilitated Regulatory Pathways (FRPs): regulatory pathways designed to accelerate submission, review and approval of medicines where there is an unmet medical need by providing alternatives to standard regulatory review routes. FRPs may increase the communication and level of commitment between the developer and agency, can give a larger role to effects on surrogate end points, and may move the burden of evidence generation to the post-authorisation phase. In general, FRPs emphasise particular approaches to accelerate the process: regulators working (early) with applicants to improve trial designs, surrogate and end point selection; facilitating the ability of regulators to make a decision based on an expedited assessment of preliminary clinical data or surrogate end points; improving the processes that speed the review on a comprehensive Phase 3 data set.

In 2010, the Athenaeum Group proposed a simple, flexible blueprint that could deliver the evidence for both regulatory review and value assessment [3]. Since then, attention has focused on transformative access pathways that address diverse stakeholder input from the earliest stages of development, align regulatory and HTA/reimbursement requirements and ensure appropriate use of innovative medicines, thus explicitly connecting all components and stakeholders in the development chain. A term used for this approach is Adaptive Licensing (AL), described as a prospectively planned, flexible approach to regulation. Through iterative phases of evidence gathering to reduce uncertainties following initial regulatory evaluation and licensing, AL seeks to balance timely access with the need to provide adequate evolving information on benefits and harms so that better informed patient-care decisions can be made [4]. By comparison, current FRPs have not been designed to strategically address aligned stakeholder needs, nor do they typically require periodic post-authorisation re-approvals.

Although there is diversity in terminology – adaptive licensing, medicines adaptive pathways to patients (MAPPs), staggered approval, etc. [5] – these share certain commonalities. The explicit involvement of all stakeholders and the iterative nature of the licensing process are, together, hallmarks of AL compared with current FRPs. However, as FRPs evolve to incorporate elements of AL (e.g., multistakeholder

involvement, periodic reassessment, risk management strategies, post-authorisation assessments), FRPs may evolve into de facto AL pathways.

Despite this growing interest, no research has assessed stakeholder perception of currently available FRPs and potential AL pathways. Therefore, this study was undertaken to characterise stakeholder impressions of these pathways, to understand opinions about the key elements of AL pathways, to recognise the barriers to implementing these pathways, and to seek recommendations for overcoming these challenges.

SURVEY APPROACH

We developed and piloted a survey among six potential responders and feedback was used to finalise the survey. Participants were randomly selected from the Centre for Innovation for Regulatory Science contact database of senior management contacts at international pharmaceutical companies and regulatory and HTA agencies, patient advocacy organisations and academia. Random selection provided a mix of geography, affiliations and expertise. Invitations were sent during August and September 2014 to 252 individuals representing 90 organisations.

The survey consisted of statements relating to the respondents' current understanding of FRPs and AL pathways as well as their perception of strengths and limitations. The survey was organised in two sections: FRPs (subsections regarding the usefulness of FRPs in streamlining medicines development, regulatory approvals and market access) and AL pathways (subsections regarding AL characteristics, stakeholder support and the environment for implementation; patient and prescriber perceptions of products approved by AL pathways, challenges to and benefits of AL implementation). Questions were answered by ranking importance of statements or by using scaled ratings; a free text comment section was provided. Respondents received a basic definition of FRP and AL.

OBSERVATIONS

Fifty (56%) of invited organisations responded; 80 (32%) responses were returned (a single consolidated response was received from 8 organisations). Respondents were from 14 countries; USA (29), UK (14), Canada (7), Germany, Japan and Switzerland (5 each), Sweden (4), and Singapore (3) and two or fewer from six other countries. Respondents reflected a diversity of stakeholders; pharmaceutical company regulatory (35) and outcomes research/access (11) departments, regulatory agencies (11), HTA agencies (7), patient groups (3) and others [academics and consultants (13)].

Room for Alternative Pathways

FRPs at the FDA were generally considered fit-for-purpose (63% respondents) as were specific FDA programmes: Priority Review (54%), Accelerated Approval (50%),

Breakthrough Therapy (42%) and Fast Track (33%). In contrast, FRPs available at EMA and the Japanese PMDA were rated as fit-for-purpose by 13% and 7%, of respondents, respectively. A majority (65%) felt that companies were using FDA FRPs appropriately and this was perceived by 61% as reducing time to license. However, just 29% of respondents thought EMA FRPs reduced licensing time. This limitation was reflected in that 74% of respondents saw a need for alternative pathways at the EMA compared with 55% for the FDA. Fewer than half (42%) saw the need for alternative pathways in Japan.

Common elements of AL

Respondents selected from 21 statements and confirmed many of the key building blocks previously described for implementing AL: agreement on common evidentiary requirements supporting both regulatory and HTA decisions; stakeholder alignment to accept a balance between early access and trade-offs of uncertainties of benefits and harms; having an enabling regulatory environment (e.g., proper regulations); having well-defined product withdrawal/disengagement strategies. The vast majority (92%) agreed with the importance of having an "adult discussion" about accepting the balance between early access and trade-offs with uncertainties around potential benefits and harms to positively influence the adoption of AL pathways. The need to develop appropriate mechanisms to integrate patient voice throughout the product lifespan was seen as a high priority (81%).

These common elements support three consistent benefits of AL identified without prompts: a move toward a more pragmatic and efficient development pathway; a streamlined approach to aligning regulatory and HTA requirements; resulting in an accelerated development process that can provide earlier access to quality medicines.

Barriers to implementation

Significant obstacles to implementation were recognised (Figure 1) including a perceived reluctance of key stakeholders to make decisions based on novel clinical study designs or novel predictive end points; 29% felt this was an important barrier for companies, 58% for regulators, and 70% for HTA agencies. Only 14% of respondents agreed that sponsors, regulators and HTA/payers are collaborating effectively to define the value characteristics required of new products.

Furthermore, a perceived lack of commitment on the part of some regulatory and HTA agencies was observed as a barrier to implementing AL (Figure 2). Generally, HTA agencies were perceived as being less committed to developing and implementing AL approaches than regulatory agencies.

Facilitating AL adoption

Key factors perceived as facilitating AL adoption were working toward aligning evidentiary requirements for regulatory and HTA decisions and the initiation of

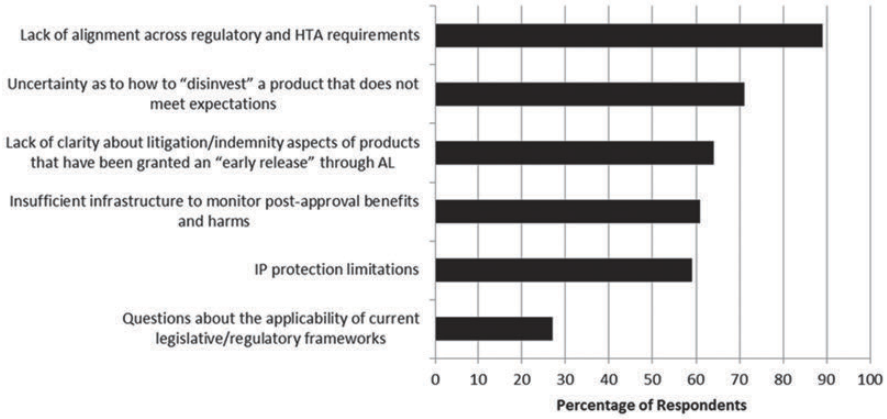

Figure 1. Percentage of agreement with specific barriers to implementation of adaptive licensing

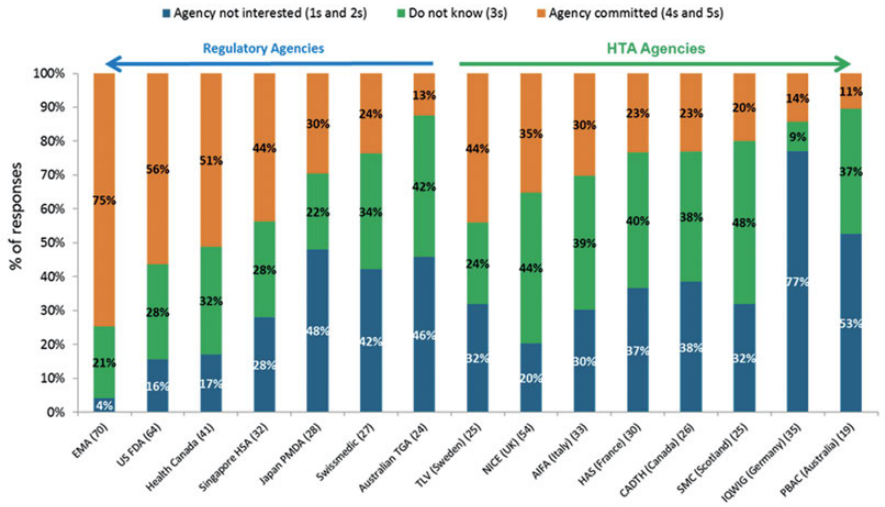

Figure 2. Respondents' ratings of how progressive and committed they believe each agency to be with regard to helping to develop and assist in the successful implementation of novel adaptive licensing pathways

HTA assessments in parallel with regulatory reviews. Many respondents believed that having a common AL approach could facilitate global development strategies. Respondents were almost equally divided as to whether AL could be used more widely for treatments for chronic and lifestyle illnesses (eg obesity, high blood pressure; 52% agreement) compared with those who felt AL should be reserved for unmet medical needs (e.g. cancer, multiple sclerosis; 42%).

Respondents held a tempered view of AL; 53% did not believe it likely that a fully implemented AL approach integrating regulatory, patient, prescriber and HTA/payer

needs with an iterative licensing process would occur in a major jurisdiction (e.g. US, EMA, Japan) within the next 5 years. By contrast, 21% felt this was an attainable goal in this time frame.

THE WAY FORWARD

These findings provide a glimpse into the diversity of opinions regarding the potential for AL to address some of the perceived limitations of current FRPs. Although key foundational AL building blocks have been identified, barriers to implementation exist.

These observations do not address current agency FRP performance or their ultimate ability to maximise benefits of their FRPs or to implement an AL pathway. Respondents were heterogeneous in their affiliations and geography; therefore, their perceptions may be largely influenced by experiences with agencies within their jurisdiction. This study did not examine the common elements of the diverse components of current FRPs used around the world, for which we are conducting a separate analysis. These observations support the need to further detail the characteristics and roles of FRPs and AL, define and build on the elements of successful FRPs, and determine optimal approaches to FRP and AL implementation.

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chapter 2.2

ACCELERATING ACCESS TO NEW MEDICINES: CURRENT STATUS OF FACILITATED REGULATORY PATHWAYS USED BY EMERGING REGULATORY AUTHORITIES

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SUMMARY

We assessed the characteristics of currently implemented expedited (facilitated) regulatory pathways (FRPs) used by national regulatory authorities (NRAs) in emerging economies to accelerate access to important new medicines. We identified NRAs with FRPs through *Cortellis Regulatory Intelligence* and agency web sites and developed a list of 27 FRP characteristics. We categorised characteristics as procedural or substantive and based them on five sequential regulatory activities. We assessed twenty-nine countries with 33 FRPs. The regions with the characteristics most extensively described by their FRPs were Middle East/North Africa and Eastern Europe while the FRPs that were least specific in described characteristics were in Sub-Saharan Africa. All FRPs addressed at least twice as many procedural as substantive characteristics reflecting the overall mix assessed.

Conclusions

We observed diversity in regional FRP characteristics suggesting a role for further engagement with emerging NRAs regarding their design and implementation. Common processes could help regulatory alignment initiatives and the WHO inform the development of novel, globally aligned accelerated development and regulatory pathways for products that fulfil serious unmet public health chllenges.

INTRODUCTION

The past 20 years have seen important new medicines for serious diseases or for unmet medical needs. Novel approaches for HIV, malaria, and cancers and recently Ebola, have highlighted the need for clear pathways for expedited regulatory review and approvals [1]. In response to the need to expedite the review of new therapies, national regulatory authorities (NRAs) around the world have implemented expedited review pathways that provide an alternative to a standard process for products that address unmet serious public health needs [2].

We characterise these expedited pathways as facilitated regulatory pathways (FRPs): regulatory pathways designed to accelerate development, submission of marketing authorizations, regulatory reviews and patient access to medicines for serious diseases where there is an unmet medical need, by providing alternatives to standard product development and regulatory review routes [3]. FRPs may increase the level of communication and commitment between the developer and the agency, can give a larger role to effects on surrogate end points, and may move some of the burden of clinical benefit and safety evidence generation from the pre- to the post-authorisation phase. The goal of FRPs is to speed the development, marketing authorisation and patient access to new drugs with a positive benefit-risk balance.

The importance of FRPs has also increased for NRAs in low- and middle-income countries (herein referred to as emerging NRAs). Global initiatives are supporting an expanding portfolio of products for neglected diseases [4] at a time when emerging NRAs and the World Health Organization (WHO) are expanding their commitment to assure new treatments will be widely and readily available. This has resulted in the development of country-specific pathways to expedite the regulatory review of new treatments for serious conditions, particularly where there is unmet medical need or where the therapy represents a significant innovation.

While the characteristics of FRPs being used or piloted by stringent regulatory authorities (SRAs; defined as a member of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ([ICH], an ICH observer or associated with an ICH member through a mutual recognition agreement) [5] have been reviewed, [6] no systematic assessment has been conducted of the characteristics of formal FRPs implemented by emerging NRAs.

Therefore, we undertook this descriptive study with the objective of assessing the characteristics of currently implemented FRPs that are used by emerging NRAs to accelerate access to important new medicines. Such an assessment is necessary to understand the diversity and similarities of these FRPs, to help with the on-going assessment and development of national regulatory systems, to help standardise approaches to accelerated medicine reviews, and to provide evidence for international organisations to help focus their strategies for increasing regulatory capacity within emerging NRAs. Furthermore, common FRP processes could help inform and speed

the development of novel, globally aligned, accelerated development and regulatory authorization pathways.

METHODS

We conducted this study between January 2015 and April 2015 and developed a list of emerging NRAs that would likely have an FRP in place, based on prior assessments of the regulatory capacity of emerging medicines regulatory systems [7-9]. The list was supplemented by a search of *Cortellis Regulatory Intelligence* (a ThomsonReuters database) using Boolean combinations of the following search terms: priority, expedited, fast track, accelerated review or approval, neglected disease, unmet medical need.

We developed a list of 27 FRP characteristics (Table 1). These were based on an assessment of characteristics of FRPs in SRAs, along with elements of FRPs identified by a perception survey, [3] and additional characteristics identified by the authors. We organised these characteristics by two groupings to determine the emphasis of characteristics addressed by the FRPs.

- As to whether the characteristics were "procedural" (rules/activities related to overall process; 18 characteristics) or "substantive" (those used to determine how the evidence supports the outcome; 9 characteristics)

- Based on 5 sequential regulatory activities: those describing ways for agencies to assist the sponsor to facilitate the submission or review (6 characteristics); criteria for the acceptance of the regulatory dossier (9 characteristics); review process attributes (4 characteristics); decision criteria (4 characteristics); post-authorisation and disengagement activities (4 characteristics)

We developed an assessment methodology to enable consistent categorisation of each characteristic addressed by each FRP. Using a standard characteristic assessment form, we assessed characteristics based on whether they were present or not (yes/no binary assessments) or using a more specific assessment scale (e.g., ordinal). Two of the authors independently assessed each characteristic; KZ conducted the first assessment, LL was the second assessor. The assessors resolved interpretive disagreements through consensus discussion.

To confirm our interpretation of the public information, we sent the characteristic assessment form for each country to contacts in the respective emerging NRA to review the author interpretations. If the NRA made changes, we asked the respondents to comment on the change. When we did not receive a response from the NRA, we sent the assessment form to a local non-governmental regulatory expert for comment. If no comments were received, initial author findings were used. Characteristics for each FRP, therefore, were those addressed within the publicly available documentation

together with those described by expert commentary. We received responses over three months.

For each characteristic, we compared the number of FRPs that addressed the characteristic to the total number of FRPs in this cohort. We then identified the most frequently observed classification assessment for each characteristic and calculated a frequency percentage using the number of FRPs that addressed the individual characteristic as the denominator. For each FRP we compared the number of characteristics addressed with the maximum possible characteristics (27) to determine the proportion of characteristics addressed per FRP. We calculated the frequency of procedural and substantive characteristics, with the median number of characteristics determined by geographic region. We hypothesised that no emerging NRAs would have all 27 characteristics addressed in its public documentation.

RESULTS

We initially identified 67 countries as having the potential to have an FRP. Further searches using *Cortellis Regulatory Intelligence* and publicly available web-based resources (e.g., agency web sites) determined that 31 of these countries did not have FRPs (false positives). Of the remaining 36 with a description of some form of FRP, only cursory descriptive information was found for 7 countries (excluded from the analysis). Therefore, 29 countries had publicly available information that provided descriptions of their FRPs.

We received responses on characteristics assessment forms from 17 countries describing 19 FRPs; we did not receive country input from 12 countries describing 14 FRPs. We therefore, assessed 33 FRPs from 29 countries.

Overall FRP Characteristics

Table 1 presents how often FRPs addressed a characteristic and the most common assessment for each characteristic. For each FRP, we summed and compared the number and distribution of characteristics addressed by country and region (Table 2).

The regions with the most addressed characteristics (median number), were Middle East/North Africa (17) and Eastern Europe (17). Sub-Saharan African FRPs had the fewest characteristics addressed by their FRP (9).

Consistent with the predominance of procedural characteristics in our categorisation scheme, all FRPs addressed at least twice as many procedural than substantive characteristics. The most commonly addressed procedural characteristics were having a standard operating procedure (SOP) or guidance for submitting the dossier (30/33; 91%) and an SOP on how the dossier will be reviewed (30/33; 91%). The most commonly addressed substantive characteristic was whether the product must be used to treat a serious condition or where there is an unmet medical need (29/33; 88%).

Table 1. Most common response values for each FRP characteristic

	Procedural or substantive	Number of FRPs describing the characteristic (% of 33 FRPs)	Description
Agency assistance	Proc	30 (91%)	A standard operating procedure or guidance for submitting the dossier and managing the submission is publicly available
	Proc	30 (91%)	An SOP for how the dossier will be reviewed by the agency is publicly available
	Proc	27 (82%)	An application or processing fee required by agency
	Proc	26 (79%)	A product that uses the FRP will benefit from opportunities for frequent interactions of the sponsor with the agency's review team
	Proc	23 (70%)	The agency has established a special team/office to handle products that are submitted via the FRP
	Proc	15 (45%)	How quickly must the agency respond to a request for a designation for an FRP?
Acceptance criteria	Subs	29 (88%)	The product that will be subject to an FRP must be used to treat a serious condition or where there is unmet medical need or demonstrates significant innovation
	Proc	29 (88%)	The FRP designation is requested or granted at the time of the NDA submission
	Proc	29 (88%)	The FRP can be used can be used for a biologic
	Proc	28 (85%)	The FRP can be used can be used for a vaccine
	Proc	27 (82%)	The FRP designation is requested or granted at the time of the IND/CTA application
	Proc	27 (82%)	The application must be filed electronically
	Proc	25 (76%)	The FRP can be used for any type of application (original or supplement)
	Proc	22 (67%)	A product that is designated an orphan product by this or another jurisdiction automatically is reviewed by the FRP
	Subs	19 (58%)	The sponsor must demonstrate that preliminary clinical evidence indicate that the drug might show substantial improvement on a clinically significant endpoint(s) in order to qualify for review via the FRP
Review process	Proc	24 (73%)	What is the target time (agency time) for the review [from submission to reaching regulatory decision for the FRP]?

Assessment System Classification	Most Frequently Observed Assessment Classification	Number of FRPs describing the most Frequently Observed Assessment Classification (%)*
1=no 2=yes	2	26 (87%)
1=no 2=yes	2	20 (67%)
1=no 2=yes 3=yes but orphans excluded	2	26 (96%)
1=no 2=yes	2	19 (73%)
1=no 2=yes 3= ad hoc	1	14 (61%)
1=no/NA 2=within 30d 3=within 60d 4=within 90d	2	11 (73%)
1=no 2=yes	2	25 (86%)
1=no/NA 2=before 3=with 4=after	3	19 (66%)
1=no 2=yes 3=only if certain criteria are met	2	27 (93%)
1=no 2=yes 3=only if certain criteria are met	2	27 (96%)
1=no/NA 2=before 3=with 4=after	4	12 (44%)
1=no 2=yes	1	22 (81%)
1=no 2=yes	2	13 (52%)
1=no 2=yes 3=only if certain criteria are met	1	15 (68%)
1=no 2=yes	2	13 (68%)
1= no/NA 2=up to 60d 3=61-90d 4=91-120d 5=121-180d 6=181-240d 7=241-365d 8=>365d	3	9 (38%)

Table 1. (continued)

	Procedural or substantive	Number of FRPs describing the characteristic (% of 33 FRPs)	Description
	Subs	22 (67%)	The application requires a certificate of pharmaceutical product (CPP) or other legalised document before product approval
	Proc	21 (64%)	Non-agency experts may be asked to review the dossier and make recommendations
	Proc	16 (48%)	A "rolling review" of independent sections of the dossier submitted at different times is permitted
Decision criteria	Subs	25 (76%)	The product must have marketing experience in a prior market jurisdiction before it can be approved via an FRP by your agency
	Subs	18 (55%)	Clinical data collected in your country/region must be a part of the application.
	Subs	16 (48%)	Does the agency recognise EMA article 58 approvals as a way to expedite approvals of important new medicines?
	Subs	14 (42%)	Approval can be based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit
Post-authorisation activities and disengagement	Proc	28 (85%)	Does the product that has undergone review via an FRP need a periodic re-approval?
	Proc	26 (79%)	The product must be withdrawn if it no longer meets explicit criteria set as a condition of approval.
	Subs	18 (55%)	The sponsor must commit to conducting post-approval studies to verify/address anticipated clinical benefit/effect
	Subs	18 (55%)	A risk management plan is required as a condition of approval.

Characteristics: Proc= Procedural ; Subs= Substantive
* Calculated as: The most frequently observed classification assessment /number of FRPs describing the characteristic.

We present a summary of the most frequently observed characteristics (addressed by 70% or more of the FRPs) in Figure 1. Of the 15 common characteristics, 11 were procedural and 4 substantive.

We based the following observations on organising the characteristics according to the five sequential regulatory activities. Percentages reflect the most frequently observed response as a proportion of the total number of responses for that characteristic.

Assessment System Classification	Most Frequently Observed Assessment Classification	Number of FRPs describing the most Frequently Observed Assessment Classification (%)*
1=no 2=yes 3=negotiable	2	15 (68%)
1=no 2=yes	2	16 (76%)
1=no 2=yes	1	10 (63%)
1=none required 2=less than one year 3=1y or less 4=more than 1 year 5=yes but time not specified	1	14 (56%)
1=no 2=yes	1	13 (72%)
1=no 2=yes	1	12 (75%)
1=no 2=yes	2	11 (79%)
1=no 2= every year 3=other longer term	3	20 (71%)
1=no/NA 2=yes 3=provisional withdrawal	2	20 (77%)
1=no 2=yes 3=negotiated	2,3	14 (78%)
1=no 2=yes 3=negotiated	2	12 (67%)

Enabling assistance to facilitate the submission or review

Most FRPs offered the potential for the regulators to provide some form of pre-submission assistance to sponsors (Table 1). SOPs or guidelines that inform the submission expectations and address the review process usually supported this activity. A majority (19/26; 73%) of FRPs provided opportunities for frequent interactions between the sponsor and agency's review team; however, most (14/23; 61%) did not specify the establishment of a special team or office to manage products

Table 2. Analysis of distribution of FRP characteristics by country

		Name of FRP	Total rated characteristics	% of total (27) characteristics	Number of procedural characteristics	Number of substantive characteristics
Latin America	Chile	High sanitary priority	19	70%	14	5
	Columbia abbreviated	Abbreviated route for biotechnology products	13	48%	9	4
	Columbia Exceptional Circumstances	Exceptional circumstance for identified patients for nonregistered medicines	9	33%	6	3
	Brazil	Priority review	16	59%	12	4
	Mexico	Accelerated marketing authorization	8	30%	6	2
		Median	**13**	**48%**	**9**	**4**
Eastern Europe	Ukraine	Priority review	13	48%	12	1
	Serbia	Abridged Procedure/Conditional Market Authorisation	17	63%	15	2
	Kazakhstan	Accelerated Pathway	18	67%	13	5
		Median	**17**	**63%**	**13**	**2**
Middle East and North Africa	Israel	Priority review/Accelerated approval	11	41%	7	4
	Turkey	Fast Tracking of License Applications	6	22%	5	1
	Saudi Arabia	Accelerated approval/fast tracking	17	63%	12	5
	UAE	Fast track	17	63%	11	6
	Iran	No specific name	21	78%	12	9
	Egypt	Fast Track procedure	14	52%	12	2
	Tunisia	No specific name	18	67%	11	7
		Median	**17**	**63%**	**11**	**5**
Sub-Saharan Africa	Ghana	Based on WHO Prequalification Programme	9	33%	6	3
	Kenya	Fast-tracked registration (Locally manufactured and Priority Medicines)	9	33%	7	2
	Tanzania	Fast Track Evaluation	8	30%	6	2
	Uganda	No specific name	11	41%	6	5
	South Africa	Expedited Review Process	9	33%	8	1
	South Africa	Abbreviated Medicine Review Process	7	26%	6	1
		Median	**9**	**33%**	**6**	**2**

2.2 FRPS USED BY EMERGING AUTHORITIES

Table 2. (continued)

		Name of FRP	Total rated characteristics	% of total (27) characteristics	Number of procedural characteristics	Number of substantive characteristics
Asia	China	Special Review for innovative drug registration	18	67%	12	6
	India	Emergency	12	44%	9	3
	Taiwan	New drug priority review	16	59%	11	5
	Taiwan	Bridging Study Evaluation (BSE)	12	44%	8	4
	Korea	Fast Track review	20	74%	13	7
	Malaysia	Priority review	20	74%	12	8
	Philippines	Facilitation of Applications for Product Registration	20	74%	13	7
	Indonesia	No specific name	8	30%	8	0
	Thailand	Priority review /accelerated approval	8	30%	7	1
	Vietnam	Priority approval (accelerated approval)	9	33%	8	1
	New Zealand	Priority Assessment	13	48%	11	2
	New Zealand	Abbreviated Evaluation	11	41%	11	0
		Median	**13**	**46%**	**11**	**4**

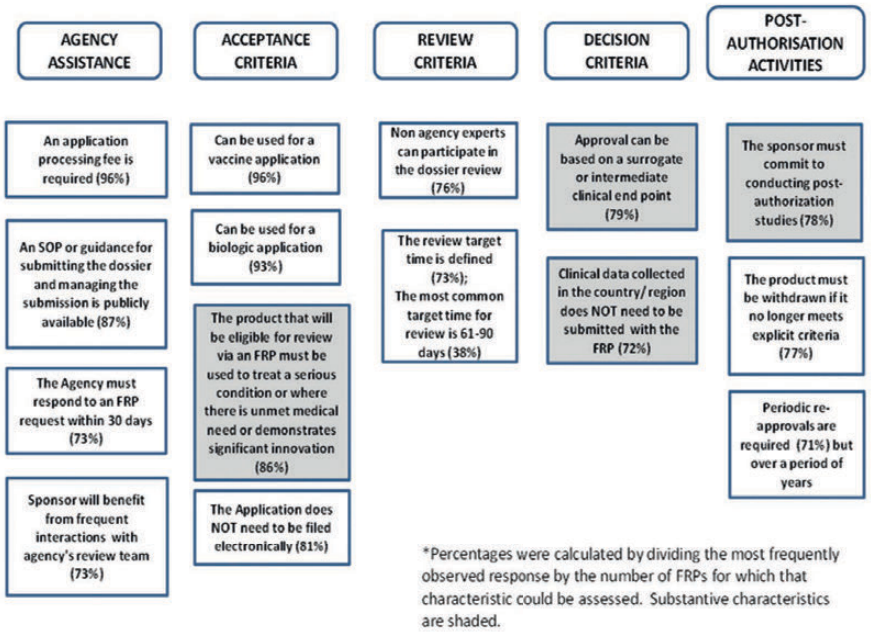

Figure 1. Common Facilitating Practices Observed in FRPs*

submitted via the FRP. Where required, the processing fee varied widely, from less than US$ 1,000 to a multiple of the standard submission processing fee.

Criteria for the acceptance of the regulatory dossier

While most (25/29; 86%) FRPs focused on products for serious diseases or unmet medical need many (15/22; 68%) did not automatically consider orphan products as candidates for FRP review. Most FRPs (>93%) were applicable whether the product was a drug, biologic or vaccine, and for both initial and follow-on supplemental marketing authorisation applications (13/25; 52%). FRPs typically (19/29; 66%) asked that a request for an expedited designation be made at the time of the marketing application submission, unlike SRAs, where the timing of the request for use of an FRP is usually formally defined within the development timeline [10].

Review process attributes

Of the 24 FRPs for which a review target time was defined, all but one had a target of 180 days or less and 13 (54%) had a target of 90 days or less. A Certificate of Pharmaceutical Product (CPP) was a condition for approval for 15/22 (68%) FRPs. Sixteen of 21 (76%) indicated that external experts can be used in the review process.

Decision Criteria

For 11/25 (44%) of FRPs, the product must have been approved in another jurisdiction as a condition of marketing authorisation; generally where an FRP indicated that a CPP was required it also required prior marketing experience. The large majority (13/18; 72%) of FRPs did not require having clinical data collected in the target jurisdiction. Twelve of 16 (75%) FRPs did not indicate that the agency recognises EMA article 58 approvals as a way to expedite approvals of important new medicines. Eleven of 14 (79%) FRPs acknowledged the ability to rely on a clinically relevant effect on a surrogate or intermediate endpoint for an approval.

Post-authorisation and disengagement activities

Periodic re-approvals were required by 20/28 (71%) FRPs and the re-licensure timing extend to intervals of longer than one year. Post-approval commitment requirements in the form of post-authorization studies (14/18; 78%) and risk management plans (12/18; 67%) were often required. Most FRPs (20/26; 77%) were designed such that the NRA could withdraw the product license if the expected effects or benefit-risk profiles were not observed following a post-approval re-assessment.

DISCUSSION

We undertook this study to begin to understand more fully the characteristics of FRPs used by emerging NRAs, and the study may serve as a starting point for further research and discussions around the use of FRPs in a global regulatory environment. Despite their growing implementation, there are no international guidelines or consensus for the basic elements or best practices associated with FRPs. Consequently, there exists an opportunity to better understand the direction in which emerging NRAs are moving to create, implement and use FRPs.

We observed many commonly addressed characteristics (Figure 1); however, none of the individual characteristics were unique to FRPs. An FRP requires a society willing to accept the uncertainty about benefits and risks (with the belief that the initial data generated is predictive of clinical benefit) together with an enabling, transparent regulatory environment wherein the NRA can work closely with the applicant [3,11]. Key to transparency is having a publicly available SOP or guidance on the submission process; 91% of FRPs indicated the availability of an SOP on how to prepare the submission. Further, making review process guidances available (as indicated by 91% of FRPs) supports the WHO Good Review Practices goals of timeliness, predictability, consistency, transparency, clarity, efficiency and a high quality review [12].

Certain elements of FRPs require faster work by the regulator, even if applied to a standard data set; 54% of FRPs had a review target time of 90 days or less (compared with 6 months for an FDA Priority Review) and in contrast to 180 days or

more for FDA standard reviews. This is a commendable target that can be supported by several approaches. Emerging NRAs are piloting opportunities to focus their resources and these have included determining which products to put through an accelerated Expert Review Panel [13] by a more rapid regulatory review using a risk-based triage approach (verification or abridged reviews relying on information from predicate decisions by SRAs) [14], or through work-sharing arrangements with other agencies or WHO. Relying on the work products of another agency's approval or WHO prequalification (PQ) listing, therefore, can be an effective way to use prior experience to inform a local approval [15].

We did not assess how WHO PQ of a product specifically applied to these FRPs. The WHO PQ program and its "collaborative" process and work sharing programs have been used as a way of providing information and capacity to support emerging NRAs regulatory decision-making [16].

While timeliness is important, agencies must ensure a quality review, and the quality of their decision can be strengthened by enlisting multi-stakeholder advice. This is often reflected in the use of an Advisory Committee comprising non-agency experts [11]. Herein, 76% FRPs indicated that external experts can be used as part of the review process. The use of external experts is not without challenges. While their input provides diverse opinions that help define the uncertainty around a new therapy adding to the robustness of the decision-making process, this is often a time consuming step.

Some FRPs accelerate the process by empowering the regulator with the flexibility to base a decision on an assessment of clinical data obtained at an earlier trial stage than pivotal Phase 3; 79% of FRPs provided the ability to base a decision on an intermediate or surrogate end point. This is consistent with certain FRPs used in SRAs and a general trend toward expediting medicine development, review and access [17].

A large proportion (72%) of FRPs did not require submission of clinical data collected in the target jurisdiction as an approval requirement. This relative de-emphasis on local data for the initial approval is counterbalanced in that many FRPs (67%) required a risk management plan and for there to be a commitment to conduct post-authorisation studies (78%).

An effective FRP combines expedited pre-authorisation review procedures with robust post-authorisation monitoring. Many emerging NRAs do not have the post-authorisation systems to closely monitoring the product as is often required by SRAs "accelerated" or "conditional" approvals, especially when based on, as yet, unvalidated surrogates. As the pharmacovigilance infrastructure expands in low- and middle-income countries, a practical approach to real-world monitoring, reporting and feedback on the safety and efficacy of products approved via an FRP will play a critical role in contributing to the effectiveness and acceptance of FRPs [18].

Ultimately, the regulator balances the benefits and harms throughout the product's lifespan in the context of its jurisdiction; applying a systematic, structured approach to the documentation of the benefits and risks can assist in communicating regulatory decisions [19], in particular when they are made as a result of an FRP. FRPs will be most successful where there is adequate ability to collect on-going post-authorization safety and efficacy data.

Whether emerging NRAs have the capacity to address the time and scientific demands of these FRPs is an open issue. Some may have limited staff or access to information with which to make an expedited regulatory decision. These less well-resourced NRAs may rely on reviews and inspections that are part of approvals by an SRA or WHO PQ. However, relying on predicate approvals by SRAs can have limitations: awaiting the regulatory review by an SRA can delay the decision made by an emerging NRA and determining from where to obtain the CPP can result in a lag time to submission. In addition, the SRAs benefit-risk assessment focuses on circumstances in their own jurisdiction's health care systems and institutions. These differ greatly from those in emerging economies and may make the SRA benefit-risk assessment less relevant. The WHO PQ process and the EU's Article 58 process are both procedures that focus on the benefit-risk profile of a product with respect to emerging economies.

Using the descriptive results herein, emerging NRAs could benefit by determining how the characteristics of their FRPs compare with practices used by other similarly resourced NRAs (Table 1). Understanding commonality of process can provide a factual basis for establishing aligned FRPs and investigating work-sharing opportunities. Developing regionally aligned regulatory processes to build and share capacity is a goal in many jurisdictions (e.g., initiatives by East African Community/African Medicines Regulatory Harmonisation; Gulf Cooperation Council; Pan American Health Organization – CARICOM initiative; Asia Pacific Economic Cooperation) [20]. As emerging NRAs move towards alignment and regionalization of decision-making, the role of FRPs should form part of the strategy.

However, FRPs are not panaceas for expedited access and their value must be balanced by limitations. As observed in this study, post-authorisation commitments are an integral part of most FRPs. To date, however, compliance in SRAs in completing these commitments has been limited [21] and it is not clear whether this would be any different in emerging NRAs. FRPs may also be prone to type I errors, e.g. prematurely approving possibly non-efficacious or unsafe products.

Some limitations should be recognised when interpreting these results. We based our assessment of the characteristics on public-domain documentation that was sometimes limited; furthermore, we recognise that some of the publicly available information required significant contextual interpretation. We plan to continue our interactions with emerging NRAs to seek more details and clarifications regarding their

FRPs. We would also like to gain a better understanding of how often FRPs are used as an alternative pathway, what are the facilitators and barriers to their use, and whether target timelines are being met in practice. Finally, the discussion of accelerated access to medicines at some point must address the role of health technology assessment/payers, which is proving increasingly complicated for emerging economies. Our study focussed on regulatory aspects of FRPs and their pharmacoeconomic implications should be the subject of future research.

CONCLUSIONS

This study is a first step in describing common characteristics of FRPs from emerging NRAs. We observed diversity in regional FRP characteristics, suggesting a role for further engagement with emerging NRAs regarding the design and implementation of their FRPs. FRPs will have a meaningful role in accelerating access to important new medicines. Sponsors of marketing applications for products that may fulfil unmet, serious public health challenges should seek to interact early with the NRA to determine the current state of this dynamic field, and address the current requirements based on agency feedback. With further research and experience, we would hope to suggest FRP characteristics that could be successfully implemented by emerging NRAs. Finally, as FRPs also have been discussed in the context of the International Conference of Drug Regulatory Authorities (ICDRA), WHO may wish to consider issuing guiding principles for FRPs that may help to introduce more FRPs in countries where they are still missing, and establishing consistency among existing FRPs.

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chapter 3

PROCESSES THAT ENABLE A QUALITY REGULATORY REVIEW

chapter 3.1

EXPEDITING PATIENT ACCESS TO MEDICINES BY IMPROVING THE PREDICTABILITY OF DRUG DEVELOPMENT AND THE REGULATORY APPROVAL PROCESS

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** This chapter is an extended version of the published article.*

INTRODUCTION

Ideally, well-designed global pharmaceutical development programmes that include simultaneous submissions to multiple regulatory agencies can result in predictable and relatively risk-free regulatory approvals and expedited access to medicines for all patients. The Workshops described herein investigated current trends in development and submission strategies along with regulatory review performance data to consider whether barriers to predictable expedited approval outcomes can be overcome through innovative clinical development approaches or through a better understanding of review processes and procedures especially as these relate to the perception of a product's benefit and risk profile.

BACKGROUND

Many pharmaceutical development programmes are based on a global strategy that includes the option of simultaneous dossier submissions to key regulatory agencies, with the expectation of a streamlined approval process. However, a perception exists that simultaneous submissions may face unpredictable approval delays, sometimes associated with unexpected requests for additional clinical data or region-specific information that increase the chances of rejection or dissimilar review outcomes from different regulatory agencies. Therefore, individually and through group initiatives such Innovative Medicines in Europe and Critical Path in the United States, companies and agencies are addressing ways to improve the consistency of the submission dossier through the use of innovative trial designs and the use of new technologies that have the potential to comprehensively establish a new product's efficacy and safety profile thereby providing data relevant to all reviewing agencies, which should accelerate the review process.

The CMR International Institute for Regulatory Science (the Institute) Workshops on Predictable Outcomes, held in Washington, DC in September 2008 and on Expediting Patient Access to Medicine, held in Surrey, UK in March 2009, brought together experts from regulatory agencies, pharmaceutical companies, and academia to examine the practicalities of achieving simultaneous submission as part of a global development programme and the critical success factors necessary to achieve predictable review outcomes. This report summarises the key findings from 27 Workshop presentations and 5 syndicate session discussions. A list of Workshop Chairs and Presenters and Syndicate Chairs and Rapporteurs is shown in the Appendix.

MAKING THE REVIEW OF MEDICINES MORE PREDICTABLE

The current climate in the drug industry has been described as a "perfect storm." Regulatory authorities must balance ever-increasing pressures to expedite their constituency's access to new medicines and the industry's need for incentives for innovation against requirements to review comprehensive safety assessments and

cost-effectiveness data, all with the expectation of shortened regulatory review times [1]. At the same time, despite constant increases in industry research and development expenditures, there has been a steady decrease in the number of new molecular entities submitted for review, with only 10% of compounds that reach the first human-dose milestone reaching the market [2]. Despite these complications, improving the likelihood of making a safe and effective innovative medicine available to the public in a timely manner remains the common goal for agencies and sponsors.

The regulatory approval system should be relatively predictable and risk-free for medicines developed in accordance with current International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. However, it continues to take an average 14 years for a pharmaceutical company to bring a product to the market [2]during which time the regulatory guidelines and scientific advice may have changed to keep pace with scientific progress. These changes can be reflected in what may appear to be unpredictable regional regulatory requirements that result in unexpected delays in development, extend regulatory review times and that may ultimately result in divergent review outcomes.

In reviewing the critical success factors that contribute to the predictable development and regulatory review of new medicines, Workshop participants identified early and constant sponsor-regulator dialogue as a major positive contributor. Developed to encourage the open exchange of information, the Institute's "Scorecard Programme" provides a structured communication mechanism through which pharmaceutical companies and regulatory agencies can evaluate each other's processes and work products on dossier-specific activities. Results from a small pilot study of the Scorecard Programme showed that companies would like to have improved access to agency reviewers and to see agencies develop processes to enhance transparency in the decision-making process; agencies would like companies to improve their extent of pre-submission communications to better inform the agency of the nature of the dossier. Participants agreed that feedback mechanisms such as the Scorecard were most helpful when the results of the discussions were openly communicated and used as tools to effect change. The Scorecard programme is entering its next phase of development, by validating the tool with additional agencies and sponsors.

Benefit-risk models can also form the basis for more open discussions between agencies, sponsors and target users of a product's profile and should be applied as early in the development process as possible to enhance predictability of the review outcome. The adoption of a standardised model of benefit-risk evaluation would allow the equivalent, on-going global assessment of a product across regions. On-going development and refinement of the current EMEA benefit-risk template [3] integrating experiences from other models such as the Institute's Benefit-Risk

assessment framework, could serve as an assessment and communication model for other jurisdictions.

A complete list of critical factors that can result in successful simultaneous submissions with lower risks of divergent outcomes was identified at the Workshop and is organised by drug development stage (Figure 1).

Key factors include early planning for target labelling and obtaining appropriate data to differentiate the new product from existing therapies. This planning should take into consideration input from all stakeholders, including Health Technology Assessors (HTAs). This latter group is too-often included in the decision-making process after regulatory approval, with the finding that data collected during the development programme were insufficient to permit a valid cost-benefit analysis, resulting in the product's omission from national or private insurer formularies. Table 1 provides prospective and retrospective measures identified by Workshop participants that can

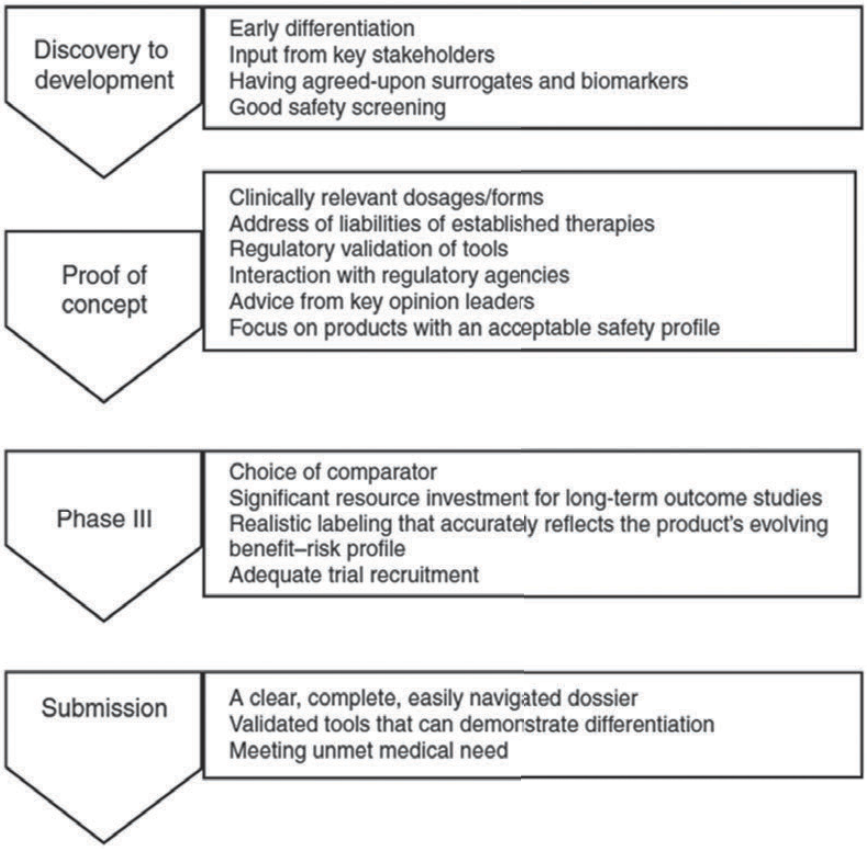

Figure 1. Critical success factors in drug development organized by stage.

Table 1. Measures to improve the predictability of regulatory review*

Prospective measures	Retrospective measures
Identify cases in which there are no regulatory precedents for the introduction of new technologies and concepts. The phase 3 timeframe could be used to educate agencies about novel or complex compounds, and identify data gaps required for the agency to make an informed decision. Create a new category for truly novel (but not first in class) compounds or applications that employ novel design paradigms. This could allow for a new pathway to allow additional facilitated discussion, and an opportunity for continuous, flexible and broader dialogue Improve submission quality. After 10 years experience with the ICH Common Technical Document, some companies are still being criticised for the quality of their submissions. Continuously develop the current EMEA benefit-risk template: focus on critical issues, determine value, make it a model for other jurisdictions, acknowledge output may be qualitative or at best semi-quantitative, and have a goal of standardisation. Be aware that multiple filters on regulatory advice could create different interpretations.	Conduct open, frank discussions between companies and agencies following a dossier review. Utilise feedback mechanisms (from internal reporting, scorecards, etc) to detect procedural flaws, communicate internally between different units and bring about change. Peer reviews, quality management audits and benchmarking are key feedback mechanisms. Change the status of the Institute's Scorecard Project from retrospective to prospective. The next phase of study should include an appropriately large dataset consisting of multiple companies (Institute membership companies) and multiple dossiers across therapeutic areas. It also must extend beyond the current participants to included emerging regulatory agencies. Unsuccessful dossiers should also be included in the study. Redesign scorecards to be more straightforward and easier to use. A real-time, on-line evaluation with easy-to-use, drop-down menus is one potential option to consider for scorecard assessment; data would immediately be uploaded to a central repository. Then the data could be useful in performance management.

*From Syndicate discussion; Chair: Dr Thomas Salmonson; Rapporteur: Tracy Baskerville

be taken to improve the predictability of a drug development programme and its subsequent review.

ARE SIMULTANEOUS GLOBAL SUBMISSIONS POSSIBLE?

When part of a global development programme, simultaneous dossier submission to multiple regulatory agencies can potentially expedite access to new medicines. A *simultaneous submission* was defined as one in which the applicant submits the same data, within 90 days, to multiple regulatory authorities. Data collected by the Institute were presented for dossier submissions for 731 new active substances approved between 1997 and 2008 in six mature pharmaceutical markets, revealing the pattern of a tiered submission strategy, with first submissions to the United States Food and Drug Administration (FDA) and European Medicines Agency (EMEA,) followed by second-tier submission to Health Canada, Swissmedic and Australia's Therapeutic Goods Administration (TGA) (Table 2).

Within this second tier, compounds with priority designation were submitted within 90 days after first submission, and those with standard designation, within 180 days. Although third-tier submission to the Japanese Pharmaceutical and Medical Devices Agency (PMDA) is lagging, the gap is being reduced from a median of 2.9 to 1.2 years after the first submission [4].

ARE SIMULTANEOUS SUBMISSIONS AN APPROPRIATE GOAL?

Workshop participants agreed that a fundamental question needs to be asked before considering whether a drug is a candidate for a potential simultaneous dossier submission, namely, how will this strategy ultimately benefit the patient? Although there are parts of the world where medicines are often not available until late in the global registration process, there are examples of medicines for which expedited access is not critical and for which simultaneous submissions or parallel review would not necessarily be appropriate. These include products such as the so-called "lifestyle drugs" (e.g., for erectile dysfunction or male-pattern baldness). National or regional guideline differences can also impact a drug's potential for simultaneous submission. In oncology, for example, overall survival data are required for approval in Japan, but not in Europe, thereby requiring different data packages for each submission and limiting the possibility of a simultaneous submission. In contrast, homogeneous global expectations for type 1 or 2 diabetes drugs may make them appropriate candidates for simultaneous submission.

Reasons to consider a sequential rather than simultaneous submission include the building on the feedback accrued from independent sequential agency reviews, from use of a therapy under real-world conditions in a primary market and the accumulated post-market experience in secondary jurisdictions.

OVERCOMING BARRIERS TO SIMULTANEOUS SUBMISSIONS

Increasingly, complex non-standardised regional regulatory environments are a real and recognised impediment to global submissions. Barriers to simultaneous

Table 2. Tiered submission strategies

Agency comparison	Total NAS	Submission < 90 days	Approval < 90 days
Tier-one submissions			
FDA – EMEA	98	54 (55%)	13 (13%)
Tier-two submissions			
Health Canada – Swissmedic	115	42 (37%)	22 (19%)
Health Canada – TGA	111	50 (45%)	25 (23%)
Swissmedic - TGA	113	52 (46%)	22 (19%)

NAS- New Active Substances

submission and review for sponsors and agencies identified at the Institute Workshops are detailed in Table 3.

Despite these limitations, global drug development programmes can form the successful basis for simultaneous submissions. The recent near simultaneous approval of methylnaltrexone bromide for opioid-induced constipation across European Union, the Unites States and Canada was cited as an example of multiple multinational requirements being met with global solutions, resulting in a remarkable consistency in labelling. The key factors identified for this medicine's international approval were the fulfilment of an unmet medical need, extensive interaction with the local regulatory agencies prior to each submission, and the sponsor's global development teams working in parallel.

Pharmaceutical developers have instituted various means to effectively manage the critical success factors for global team alignment such as an internal intranet-

Table 3. Potential barriers for simultaneous submission*

Barriers for Sponsors
The company structure and decision-making framework may not be coordinated well enough to allow for simultaneous submissions.
Because of different clinical practice or regulatory guidelines, a global data set may not serve for all the target countries.
Owing to the multiple rounds of review that are often necessary, companies may be unwilling to wait for the amount of time necessary to achieve global alignment of advice from all agencies of interest.
There may not be sufficient funds, or the opportunity may not be deemed as having sufficient capacity for return on investment to underwrite the cost of the development program to achieve simultaneous submission.
Because review and queries from sponsors for a new medicine should be handled by the same core group of regulatory agency personnel, the capacity of internal expert resources to handle queries from multiple agencies could present a significant barrier.
Although a basic requirement, the time required for translations may be an impediment.
There are often regional differences that impact other modules of the Common Technical Document (CTD) than module 1, which is designed to accommodate those regional differences.
Barriers for Regulatory Agencies
Differences in the availability and use of technology, such as that necessary for electronic CTD submission or secure channels for electronic communication can impede simultaneous submissions.
Other issues of communication challenge include extreme time zone differences and language barriers.
Review management processes, procedures and schedules differ across agencies.
Lack of clarity on population definition, can have a negative impact on simultaneous submissions; that is, are differences between acceptable populations intrinsic results of genetic heterogeneity or do they represent extrinsic factors such as regional medical practice, product use, or clinical trial ethics, recruitment, conduct and data analysis?
Differences exist in the acceptability of surrogate endpoints or biomarkers across global agencies.

*From Syndicate discussion; Chair: Sir Alasdair Breckenridge; Rapporteur: Dr Kathryn Broderick.

based clinical trial tool kit. Increasingly, companies are also optimising their global regulatory strategies by implementing collaborative, centralised programmes that support global submissions by housing, submitting and tracking all required regulatory documentation and necessary regional amendments throughout the development, review and post-approval phases. Other recommendations to enable simultaneous global submissions are listed in Table 4.

REGULATORY DIVERGENCE

Even when the goal of simultaneous global submissions is achieved, regulatory agencies may render differing decisions. The most obvious and extreme possibility of divergence in these decisions is that between approval and non-approval. Other examples of disparity include receiving a broad versus a narrow indication, differences in the types and numbers of claims in labelling, and differences in post-approval commitments. There may also be divergences in the requirement for risk management plans, the types of risk-minimisation tools required and the detail of safety information and its prominence in the labelling.

In deconstructing the documented divergences, it is important to understand whether they were based on real differences in a benefit-risk threshold or on evidentiary standards. The reasons for divergent evidentiary standards fall into several categories. The first are the well-accepted population differences detailed in the ICH E5 Guideline [5]: intrinsic genetic differences in population biology that influence drug activity or safety profiles (e.g., beta-receptor responsiveness, HER-2 activity) and extrinsic differences in healthcare environments such as the infrastructure to deliver quality healthcare. Additional causes for divergent outcomes are the influences of cultural or political approaches to healthcare; for example, two regulatory groups, which despite exhaustive mutual consultation, continue to maintain differing schools of thought as to whether a development programme should employ placebo or active controls. Potential causes for divergent regulatory opinions that emerged from

Table 4. Recommendations to enable simultaneous regulatory submissions*

Determine each medicine's suitability as a candidate for simultaneous submission.
Use processes already in place to gain clarity: seek and engage in scientific advice as frequently as possible, potentially in parallel, with open discussions regarding plans for a simultaneous submission.
Continue ongoing work to formalise a standardised benefit-risk methodology.
Commission work to identify true intrinsic and extrinsic population differences.
Seek out creative means to enable data sharing and communication through information technology solutions.

*From Syndicate discussion; Chair: Sir Alasdair Breckenridge; Rapporteur: Dr Kathryn Broderick

Workshop discussions are listed in Table 5 and recommended methods to avoid disparities can be found in Table 6.

DIVERGENT FDA AND EMEA DECISIONS: A CASE STUDY

In the 15 years between January 1995 and March 2009, the EU rejected 31 applications that the US approved, whilst the US rejected 24 applications that received EU approval. The most common agency reasons for their negative decisions were for requests for additional data (EU, 12; FDA 15) clinical safety reasons (EU 14, FDA 11) and clinical efficacy reasons (EU, 16; FDA, 9). In the period from 2006 to 2008, however, there were only 2 (4%) applications that the EU rejected that the FDA approved and 7 (15%) applications that the US rejected that received EU approval. One of these divergent decisions was for tedisamil sesquifumarate. Tedisamil, a class III anti-arrhythmic agent for the rapid conversion of recent onset atrial fibrillation to normal sinus rhythm, was approved in the EU via the decentralised procedure but was judged to be not approvable by the US FDA in 2007. Although the sponsor was able to resolve EU reviewer concerns by changing the recommended dosing, revising the label, and entering into a commitment to a risk management plan, the FDA decision specified that issues of safety, complex dosage administration, gender-associated differences in response, and the need for a non-pharmacotherapy comparator were not resolvable. It was recognised in retrospect that the agency's desire specific types of data would have been best communicated earlier in the development process to avoid this divergent outcome

OVERCOMING DIVERGENT DECISIONS: A PROPOSAL

"Clusters" of therapeutic expertise exist within the FDA and EMEA, with these experts maintaining close interagency contact and awareness. The clusters function

Table 5. Potential reasons for divergence in regulatory decisions*

Inter-agency differences in:
Evidentiary standards
Societal values
Health care systems
Technologic capabilities and living standards
Reimbursement systems (HTA) and their linkage to marketing authorisation process
Decision-making processes
Comfort with uncertainty (in risk or in benefit)
Frameworks for benefit/risk assessment
Laws and regulations (with ability to monitor and enforce)
How issues are prioritised and resources are utilised

*From Syndicate discussion; Chair: Dr Tomas Salmonson; Rapporteur: Dr Victor Raczkowski.

Table 6. Recommendations for mitigating the risk of divergent regulatory outcomes*

Recommendation	Methods
Develop effective and efficient processes by which regulatory authorities strive to harmonise views on the adequacy of a sponsor's development plan and provide feedback; to obtain timely marketing authorisation for the indication being sought and also to support a timely and favourable Health Technology Assessment	Survey regulatory authorities and pharmaceutical companies on their experience and lessons learned regarding the different methods of obtaining regulatory guidance from more than one regulatory authority: through joint, serial, or parallel advice Evaluate the joint scientific advice process for lessons learned, and results should provide a foundation of best practices, especially in simplification of logistics and faster process
Establish agreed frameworks for benefit-risk assessments to improve the underlying science supporting benefit-risk decisions; improve the process, reliability, predictability, and quality of benefit-risk decisions; create greater alignment and clearer communication among stakeholders	Develop a survey for regulatory authorities and industry to gather specific data on which factors most influence the ultimate benefit-risk evaluation. Include the following fields to assess multiple dimensions of benefit-risk assessments: evidentiary standards , societal values, decision-making processes , comfort with uncertainty (in risk *or* in benefit), frameworks for benefit/risk assessment
Develop a Global Tool Box for risk management plans. Tools actually selected and used to mitigate risk may be highly dependent on the health system, societal values, and other factors in the region or country of interest	Evaluate which tools can be used most effectively in each region/country Perform a survey among regulators and industry to evaluate best practices for use of tools in different regions/countries
Evaluate the impact of local requirements on regulatory approval. Assess the degree to which, if at all, local requirements such as bridging studies have had an impact on approval in different regions/countries	Perform a survey of regulatory authorities and industry to obtain data on impact of specific local requirements, exploring societal values, scientific validity and other factors
Develop and harmonise guidelines for evaluation of new therapies for specific diseases	Identify the specific factors that can support or limit homogeneity from one country or region to another

*From Syndicate discussion; Chair: Dr Tomas Salmonson; Rapporteur: Dr Victor Raczkowski.

as a peer-review system for regulators across agencies and may offer enhanced opportunity for parallel advice to sponsors. Although it is hoped that the interagency therapeutic clusters would provide the opportunity for discussion before decisions are made, a suggestion proposed at the Workshop will be considered for action by both agencies to formalise the informal interagency consultation that currently exists, with a process through which companies receiving divergent opinions from the FDA and EMEA could request a tripartite discussion of the decisions.

ENHANCED CLINICAL TRIAL DESIGN AND EXPEDITED ACCESS

As many as 40% of compounds in phase 3 development ultimately fail to achieve clinical trial objectives [6] and these late-stage failures contribute to the steady rise in drug development costs, which are predicted to reach over 80 billion US dollars by 2011 [2]. In the learn-and-confirm paradigm recently adopted by some sponsors, confidence in and knowledge about a compound's mechanism of action, safety, and differentiation are captured much earlier in the drug development process. In this model, smaller, leaner phase 2 studies test viability, later phase 2 trials confirm activity, characterise dose-response and contribute to an understanding of pharmacokinetics/pharmacodynamics, and phase 3 trials are simple, streamlined and focussed, with a low rate of failure. Modelling, through the analysis of existing data, is also used to quantify drug activity, predict and characterise safety and to provide the basis for differentiation, potentially accelerating the time through trials and to dossier submission while maintaining an appropriate benefit-risk balance throughout the development cycle.

The FDA Office of Critical Path Programs and Duke University recently joined together as founding members of a public-private partnership: The Clinical Trials Transformation Initiative (CTTI). Through CTTI, government, industry, academia, patient advocates, clinical investigators and others conduct projects in support of its mission to identify practices that will increase the quality and efficiency of clinical trials. Although CTTI will concentrate initially on the design and conduct of clinical trials in the United States, it seeks to identify practice improvements that can be applied internationally. Two projects, *Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials and Improving Serious Adverse Event (SAE) Reporting to IND Investigators* are on-going and both projects are expected to generate output within approximately 1 year.

BIOMARKERS AND PERSONALISED, EXPEDITED MEDICINE

Biomarkers have become the basis of critical metrics to demonstrate compound efficacy and safety as well as to identify the patient populations most likely to respond while being at the lowest risk for safety issues. They have assumed centre stage in many clinical trial designs, as advances in imaging and other biometric and biochemical technologies have improved the type and quality of measurable characteristics. In Europe, biomarkers have had a major impact on the development of new oncology therapies, with 27% of cancer treatments approved between 2000 and 2008 being indicated for patients with specific genetic biomarkers [7]. In the United States, the FDA website hosts a list of more than 100 examples of products whose labelling is associated with use in populations with 28 different genomic biomarkers [8].

Although post-hoc analyses can be part of the regulatory review of drugs with specific activities or contraindications associated with pharmacogenetic variations,

ideally, efficacy and safety analyses should be performed on treatment results from patients who have been prospectively stratified into groups with positive or negative genomic findings, where all patients are included in the trial and in the analysis of its results.

Pharmaceutical research is gradually shifting to form the basis of "personalised medicine," in which smaller focussed efforts to validate specific targets and patient selection based on these characteristics could increase overall efficacy rates and reduce adverse events. This targeted approach to development provides the evidence base that is key to improving the probability of technical and regulatory success, thereby expediting access to therapies with optimised benefit-risk profiles.

This new paradigm has already shown a positive impact on therapies developed for the treatment of differentiated hematologic cancers, for which the 5-year survival rate two decades ago had been approximately zero and today approaches 70% [9]. Whilst the use of screening tools will potentially reduce the pool of patients who will best benefit from a specific treatment, the improved efficacy results among these patients may reduce barriers to reimbursement/access, provide a more rational basis for determining pricing and should ultimately improve compliance and health outcomes. Improved efficacy or enhanced safety among targeted patient cohorts could also potentially result in streamlined development programmes with smaller, less costly and timelier clinical trials and expedited regulatory review, which together will reduce the barriers to new therapies.

The Innovative Medicines Initiative (IMI), a unique and innovative collaboration, was established by the European Federation of Pharmaceutical Industries and Associations and the European Commission. The drivers for the development of the IMI were to shorten the timelines and enhance the predictability of drug development, to apply the practical benefits of the wealth of opportunities represented by the advance in genomics, to increase cooperation between healthcare stakeholders during the development process and to enhance European competiveness. Fourteen project proposals for research in predictive safety and pharmacology, identification and validation of biomarkers, patient recruitment, and benefit-risk assessment in 5 disease areas were approved in March 2009, which are all expected to be initiated by the end of 2009.

SURROGATE ENDPOINTS

A surrogate endpoint is a biomarker that is intended to substitute for a clinical endpoint and that is expected to predict clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence [10]. In a number of priority diseases such as oncology, surrogate endpoints including imaging, relative response, time to progression and progression-free survival and overall survival are accepted as part of the regulatory review, albeit with some regional differences in their acceptance or regarded importance.

There are multiple potential issues of concern, however, to regulators that surround the use of biomarkers and surrogate endpoints in phase 3 trials that relate to the variability of multifactorial disease, the heterogeneous risk levels of the treated population, the confounding effects of multiple therapies, the extrapolability of results to other drugs with the same or differing mechanisms of action, and the requirement for direct rather than surrogate indications of safety. The development of global standards for approving and analysing biomarkers, imaging protocols and surrogates remains a critical need.

CONCLUSIONS

New approaches to global development and simultaneous submissions, enhanced clinical design, and the use of tools such as biomarkers and surrogate endpoints are evolving rapidly and may result in a greater predictability in the drug development process, the convergence of regulatory outcomes and improved targeted therapies with better benefit-risk profiles. Issues and challenges surrounding these developments such as the establishment of standardised benefit-risk models, the validation of tools and measurements and the mitigation of cultural differences in the development and review process must continue to be addressed by all stakeholders to assist companies, regulators, healthcare providers and payers in their efforts to deliver optimal, expedited health outcomes to all patients.

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chapter 3.2

REGULATORY REVIEW: HOW DO AGENCIES ENSURE THE QUALITY OF DECISION MAKING?

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INTRODUCTION

This January 2013 workshop brought international regulators and multinational pharmaceutical company representative together to focus on best practices that underlie regulatory decision making, thereby facilitating the transparent, timely, procedurally predictable and good-quality evaluation of new medicines. Participants investigated frameworks used by agencies, discussed challenges for regulatory agencies in making quality decisions, investigated the role of other stakeholders, and made recommendations of activities and processes that agencies and companies can consider to enable quality decision making.

BACKGROUND

It is well established that the elements of a good quality regulatory review of a market authorization dossier are, clarity, transparency, consistency and timeliness, and that it is important that the processes used by an agency, whether to review a new medicine or in its daily activities, support these elements [1]. This philosophy has been subscribed to by a wide range of agencies with the introduction of Good Review Practices (GRevP) and Good Review Management Practices (GRMP) [2,3] GRevPs are review standards (such as standard operating procedures and templates) and related initiatives (such as reviewer manuals and training programs) designed to ensure the timeliness, predictability or consistency, and high quality of reviews and review reports. Their implementation is fostered through GRMPs.

The decisions agencies make are guided not only by the regulatory frameworks that define their decision-making responsibilities but also by scientific constructs and societal attitudes toward public health within their jurisdiction [4]. Regulators make numerous decisions regarding products and other matters daily. More specifically, the activities and processes that agencies use to ensure that a science-driven dossier review is undertaken can be identified; however, these need to be built around decision frameworks, which are less well articulated but are equally important as agencies evolve to ensure good quality decision making.

This workshop, held in Beijing, China in January 2013 and developed by CIRS – the Centre for Innovation in Regulatory Science in cooperation with the Chinese Center for Drug Evaluation, brought regulators from 11 countries, the EMA and the WHO and representatives from 16 multinational pharmaceutical companies together to focus on practices that can help regulators enhance their decision making activities thereby facilitating the transparent, timely, procedurally predictable and good-quality evaluation of new medicines. The Workshop extended concepts explored previously by these stakeholders [5] by investigating the decision-making frameworks used by agencies, discussing the challenges for regulatory agencies in making quality decisions, and encouraging participants to make recommendations of activities and processes that agencies and companies can consider to enable quality decision making.

WHAT IS A GOOD-QUALITY REVIEW?

The quality of the review and quality of decision making, although the former should facilitate the latter, are two distinct aspects of a complex process. Therefore, agencies are seeking ways to ensure that they are not only undertaking a good-quality review process but that they are also making a good-quality regulatory decision. Herein we focus on the elements of good decision making.

The science of decision making is well described [6] and common features that characterize good-quality decisions include the use of a validated decision framework; having creative, feasible options; basing decisions on meaningful, reliable evidence; identifying ideals and tradeoffs; using logically correct reasoning; and making a commitment to action [7]. The question remains: how are these being built into the regulatory decision process and how are agencies encouraging quality decisions throughout their organization?

Determining whether a "quality" decision has been made is challenging: assessing the consequences of the decision may be instructive, but the assessment may be impractical and will differ depending on stakeholder perspective. Therefore, the use of decision frameworks within an agency should encourage a quality review leading to well-informed, quality decision making with meaningful well-communicated outcomes. Similarly, the use of good decision frameworks by companies can structure discussions around internal assessment of their findings, inform development decisions, and guide the preparation of quality dossiers.

PRACTICES THAT UNDERPIN GOOD DECISION MAKING

Regulatory agencies need clear and precisely defined processes, consistent application of those processes and well-trained personnel to meet their remits. Workshop participants concluded that a number of distinct regulatory activities could benefit from specific decision frameworks: these activities include managing the processes for acceptance of the dossier file; ensuring consistent scientific assessment by reviewers, senior scientists and external committees; aiding in conflict resolution; describing the benefit-risk decision; and documenting the decision to approve or reject an application.

While GRevPs play an important role in supporting quality decision making, agencies vary widely in their implementation. The Asia Pacific Economic Cooperation (APEC)-sponsored "Best Regulatory Practice of Medical Products, A Strategic Approach for GRevP" project, seeks to characterize and align the implementation of GRevP across member economies and to provide a common platform for regulatory dialogue [2].

Well-characterized decision processes need to be embraced by all staff, from the reviewer through to the final decision maker, and strong commitment by the organization's management is at the heart of embedding decision frameworks

into an agency. Management leadership, strengthening individual skills and building on personal values such as honesty and conscientiousness were noted to form the elements needed to embed effective, transparent decision making into an agency's culture.

Therefore, the "embeddedness" of GRevP within an organization is a prerequisite to quality decision making, which is facilitated by decision frameworks. In this regard, in 2012 the Chinese CDE requested that CIRS conduct an independent survey of senior agency leadership to identify gaps in quality systems, to establish a baseline on the agency's knowledge, practice and attitude related to GRevP, and to use these results to lead to a new cycle of improvement and enhanced competency and capacity building. The survey found that there is a strong understanding by CDE senior management of the value that GRevP brings, that principles for decision making should be clearly explained, and that a good review reflects the agency's values and commitment to continuous improvement of agency practice. To maintain the goal of embeddedness of best decision practices, regulatory agencies should continuously evolve their processes and practices to ensure implementation of optimized tools and techniques.

Developing agencies that are evolving rapidly and that may also be resource-constrained and under growing workload burdens can facilitate the implementation of decision frameworks by adapting or adopting strategies from agencies experienced in the implementation of GRevP and GRMP and aligning with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-based and other internationally accepted guidelines. Following the concepts of "say what you do – do what you say" and "use and improve" can foster quality decision making practices [8].

HOW FRAMEWORKS ENHANCE DECISION MAKING

Regulators are faced with an increasingly challenging environment. The practice of medicine has become more complex and new advanced therapies are reflecting this complexity and the public expects its medicine control agencies to reflect the most expert understanding of these new sciences. In addition, where decision timelines are mandated by legislation, regulatory decisions could theoretically be influenced by time-constrained assessments of the dossier.

Decision frameworks can facilitate a more complete understanding of the factors that lead agencies to their complex decisions, particularly where different conclusions are reached by individual agencies when presented with essentially the same application data. The growing pressure to increase transparency and accountability and to provide explanations as to how decisions are reached favors the use of structured decision frameworks. Divergent regulatory decisions can be better communicated by the use of structured frameworks.

A structured decision framework defines the decision problem, clarifies the objectives, allows for a decision on the alternatives, describes the consequences, assesses the tradeoffs, evaluates the uncertainties, accounts for individual risk tolerance, and facilitates the review of current and future decisions [6]. The QoDoS (The Quality of Decision-Making Orientation Scheme) process, is a tool designed: to test if structured decisions are being made; to help determine where biases exist; and to improve organizational decision making for pharmaceutical companies and agencies. QoDoS is being co-developed by Cardiff University School of Pharmacy and CIRS, and has been assessed by 120 participants whose responses are being used to refine the tool. Initial results indicate that structured decision processes are used inconsistently by most organizations (Figure 1).

A practical example of an approach to ensuring quality decision making is reflected in the work being undertaken to encourage the use of an internationally acceptable framework for the benefit-risk assessment of a new medicine, which encourages a written documentation approach and appropriate ways to communicate the decision findings [9]. The Unified Methodologies for Benefit Risk Assessment (UMBRA) framework provides an 8-step structure to which various benefit-risk frameworks and methodologies can be mapped, and is being piloted by a geographically diverse group of regulatory agencies and multinational companies [10]. This approach involves 1) framing the decision context, identifying benefits and risks by 2) building a Value Tree then 3) refining the Value Tree, 4) assessing the relative importance of the benefits and risks, 5) evaluating the therapeutic options 6) evaluating uncertainty around the various elements 7) providing a concise presentation of results, including visualizations and 8) applying expert judgment to make and communicate a decision.

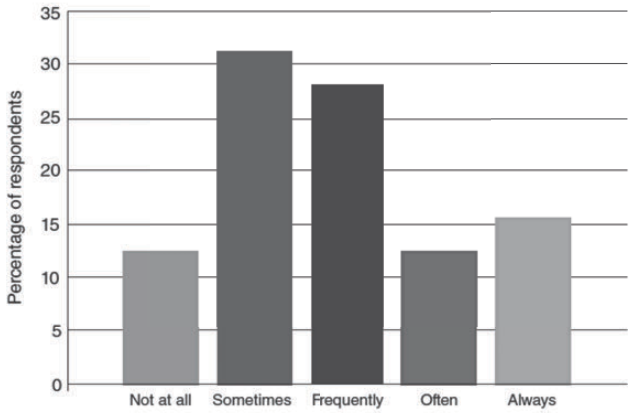

Figure 1. Frequency of use of a structured decision-making process by surveyed organizations (n = 32; from research performed by Walker S, Salek S, and Donelan R: presented by S Walker at workshop; reproduced with permission)

ENSURING QUALITY DECISIONS

Agency reviewers need not and should not work in isolation. Their quality decisions can be enhanced by external input from diverse stakeholders such as FDA Advisory Committees, EMA experts (CHMP Rapporteurs Advisors/Experts; Scientific Advisory Groups) and patient representatives. Table 1 summarizes key elements of good external input into the review and decision process.

But good decision processes should not be pursued solely by regulatory agencies. Effective decision making on the part of industry results in the construction of a logical and well-documented dossier that reflects a cogent decision-based development strategy. It is the consequence of input coordinated across multidisciplinary products teams that starts at the beginning of the development cycle. This encourages the ongoing review of the product's emerging profile through the use of the Targeted Product Profile (TPP) to ensure goal-focused development, characterized by continual feedback and refinement of the TPP based on accumulating data and knowledge. Decisions to proceed as the critical development milestones are attained can be informed by reviews to assess that the underlying science driving the development remains sound, with growing focus on efficacy and safety. This can culminate in a series of internal assessments of jurisdictional regulatory requirements and

Table 1. Key elements of quality external inputs into the review process

	Physician specialist	Patients	Peer Regulators
Why	Provides context for treatment and clinical relevance Provides technical expertise in specialised areas Can summarise diverse patient experiences	Allows regulators to "feel the pain" Patients and other stakeholders can better understand regulatory decision-making by interacting with regulators* Lends legitimacy to decision making	Expand knowledge and/or expertise Learning opportunity Reduce misunderstanding of divergent decisions Resource optimization
How	Standing advisory committee; ad hoc panel and experts Mandatory; guidance; or as needed	Open public forum Provide guidance as to weighting input Elicit patient views through website Via patients in clinical trials Through formally structured processes	Mutual recognition of reviews Joint or shared reviews Ongoing confidence building interactions (eg, collaborative training)

These represent potential inputs that could contribute to enhancing a quality review. Not all of these may be possible in all jurisdictions because of legal and other constraints.
*. Other stakeholders can include national government agencies; the applicant; the industry; healthcare providers: nurses, pharmacists, social workers; HTA/payers; caregivers; non-government organizations.

dossier quality that lead to confirmation of the decision to file an appropriately designed dossier.

In addition, while GRevPs are important and helpful for regulatory agencies, it is equally important that at a time when novel types of products are seeking marketing authorization, reviewers should have a flexibility of approach and an appreciation of the novelty of the underlying science.

PARTICIPANTS RECOMMENDED

- further characterization of decision enablers (i.e., GRevP templates, decision systems such as benefit-risk frameworks);
- understanding factors that contribute to sound regulatory decision practices;
- maximizing the benefits of external inputs;
- maintaining competency through training;
- and improving the structure of submissions (eg, using hyperlinks in electronic submissions connecting the proposed product label to supporting evidence).

In summary, the quality of the review forms the basis for the quality of decision making. A quality decision, from both the agency and company points of view, is facilitated by the use of structured processes that encourage the documentation and communication of the factors leading to the decision.

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chapter 4

EVIDENCE-BASED FRP ASSESSMENTS

chapter 4.1

OBSERVATIONS ON THREE END POINT PROPERTIES AND THEIR RELATIONSHIP TO REGULATORY OUTCOMES OF EUROPEAN ONCOLOGY MARKETING APPLICATIONS

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INTRODUCTION

The development of medicines for the management of oncologic diseases represents a continued focus of pharmaceutical companies. In March 2014, the clinicaltrials.gov website listed 3,407 open, industry-sponsored studies in oncology indications of a total of 10,373 studies (32.8%) [1] and the European Union Clinical Trials Register listed 3,768 ongoing oncology studies (23.9% of total ongoing studies) [2]. Between 2009 and 2013, the European Medicines Agency granted marketing authorisation to 34 oncology marketing authorisation applications (MAAs) [3]. In 2012, seven (33%) of the total 21 new molecular entities (NMEs) granted a market authorisation by EMA were oncology products [4]; in 2013, 13 (41%) of 32 new EMA approvals were for oncology indications [5].

The EMA has promulgated guidelines to provide a structure to facilitate and expedite the development of oncology products and to more transparently communicate its expectations for demonstrability of clinical efficacy [6]. The EMA "Guideline on the Evaluation of Anticancer Medicinal Products in Man" notes that confirmatory trials should demonstrate that the investigational product "provides clinical benefit" supported by sufficient evidence to demonstrate that the chosen primary end point can provide a valid and reliable measure of clinical benefit in the target patient population. Yet, between 2009 and 2013, of 50 MAAs submitted to the EMA for oncology indications, we have observed that 16 (32%) had a negative outcome, suggesting that data supporting the clinical benefit submitted were insufficient to outweigh potential safety issues.

The choice of the most relevant end points as indicators of oncology efficacy, while informed by regulatory guidance, also reflects a flexible approach to medicines development and review. Hard clinical end points reflect objective measures that is, overall survival (OS), duration of response, death. A surrogate end point (a quantitative measure that substitutes for a clinically meaningful end point and that can predict a change in the outcome based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence) that is, progression-free or disease-free survival (PFS/DFS) or overall response rate (ORR) might be more subjective [7-9].

The basis for the approval of a new medicine is a favorable benefit-risk profile: the demonstrability of efficacy together with an acceptable safety profile. The regulator is challenged with balancing the need for rapid market access to these novel therapies with an acceptable level of benefit-risk uncertainty [10]. The combination of hard and surrogate efficacy end points provides researchers and assessors with tools to characterize a new therapy's profile of clinical activity. Common oncology primary end points include OS, PFS/DFS and cure rate. OS has been the historic gold standard of clinical benefit [6,10,11]. It is a favored hard end point because it is simple and easy to measure, objective and easy to interpret, but must be interpreted carefully because it may be influenced by crossover therapy and subsequent sequential

therapies [7,10,12]. However, measures of clinical benefit often are observed more quickly with the surrogate PFS [13]. The EMA has noted that a convincingly demonstrated favorable effect on OS is the most persuasive outcome of a trial from both a clinical and methodological perspective. Prolonged PFS/DFS are often considered relevant measures of patient benefit when the magnitude of the treatment effect is sufficiently large to outbalance safety problems [6].

However, using common end points and the magnitude of their outcomes are not always determinants of a successful oncology MAA. Shea and colleagues evaluated 54 NMEs that received FDA approval for oncologic indications between 2002 and 2012. Two thirds of regular approvals were based on end points other than OS (a hard end point) and more than three quarters of accelerated approvals were based solely on the results of a response rate analysis (a surrogate end point) [14]. In an assessment of European MAAs across all therapeutic areas (2009-2010), 47 of the overall 68 MAAs reviewed clearly confirmed a statistically significant effect on the primary outcome and 39 (83%) of these MAAs were approved. For 11 MAAs, uncertainties remained regarding the statistical significance of the end point, 6 of which were nonetheless approved [15]. Irrespective of the efficacy end point selected, the EMA emphasizes that it is the magnitude of the treatment effect for all relevant outcome measures that forms the basis of their benefit–risk assessment [6].

These experiences suggest that the type of end point (hard/surrogate), the magnitude of an end point outcome, and the statistical significance of the outcome play important roles in defining the clinical activity of an intervention and the regulatory outcome of the dossier review. However, there is little empirical evidence relating these 3 important end point properties with approvals and failures of oncology product MAAs. Therefore, we have taken this opportunity to better understand these 3 end point properties.

The objective of this study was to explore the relationship of these 3 end point properties to regulatory outcomes for oncology products MAA in Europe. The broader aim of this study is to provide evidence that can help guide the clinical development and submission of MAAs that more fully characterize and convey the clinical relevance of the efficacy of new oncology products.

METHODS

All EMA MAAs for products intended for use in an oncology indication and which had a regulatory outcome (approval, non-approval or withdrawal by the sponsor) during the 5-year period of January 1, 2009 through December 31, 2013 were included in this study. First submissions (for initial or subsequent new indications) only were assessed in order to compare initial data packages for common indications.

MAAs were identified from the publicly available EMA activity database [3] and were cross-referenced to the CIRS Regulatory Review Times Database™, and were

categorized by indication [4,5]. Because of the diversity of pathologies for which these medicines have been developed, we categorized the MAAs into 10 groups based on disease categories: lymphoma/multiple myeloma, lung cancer, breast cancer, skin cancer, leukemia, urologic cancers, prostate cancer, osteosarcoma, gastrointestinal cancers, and other cancers (malignant ascites, medullary thyroid cancer, glioma).

The EMA public assessment reports (EPARs) or withdrawal assessment reports (WEPARs) were obtained from the EMA website. Approved MAAs were categorized as such. Non-approvals and withdrawn applications were categorized as "failed applications." MAAs were identified as having received orphan drug designation and by review type.

Primary and secondary efficacy end points were identified for the primary pivotal study identified in the "Main Study(s)" section of each EPAR or WEPAR. When a combined analysis of more than 1 pivotal study was described, the results of the combined analysis cohort were assessed.

End points were categorized as hard or surrogate based on a consensus of published experiences and guidances [6,7,16,17]. However, for end points not previously categorized, a consensus by the authors was used to assign the categorization.

For this study, PFS included the terms DFS- disease-free survival, recurrence-free/ relapse-free/event-free/ survival, and distant metastasis-free survival. The magnitude of end point outcome in months was recorded as the median for each instance of OS and PFS used as a primary end point and for which a statistical value was also reported.

End point analyses described in the EPARs and WEPARs typically compared the medicine of interest with a standard active comparator therapy or to placebo. The level of statistical significance of the effect for each end point was categorized as: $P<.001$, $P<.01$ (but $P\geq.001$), $P<.05$ (but $P\geq.01$), not statistically significant ($P\geq.05$), or not rated. End points for which a hazard ratio was reported in the absence of comparative statistical tests were excluded from this analysis.

Between-group comparisons (approved vs failed) for the use of hard and surrogate end points, and the level of statistical significance of the effect were made using an unpaired, two-tailed t-test.

RESULTS

Fifty MAAs (for 49 products) were included in this study (Table 1) comprising 34 approved and 16 failed applications. One product (Erbitux) was counted as 2 applications: a failed application in 2012 (for advanced or metastatic non-small cell lung cancer) and an approval in 2013 (for metastatic cancer of the colon or rectum).

Analyses presented are based on the number of MAAs. One approved MAA (Erbitux 2013) and 5 failed MAAs (Velcade 2012; Revlimid 2012; Erbitux 2012; Tyberb 2012; Cylatron 2009) were for products previously approved for other oncologic

Table 1. List of EMA approved and failed MAAs for the period of 2009-2013 included in this analysis

Approved (n=34)						Failed (n=16)			
Category	Year of Action	MAA Trade (generic)	Review Type	Approval Type	Orphan (n=9)	Year of action	MAA Trade (generic)	Review Type	Orphan (n=8)
Lymphoma-MM	2009	Mozobil (plerixafor)	Standard	Standard	Orphan	2009	Vorinostat	Standard	Orphan
	2012	Pixuvri (pixantrone)	Standard	Conditional*	No	2012	Velcade (bortezomib)	Standard	No
	2012	Adcetris (brentuximab vedotin)	Standard	Conditional*	Orphan	2012	Revlimid (lenalidomide)	Standard	Orphan
	2013	Imnovid (pomalidomide)	Standard	Standard*	Orphan	2012	Folotyn (pralatrexate)	Standard	Orphan
						2013	Istodax (romidepsin)	Standard	Orphan
Lung	2009	Iressa (gefitinib)	Standard	Standard	No	2009	Zactima (vandetanib)	Standard	No
	2012	Xalkori (crizotinib)	Standard	Conditional*	No	2009	Opaxio (paclitaxel poliglumex)	Standard	No
	2013	Giotrif (afatinib)	Standard	Standard*	No	2012	Erbitux (cetuximab)	Standard	No
Breast	2011	Halaven (eribulin)	Standard	Standard*	No	2009	Ixempra (ixabepilone)	Standard	No
	2013	Perjeta (pertuzumab)	Standard	Standard*	No	2012	Tyverb[1] (lapatinib)	Standard	No
	2013	Kadcyla (trastuzumab emtansine)	Standard	Standard	No				
Skin	2011	Yervoy (ipilimumab)	Standard	Standard*	No	2009	Cylatron (peginterferon alfa 2b)	Standard	No
	2012	Zelboraf (vemurafenib)	Accelerated	Standard*	No	2009	Contusugene ladenovec	Standard	No

Table 1. (continued)

	Approved (n=34)					Failed (n=16)			
Category	Year of Action	MAA Trade (generic)	Review Type	Approval Type	Orphan (n=9)	Year of action	MAA Trade (generic)	Review Type	Orphan (n=8)
	2013	Tafinlar (dabrafenib)	Standard	Standard*	No				
	2013	Erivedge (vismodegib)	Standard	Conditional*	No				
Leukemia	2010	Arzerra (ofatumumab)	Standard	Conditional*	Orphan	2011	Tekinex (omacetaxine mepesuccinate)	Standard	Orphan
	2012	Dacogen (decitabine)	Standard	Standard*	Orphan				
	2013	Bosulif (bosutinib)	Standard	Conditional*	Orphan				
	2013	Iclusig (ponatinib)	Accelerated	Standard*	Orphan				
Urologic	2009	Javlor (vinflunine ditartrate)	Standard	Standard	No	2009	Oncophage (vitespen)	Standard	Orphan
	2009	Afinitor (everolimus)	Standard	Standard	Orphan				
	2010	Votrient (pazopanib)	Standard	Conditional*	No				
	2012	Inlyta (axitinib)	Standard	Standard*	No				
Prostate	2009	Firmagon (degarelix)	Standard	Standard	No				
	2011	Jevtana (cabazitaxel)	Standard	Standard*	No				

Table 1. (continued)

	Approved (n=34)					Failed (n=16)			
Category	Year of Action	MAA Trade (generic)	Review Type	Approval Type	Orphan (n=9)	Year of action	MAA Trade (generic)	Review Type	Orphan (n=8)
	2011	Zytiga (abiraterone acetate)	Accelerated	Standard	No				
	2013	Xtandi (enzalutamide)	Standard	Standard*	No				
	2013	Provenge (sipuleucel-T)	Standard	Standard*	No				
	2013	Xofigo (radium Ra223 dichloride)	Accelerated	Standard*	No				
Osteosarcoma	2009	Mepact (mifamurtide)	Standard	Standard	Orphan	2012	Jenzyl (ridaforolimus)	Standard	Orphan
GI	2011	Teysuno (tegafur, gimeracil and oteracil)	Standard	Standard*	No				
	2013	Stivarga (regorafenib)	Accelerated	Standard*	No				
	2013	Erbitux (cetuximab)	Standard	Standard	No				
Other malignant ascites	2009	Removab (catumaxomab)	Standard	Standard	No				
Other medullary thyroid cancer	2012	Caprelsa (vandetanib)	Standard	Conditional*	No				
Other glioma						2010	Cerepro (sitimagene ceradenovec)	Standard	Orphan

In combination with paclitaxel for metastatic breast cancer
* Additional monitoring required

indications and which were seeking new indications. Nine approved and 8 failed MAAs received orphan drug designation. Five approved MAAs were reviewed through the accelerated route.

Hard and Surrogate End Point Use

End points that were used in 6 or more MAAs are shown in Table 2. The remaining end points were disease specific (ie, puncture-free survival, time to alkaline phosphatase progression, duration of major cytogenic response).

The most commonly used hard end points were OS and the duration of response/stable disease. OS, used either as a primary or secondary end point, was a component of 31 (91%) of the 34 approved applications and 10 (63%) of the 16 failed MAAs. The most commonly used surrogate end points were PFS, response rate, health-related quality of life (HRQoL) assessments, and time to response. PFS, used either as a primary or secondary end point, was a component of all 34 approved applications and 13 (81%) of the 16 failed MAAs.

Among the 34 approved MAAs, 40 primary end points were assessed (some MAAs used more than 1 primary end point); 14 of these were hard end points (primarily OS) and 26 were surrogate end points (primarily PFS). The 16 failed MAAs described 18 primary end points; 7 were considered hard (primarily OS) and 11 surrogates (primarily PFS). There was no statistically significant difference (P= 0.3801) between the approved and failed MAA cohorts in the proportion of hard end points used.

Table 2. Use of hard and surrogate end points (used as either primary or secondary end points) in submitted MAAs

	Approved (n=34)	Failed (n=16)	Total (n=50)
Hard End points			
OS-Overall survival	31	10	41
Duration of response/stable disease	18	7	25
Complete response rate CR	4	2	6
Surrogate End points			
PFS- Progression Free Survival[1]	34	13	47
(Overall) Response Rate (ORR)	16	9	25
HR QoL assessments/PROs	11	2	13
Time to (first) response (TTR)	7	6	13
Objective response rate (ORR)	12	0	12
Time to progression (TTP)	7	4	11
Disease control rate	8	2	10
Time to failure (TTF)	5	1	6
Tumour reduction/change in lesion size/response rate/progression	2	4	6

Includes DFS- disease-free survival; recurrence-free survival/relapse-free/event-free/Distant metastasis-free survival

Similarly, there were no statistically significant differences in the proportion of hard end points used between approved orphan and non-orphan MAAs (P = .3890) or for failed orphan and non-orphans MAAs (P = 0.1939); no statistically significant difference was observed in the proportion of hard end points used between the 8 approved MAAs given conditional approval and the remaining 26 approved MAAss (P = 0.7623).

Of the 34 approved MAAs, 30 used a combination of hard and surrogate end points; however, 4 MAAs (Caprelsa for medullary thyroid cancer; Firmagon for advanced hormone-dependent prostate cancer; Mepact for high-grade non-metastatic osteosarcoma; Mozobil for lymphoma/multiple myeloma) were approved solely on the basis of surrogate end points.

Overall, a mean of slightly more than 4 surrogate end points were used per approved MAAs compared with slightly more than 2 for the failed MAAs. Approximately 2 hard endpoints were used for each approved or failed MAA.

Patient-reported HRQoL end points were used as secondary end points for 11 of the 34 approved MAAs and 2 of the 16 failed MAAs. These surrogate end points were used in 7 of the 10 disease categories.

OS and PFS Magnitude

The relationship between the use of OS and PFS and MAA outcomes was assessed (Table 3).

Of the 50 MAAs, 47 used OS, PFS or both. A slightly higher proportion of approved MAAs (42%) used OS as a primary end point compared with failed MAAs (36%). A higher proportion of failed MAAs (57%) used PFS as the primary end point compared with approved MAAs (33%). A slightly higher proportion of approved MAAs used OS (42%) rather than PFS (33%) as their primary end point; this likely reflects adherence to EMA guidelines recommending the use of OS.

The relationship between the level of statistically significant change in OS and PFS and regulatory outcome was explored (Table 4).

Table 3. OS and PFS use

		Number of MAAs/%			
	End point Use	Approved (n=33)		Failed (n=14)	
OS	Primary	14	42%	5	36%
	Secondary	17	52%	5	36%
	Not used	2	6%	4	28%
PFS	Primary	11	33%	8	57%
	Secondary	18	55%	4	29%
	Not used	4	12%	2	14%

1 approved and 2 failed MAAs did not use either OS or PFS in the primary study.

Table 4. Relationship between the level of statistical significance of OS and PFS and outcome for end points for which a P value was provided

	OS				PFS			
	Approved (n=22)		Failed (n=8)		Approved (n=25)		Failed (n=8)	
p<0.001	7	32%	0	--	19	76%	3	37%
p<0.01	3	14%	2	25%	2	8%	1	13%
p<0.05	5	23%	1	13%	2	8%	1	13%
All significant	15	68%	3	37%	23	92%	5	63%
NS	7	32%	5	62%	2	8%	3	37%

For those MAAs in which a *P* value was reported for the end point, there was a notable difference in the proportion of statistically significant OS events among the approved MAAs (68%) compared with the failed group (37%). A similar divergence in favor of approvals was observed for PFS (92% vs 63%). Of the 22 MAAs approved for which OS was reported, 7 (32%) had statistically significant improvements of *P*<.001. Seven (32%) approved MAAs demonstrated statistically non-significant improvements in OS (Pixuvri and Adcetris [lymphoma-MM], Iressa and Giotrif [lung], Affinitor and Inlyta [urologic], Removab [other]; Figure 1); the first 6 demonstrated statistically significant improvements in PFS and Removab in puncture-free survival (its primary end point). Longer duration outcomes were generally associated with approvals even when not statistically significant. (Figure 1)

For 18 approved MAAs that had statistically significant improvements in PFS together with reported OS data, 12 (67%) also had a statistically significant improvement in OS. Of the 4 failed MAAs that had statistically significant improvements in PFS together with reported OS data, 1 also had a statistically significant improvement in OS.

For EPARs and WEPARs that provided both the specific magnitude of effect and the associated statistical significance of one or both end points, 7 MAAs were approved with OS durations that were not statistically significant; these were observed in the categories of urologic cancers (2 MAAs), lung cancer and lymphoma-multiple myeloma (2 MAAs each), and other (1 MAA). Of the 8 failed MAAs with data, 1 MAA in each of the lung cancer, breast cancer and other categories had statistically significant improvements in OS durations. (Figure 1)

In regard to PFS, 2 (1 each for prostate and gastrointestinal cancer) of 25 MAAs were approved with PFS durations that were not statistically significant. Of the 8 failed MAAs, 5 had statistically significant improvement in PFS durations; these were observed in the categories of breast cancer (2), and 1 each in lymphoma-multiple myeloma, skin cancer and osteosarcoma.

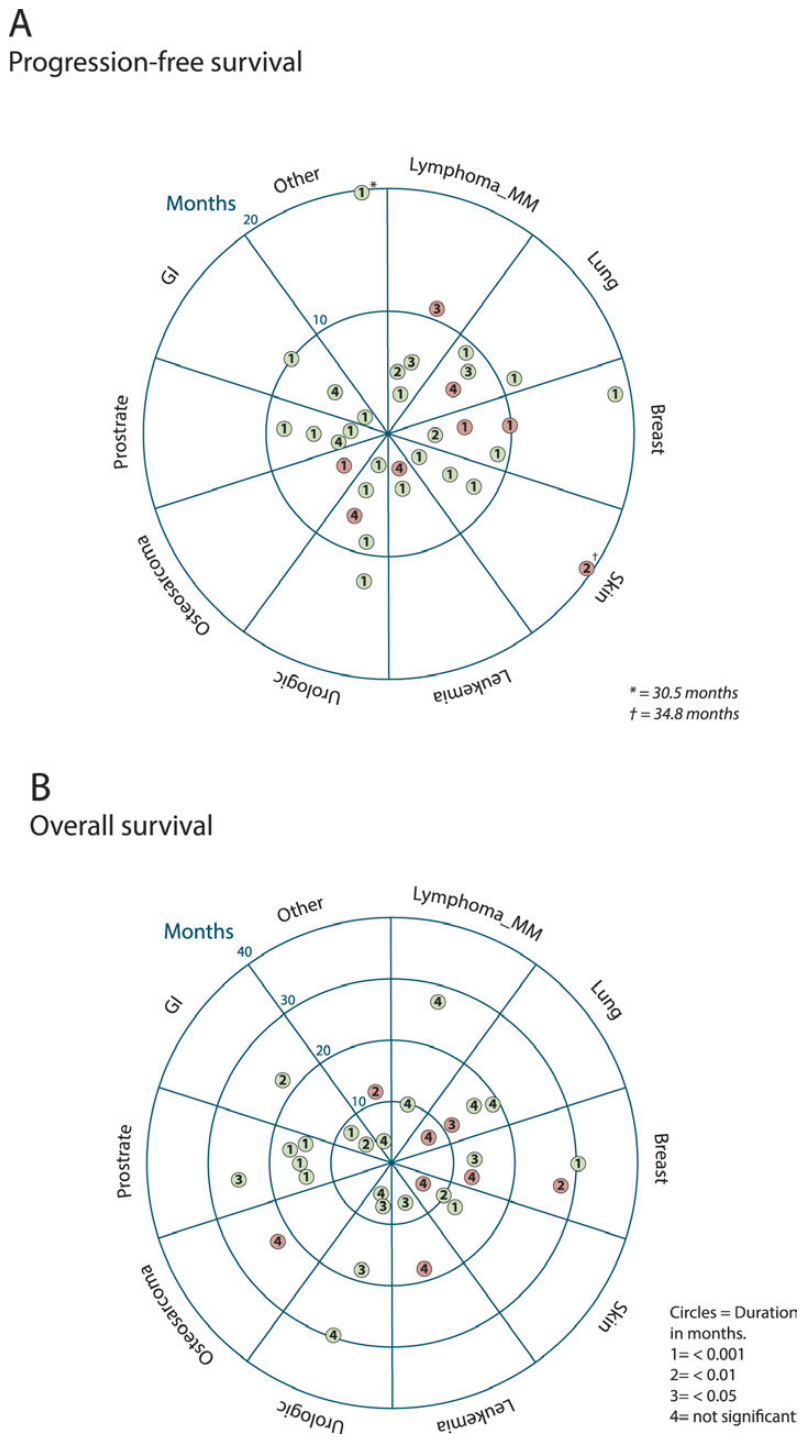

Figure 1. Relationship between the level of the statistically significant change and the magnitude of the clinical effect in OS and PFS (Green= Approved MAAs; Red= Failed MAAs)

Within the urologic category, the 4 approved MAAs had PFS within the range of 3.0 to 12.0 months, and these were all considered to be statistically significant (*P*<.001). Although the PFS of the failed MAA (6.7 months) fell within this range, it was not statistically significant (*P*=0.253); it was the only product designated as an adjuvant therapy among the 5 products in the cohort. By comparison, in the breast cancer cohort, PFS fell within the range of 3.6 to 18.5 months (*P*<.001 for 2 approved MAAs and *P*<.01 for 1). The 2 failed MAAs had median PFS durations 5.8 and 9.7 months (*P*<.001); both were designated as an adjuvant therapy among the 5 products in the cohort.

These analyses indicate that the properties of duration of clinically relevant improvement in OS and PFS and their statistical significance play a key role in regulatory approvals but are not singularly associated with approvals.

Statistical Significance of the Clinical Effect

The distribution of the statistical significance of the effects observed for any primary end points reported in a MAA is summarized in Table 5.

There was a statistically significant difference (*P*<.0001) between the approved and failed groups in the overall distribution of the level of significance, with the approved cohort being associated with a preponderance of significant improvements in primary end points of *P*<.001. For primary end points that provided a *P* value, all of the end points for approved MAAs were statistically significant compared with 64% of those for failed MAAs.

DISCUSSION

This study indicates that the 3 key end point properties of the use of a judicious mix of hard and surrogate end points, the demonstration of a clinically relevant magnitude of effect for OS and PFS, and demonstrable statistical significance of the effects of

Table 5. Distribution of the statistical significance of the primary end point outcome for primary end points for which a p value was provided

	Number of Primary End points Assessed	
	Approved (n=36)	Failed (n=14)
p<0.001	26 (72%)	2 (14%)
p<0.01	2 (6%)	4 (29%)
p<0.05	8 (22%)	3 (21%)
not significant	0	5 (36%)
	P<0.0001	
Statistically significant	36 (100%)	9 (64%)
Not significant	0	(36%)

the primary end points are observed commonly among approved oncology MAAs. If these findings were intuitive, why then does there persist a high proportion (16 of 50; 32%) of failed MAAs? Our findings confirm that the selection and use of an informed mix of clinically relevant hard and surrogate end points can clearly describe the effect profiles of oncology products and can point toward MAA success.

The choice of clinically relevant end points is subject to a variety of influences including the disease being treated, the most efficient approach to addressing divergent advice provided by multiple stakeholders such as regulators, Health Technology Assessment (HTA) agencies [18] the recommendations of clinical advisors and ethical review boards, and the ability of the sponsor to incorporate these into global protocols.

We found no statistically significant difference in the use of primary hard or surrogate end points between approved and failed MAAs or whether the products were designated orphan medicines. Overall, among the 34 approved MAAs 70% (130/185) of end points assessed were surrogates; similarly, surrogates represented 68% (42/62) of the end points associated with failed MAAs. Overall, we found that on average a mean of slightly more than 4 surrogate end points were used per approved MAA compared to slightly more than 2 for the failed MAAs. While this diversity may have contributed to a more complete characterization of the product profile, it could potentially confound the interpretation of the key benefits.

PFS was the most commonly reported end point in our study and using OS or PFS as the main end point was a key characteristic of approved MAAs. Similarly, 10 of 16 (63%) failed MAAs reported OS and 13 of 16 (81%) failed MAAs assessed PFS. A retrospective study by the US FDA of oncology products approved over the period of 2002 to 2012 found that for approvals assessed through the regular pathway (non-accelerated), OS was the most commonly used end point, serving as the basis for 36% (31 of 85 indications). However, 64% (54/85 indications) reviewed by the FDA were approved on the basis of primary end points other than OS, such as PFS or TTP [14].

Relevant end point selection influences not only the regulatory decision, but may also have an impact on subsequent HTA evaluations. A study of Canadian HTA decisions made through the Common Drug review process found that negative decisions occurred significantly more frequently for products that used "non-accepted" surrogates [18] A taskforce convened under the auspices of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has recognized that morbidity, mortality and HRQoL end points must be considered to appropriately address complex cost-benefit decisions [19,20]. A more complete description of end points and outcomes is being undertaken by the EMA in its European Public Assessment Reports (EPARs) to extend the value of these reports to HTA assessments.

Patient-reported outcomes (PROs) and HRQoL end points were used in approximately one third of approved MAAs in our study. PROs complement information from traditional end points, providing patient-centered insights into

the direct benefits of therapy [21,22]. These have been used successfully in a variety of oncology settings, including metastatic renal cell carcinoma [23].

These findings indicate that primary end points in approved oncology MAAs reflect a mix of hard and surrogates, and that the expanded use of surrogates as secondary end points is also observed among approvals. In therapeutic areas of high medical need, where outcome end points may have limitations [24] and uncertainty exists around the long-term predictive value of the MAA data set, flexibility in end point selection can provide a fuller picture of the overall clinical benefit. An appropriate mix of end points forms a key building block of a regulatory decision and a key end point property associated with MAA approval.

The second key property is a clinically relevant magnitude of effect; we focused on the results for OS and PFS. It was not within the scope of our research to assess the merits of the use of OS and PFS as primary end points, but rather to assess of relationship of the magnitude of effect of these important end points to regulatory outcome.

For MAAs that provided relevant data we observed that 17 of the 25 (68%) approved MAAs and 7 of 8 (88%) failed MAAs had PFS of duration of less than 4 months; however, the improvement in duration of response was non-significant for just 2 of the 25 approved MAAs compared with 3 of the 8 failed applications (Figure 1).

The CHMP Scientific Advisory Group for Oncology clarified expectations for improvements in PFS and OS; they noted that OS is generally the most convincing clinical benefit end point for confirmatory studies and that improvement in PFS is less important but still a clinically relevant end point. They noted that when designing studies to show a difference in PFS in metastatic disease, if the prognosis is 2-3 years OS or less, an improvement in median PFS of 3-4 months or longer is considered adequate. The CHMP did not consider it helpful to establish a minimum clinically relevant difference as any positive difference could be seen as worthwhile from a patient perspective and would vary by disease [25].

An analysis of 73 published phase 3 oncology trials found that only a small proportion (12%) showed an OS gain and of the 5 trials where OS was reported as the primary end point only one reported a significant OS gain [12]. From the clinician's point of view, a survey of 28 breast cancer oncologists found that while the respondents were equally divided as to whether the most important end point when selecting a therapy was OS (52%) or PFS (48%), notably, their assessment of a "meaningful improvement" in OS was similarly divided between 2-4 months (44% respondents) and 4-6 months (48%) [26]. In our small cohort of breast cancer MAAs, OS was 13 and 31 months (2 approved MAAs) and 13 and 28 months (2 failed MAAs).

Our observations are consistent with a survey of the factors that influence decisions made by EMA and FDA regulators regarding oncology products, wherein respondents

defined a clinical benefit as an improvement in OS, a substantial improvement in PFS or in the quality of life [27].

The third key property is demonstrable statistical significance of the effect of the primary end points. In this study there was a statistically significant difference ($P<.0001$) between the approved and failed cohorts in the overall distribution of the level of significance of the end point, with the approved cohort being associated with a preponderance of significant improvements ($P<.001$) in primary end points. These findings are not unexpected. Approved MAAs had clinical end points that demonstrated a clear measure of improvement as assessed by the statistical significance of the change. This is consistent with EMA guidance that the chosen primary end point should provide a valid and reliable measure of clinical benefit.

Although the number of MAAs was small, we explored the 7 failed MAAs (Velcade, Erbitux-lung, Ixempra, Tyverb, Cylatron, Jenzyl, Cerepro) that nevertheless demonstrated statistically significant improvements in primary end points. For these failed MAAs, the regulatory agency commented on non-statistical issues such as limitations to the ability to extrapolate the observations, the lack of other demonstrable effects, and the limitations of the study design as reasons for non-approval despite statistically significant findings. Three failed MAAs described PFS changes of $P<.001$; the agency cited the potential for severe unfavorable effects that did not outweigh the expected benefits.

Because the duration of survival increases as a result of more effective therapies, obtaining OS results has become increasingly challenging; this may be contributing to a more full recognition of the value of PFS and other surrogate end points in characterizing the benefits of new therapies. We found that for the 22 approved MAAs with available data, 7 MAAs were approved despite having non-significant OS durations (Figure 1). All of these reported statistically significant improvement in PFS and the one that did not report PFS demonstrated a statistically significant improvement in its primary end point (puncture-free survival). A lack of statistically significant improvement in OS therefore, can be balanced by strong improvements in other end points.

Accordingly, evidence of effectiveness must be carefully balanced against other mitigating factors. Regulatory success or failure can be influenced by many factors beyond the 3 key end points properties described herein. Some of the failed MAAs relied on single arm trials, the results of which were difficult to interpret and extrapolate. Other influencing factors could include whether a single or multiple main studies were presented in the MAA (and whether the types of end points used in single-study MAAs differed from multiple-study MAAs), the unmet medical need, the availability of approved or off-label alternative treatments, whether the product was first in class and therefore potentially requiring more data to satisfy regulatory uncertainty, the desire to provide new therapies that keep pace with advances in

medical practice, and whether the MAA was subject to a regular or accelerated or expedited review.

Several of the MAAs in this study were for products granted conditional authorisation or accelerated review. Because of the reliance of accelerated approval pathways and novel adaptive licensing pathways on surrogate end points that will be reasonably likely to predict a real world clinical benefit [28], the 3 end point properties described here can potentially inform how end points can maximally contribute to these paradigms.

There are a number of limitations to the interpretation of the results of this study. Our analyses were confined by the extent and detail of the data available in publicly available EPARs and WEPARs. There were too few MAAs to gain insights as to the relevance of these 3 end point properties in accelerated reviews. Analyses of MAAs have found that obtaining and following scientific advice provided by the EMA was associated with a positive approval outcome [15,29]; we did not explore the role scientific advice played in influencing the quality of the dossier or the outcome of the review process for this cohort. Although the basis for the approval of a new medicine is a favorable benefit-risk profile, we focused on efficacy endpoints and did not address the safety issues of this cohort as an influence in MAA outcome. WEPARs for failed MAAs cited an unfavorable benefit-risk profile, and this was consistent with a small or uncertain efficacy effect as characterised by the end points assessed in this study. Furthermore, it remains to be explored whether the combination of some or all of these end point properties are more predictive for regulatory outcomes and whether these findings can be extrapolated to other therapeutic areas.

An objective of this research was to provide evidence that could help guide the clinical development and submission of MAAs that well characterize and convey the clinical relevance of the efficacy of new oncology products. We believe this is of particular importance as novel flexible paradigms for drug development are being explored to reduce phase 3 failures, align evidentiary requirements requested by regulatory and HTA stakeholders, and reduce overall development time and costs [30].

Flexible regulatory pathways will need to balance early access with an adequate level of certainty about the benefits and harms in smaller patient populations. While a high level of statistical certainty would be ideal, a license might be granted at a significance level higher than the conventional 5% two-sided significance or where a non-validated surrogate marker may be considered of clinical value [31]. We have observed case-specific divergences in the applicability of the 3 end point properties, and flexibility in their application is necessary in making each development or regulatory decision. A comparative re-analysis of end point characteristics for MAAs submitted over the next 3 years may provide insights into the use and influence of novel end points, particularly as the proportion of MAAs that are reviewed through accelerated pathways is likely to continue to grow.

Using EMA oncology regulatory decisions as the basis for our work has provided insights into 3 key end point properties: of the use of a judicious mix of hard and surrogate end points, the demonstration of a clinically relevant magnitude of effect for OS and PFS, and demonstrable statistical significance of the effects of the primary end points. Our findings indicate that these end point properties are consistent with the EMA guidance and are associated with a high probability of predictable outcome. Throughout a product's life cycle, the interpretation of end point results is accompanied by a level of uncertainty that must be assessed in light of the real-world clinical outcomes, the evolving effectiveness and harms profile, and patient needs, and these 3 properties can contribute to reducing this uncertainty.

IMPLICATIONS FOR PRACTICE

Regulatory decisions made by the European Medicines Agency (EMA) impact clinical practice by determining which therapies will be available in the European oncology armamentarium. The bases for regulatory decisions are presented in the publicly available European Pubic Assessment Reports (EPARs). Regulatory success or failure can be influenced by many factors. Herein we describe three key end point properties (type of end point [hard/surrogate], the magnitude of an end point outcome and its statistical significance) which are associated with a predictable positive outcome for oncology products. Clinicians can use these properties, which are described in EPARs, to help guide their understanding of the clinical effect of new oncologic therapies.

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chapter 4.2

FACTORS RELATED TO DRUG APPROVALS: PREDICTORS OF OUTCOME?

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There is growing interest in characterising factors associated with positive regulatory outcomes for drug marketing authorisations. More than 20 years ago, observations that drugs of greater "importance" (defined by the number of literature and patent citations) were approved with shorter US Food and Drug Administration (FDA) review times, suggested that systematic identification of selected factors could provide insights into regulatory outcomes [1]. Since then, a body of work has accumulated seeking to identify factors that provide confidence around a positive regulatory outcome.

Concluding that a new drug's benefits outweigh potential risks is a complex multifactorial assessment. This requires the integration and interpretation of a variety of evidence-based technical factors (e.g. study designs, product-related characteristics, clinical evidence of efficacy, safety profile) and 'social' factors (e.g. stakeholder expectations, reviewer experience, company experience, company-regulator interactions). Understanding how these and other factors shape the review processes has been recognised as a key factor in expediting patient access to medicines [2].

There is also growing interest in how regulatory science can play a key role to "evaluate and study regulatory systems in terms of their ability to ensure patient safety, enhance public health and stimulate innovation" [3]. In this tradition, numerous empirical studies have, therefore, sought to analyse factors that contribute to predictability of regulatory success. However, despite more than two decades of research, there is limited understanding of how this research has evolved, what has been learned and what researchers, regulators and policy makers can apply from these observations to more fully characterise a product's benefits and risks, to support quality decision making and ultimately, provide greater predictability around a regulatory outcome.

The objective of this analysis was to take stock across key empirical research studies conducted in this field to provide insights into the factors that have been most consistently associated with positive and negative regulatory outcomes. We hypothesised that the analysis would confirm the importance of factors widely considered to be of relevance to drug approval decisions and directly associated with demonstration of safety, efficacy and quality per legislative requirements. However, these factors play only a part in the regulatory decision and even after considering these well-characterised factors there is unexplained variance in outcome. The nature and importance of other factors currently remains elusive and studies that have proposed and tested some of these factors have not been reviewed in systematically. While these other decision factors are heterogeneous, understanding their relationship to regulatory outcomes can help companies navigate the complex regulatory decision landscape. The practical relevance of these findings and what opportunities exist for further studies are explored.

The methodology that was used for this study is detailed in Box 1.

Box 1. Study methods

Search Strategy: A systematic literature search was performed of PubMed and EmBase databases through 30 November 2015. The starting date was open-ended to identify studies reflecting early research. We conducted Boolean searches using a combination free text terms: approval/legislation & jurisprudence; authoris(z)ation; drug approval/methods; drug discovery; drug discovery/trends; medicine regulatory approval; outcome assessment; postmarketing/trends; product surveillance; regulatory success; regulatory outcome. PubMed was also searched using MeSH terms. Additionally, we evaluated the references cited by the identified studies.

We focused our analysis on studies of cohorts of drugs for which a regulatory outcome was reported as the dependent outcome. We included studies that compared a cohort of approved marketing authorisation applications (MAAs) to 'failed' MAAs (not approved or withdrawn from review), or if based only on a cohort of approved MAAs, the analysis must have compared defined subgroups of MAAs (e.g., orphans versus non-orphans or products that were subject to accelerated, conditional or other special review pathways versus standard approvals). Studies could have been of any design, manuscript type or language; case studies and single-event studies were excluded.

Data Extraction: Information on the methodology and outcomes was collected for each study meeting the inclusion criteria: the time range of assessed medicines or marketing authorisations; study objective; study hypothesis; phase of development from which data were derived; sample size and comparison cohorts; geographic region (agency); therapeutic area; approval pathways; statistical methods; whether confounding factors were accounted for; and whether biases/limitations were described.

Factors: For each study, the described factors were identified by the primary author (LL) and verified by an independent reviewer. A study could have described more than one factor and the same factor may have been analysed several ways within the same study (each analysis instance was counted). In order to evaluate similar factors that were described in source reports using varying descriptions, we developed a common terminology lexicon; each factor was assigned to one of 24 "Common Factor Terms". In order to bring continuity to the diversity observed, each Common Factor Term was then classified to one of 4 "Factor Clusters" and the discussion of findings is based on this classification: evidentiary support (e.g., data integrity, study design, number of patients and exposure duration); product or indication characteristics (e.g., dosage form, clinical utility, innovativeness, orphan); company experience or strategy (e.g., size, development strategy, scientific advice, protocol assistance); social and regulatory factors (e.g., regulatory procedures and pathways, advisory committee recommendations) (Table 1). Assignment of Common Factor Terms to Factor Clusters was guided by the description of factors given in the primary references. Where the primary reference did not provide a description that was consistent with one of our four Clusters, the factor was assigned to the most likely cluster by consensus of the authors.

For each factor we identified if the authors presented: P value; odds ratio; whether the results derived from a univariate or multivariate analysis and if the factor was associated with a positive or negative regulatory outcome.

OBSERVATIONS

Publication Characteristics

Twenty-three empirical studies were included in the analysis (Figure 1).

Table 1. The assignment of Common Factor Terms to their respective Factor Clusters

Factor Cluster	Common Factor Terms
Evidentiary support	Deficient preclinical evidence, support for (or poor evidence) of efficacy, evidence for appropriate dose (dose-effect, PK profile well established), quantity of data, clinical relevance of study design, endpoint characteristics, endpoint qualification, appropriateness of number of patients studied, duration of studies, extent of exposure, testing in a representative population, quality of the data, use of a predictive composite score, safety evidence and concerns
Product and indication characteristics	Compound (product) characteristics (physiochemical), indication, well-defined target population, clinical utility, unmet medical need, use for a serious or rare disease, formulation of the dosage form , availability of alternative therapies, innovativeness, disease prevalence, product developed in-house, product acquired or licensed, orphan designation
Company experience/strategy	Prior approvals, company experience, company size, development strategy, clinical development plan, use of protocol assistance, use of scientific advice, adherence to scientific advice, rapidity of completing trials
Social and regulatory factors	Regulatory procedures followed, influence of advisory committee recommendations, use of facilitated regulatory pathways (e.g., breakthrough therapy); local healthcare environment or delivery infrastructure; an individual's perception of risks and uncertainties

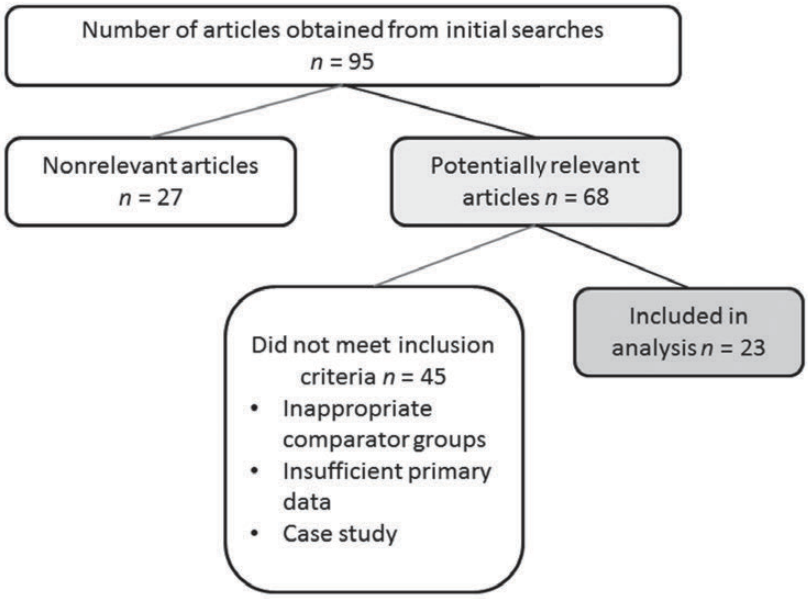

Figure 1. Overview of article identification process and article disposition

These studies were published over a 15-year period (2001-2015). From 2001 to 2009, 5 articles were published [4-8]. Interest in the topic continued to increase, with 6 relevant articles being published from 2010 to 2012 [9-14] and 12 articles appearing from 2013 to 2015 [15-26]. The time frame for which data were analysed in the studies ranged from 1981 to 2014.

The majority of studies (15; 65%) were designed to compare approved and non-approved (failed or withdrawn) marketing authorisation applications. Six studies assessed approved products only and compared specific cohorts within these (e.g., standard versus accelerated approvals; orphan versus non-orphan); all of these studies were based on US FDA approvals. The size of the analysis cohorts varied widely across the studies (20 to 2,559 products; median, 91 products): 13 (56%) of studies assessed 100 or fewer medicines.

The results focused primarily on regulatory activities by the European Medicines Agency and the FDA, each with 10 articles. Two articles assessed products from multiple geographic regions and one focused on Japan. The majority (17; 74%) of studies analysed medicines from multiple therapeutic categories and 6 (26%) focused on oncology products. All but 2 studies combined multiple approval pathways (e.g., standard, expedited); 2 specifically compared factors for standard versus expedited approvals.

While all studies described at least one objective, only approximately half (13; 57%) clearly described a hypothesis in which a specific factor or set of factors was investigated to understand their relationship to regulatory outcome. Hypotheses were widely diverse: five studies sought to support the validity of a specific factor; these assessed factors such as the role of scientific advice, company size, formulation, clinical response. Four sought to identify general learnings from the study of a particular cohort; for example, size of a target population, use of randomized trials or therapeutic innovativeness. Two sought factors that helped with quality decision making; for example, reliance on in-licensed products or rationale for selection a dosing regimen; and two sought to prove that a prediction tool could be created from a confluence of factors; for example, the ANDI (Approved New Drug Index). Because the rationale for conducting studies differed, heterogeneous factors were identified, assessed or described by the authors. For example, when the focus was on production of evidence in the drug development process, evidence-based factors appeared to be more prominent (e.g., number of patients in studies, duration of the studies, response rate) [26], with less focus on non-data-driven social factors (e.g., stakeholder interaction, company experience). Identifying factors was complicated where no clear hypothesis was stated or was difficult to determine (10; 43%).

All of the analyses were retrospective, with 18 (78%) of those assessing factors following the submission of the market authorisation dossier. Studies were heterogeneous with regard to the number of factors described and whether the analyses of these factors were univariate or multivariate. Univariate analyses were

used in 16 (70% of studies), multivariate analysis by 1 (4%), and a combination of univariate and multivariate by 6 (26%) of the included studies.

The majority (16; 70%) clearly addressed the limitations of the study or of specific biases that may have influenced the outcomes. Analysis of the relationship of factors to an outcome can be influenced by confounding factors. However, only 8 (35%) of the studies clearly described a methodology for controlling for confounding.

Factors Characteristics

A high degree of heterogeneity was observed for the factors associated with a regulatory outcome. Overall, 151 instances of factors were identified across the 23 studies and were categorised by their Common Factor Terms to one of 4 Factor Clusters (see Supplementary Table). The most common Factor Cluster was evidentiary support (52; 34%) followed by company experience or strategy (46; 31%), product and indication characteristics (45; 30%), and social and regulatory factors (8; 5%). (Figure 2)

The most common factors observed (Table 2) related to a positive outcome were: having supportive efficacy evidence (17); having a product that will treat a serious/rare disease or meets and unmet medical need (12); that scientific advice given by regulators was followed (11); and that the company had prior experience with the therapeutic area or a history of prior approvals (10). The factors observed to be most commonly related to a negative regulatory outcome were having poor evidence of efficacy (6) and deficiencies in the clinical plan methodology (5).

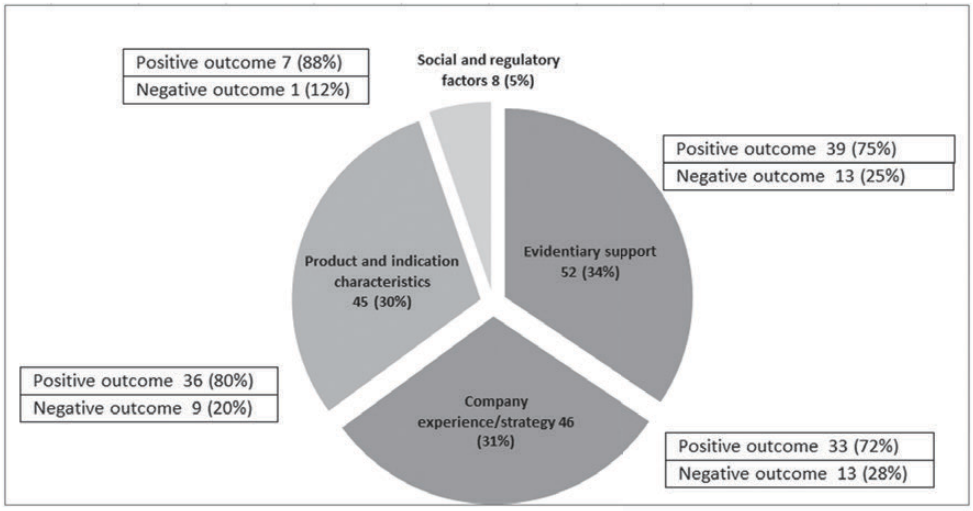

Figure 2. Categorising Factors by Factor Cluster illustrates the divergence in characteristics studied and the observed emphasis on Factors associated with a positive regulatory outcome (n=151 Factors)

Table 2. Understanding the frequency of observations of Common Factor Terms and Factor Clusters and their relationship to regulatory outcomes

Common Factor Term	Factor Cluster*	Total	Number of factors related to	
			Positive outcome	Negative outcome
Supportive efficacy evidence	Evidentiary support	17	17	
Serious/rare disease; unmet medical need	Product or Indication characteristics	16	12	4
Prior approval/company experience	Company experience or strategy	13	10	3
Scientific advice (adherence or non-adherence)	Company experience or strategy	13	11	2
Company size/sales (large vs mid- or small)	Company experience or strategy	12	9	3
Indication factors (well-defined target indication)	Product or Indication characteristics	10	8	2
Compound factors (quality, etc)	Product or Indication characteristics	8	7	1
Clinical development plan methodology	Company experience or strategy	8	3	5
Patient numbers (use of appropriate numbers for the indication)	Evidentiary support	7	7	
Endpoints (use of qualified endpoints)	Evidentiary support	6	6	
Poor evidence of efficacy	Evidentiary support	6		6
Facilitated regulatory pathways (use novel pathways)	Social and regulatory factors	4	4	
Advisory Committee recommendation (outcomes)	Social and regulatory factors	4	3	1
Dose evidence (having substantial dose-effect and pharmacokinetic data)	Evidentiary support	4	2	2
Formulation (oral vs non-oral)	Product or Indication characteristics	4	3	1
Study design (clinical relevance)	Evidentiary support	4	4	
Compound source (initial discovery company; in-licensed)	Product or indication characteristics	2	1	1
Innovativeness (novelty of the therapeutic approach)	Product or indication characteristics	3	3	
Data quality (poor quality leads to failure)	Evidentiary support	2		2
Deficient preclinical plan/evidence (leads to failure)	Evidentiary support	2		2
Composite score (a score aggregating several factors)	Evidentiary support	2	2	
Disease prevalence (understanding the target population)	Product or indication characteristics	2	2	
Safety concerns (detrimental to the benefit-risk profile)	Evidentiary support	1		1
Trial duration (of appropriate length)	Evidentiary support	1	1	
		151	115 (76%)	36 (24%)

* A Common Factor Term may have been categorised into one or more Factor Clusters, but for this analysis each was accounted for in only one Factor Cluster

Odds ratios were presented by the authors to characterise the strength of approximately half (77; 51%) of factors. Overall, 66 of 151 (44%) factors were reported to be significantly ($p<0.05$) related to an outcome. We evaluated the number of statistically significant factors by Cluster, for those factors observed in two or more studies. Two Clusters (the lack of company experience or strategy and complications with product indications or characteristics) had factors which were most often statistically significantly associated with a negative outcome.

The heterogeneity of factors was further confirmed in that none of the Factor Clusters showed a trend toward more occurrences in studies over time nor was there a trend towards a consensus around particular Clusters over time. No study assessed whether the same factors were more influential during early stages versus later stages of development.

Table 3 summarises the main characteristics and Common Factor Terms identified in each study. The 151 factors were categorised according to 24 Common Factor Terms (Tables 1 and 2). The majority (115; 76%) were positively related to product approval and 36 (24%) were negatively associated.

DISCUSSION

We assessed a diverse group of empirical studies that aimed to elucidate factors related to regulatory outcomes. We observed that the studies identified a broad mix of heterogeneous factors confirming numerous recognised "imperative" factors that point towards regulatory success; but importantly, our observations contribute to this heterogeneous research field by elucidating less recognised "compensatory" factors. These observations provide holistic evidence of the important nature of compensatory factors, which are less well characterized yet often critical determinants. This is in line with our premise that despite more than two decades of research and the identification of primarily imperative factors, few studies have focused on the contribution of other factors based on an overview of the findings. We found that non-data driven social factors often play a compensatory role yet may influence the predictability of the outcome of a product's review. Based on these observations we conclude that no factor or cluster of factors alone provides the reason for submission success or failure; because of their heterogeneity, factors cannot be applied in isolation to an outcome but need to be considered holistically in relationship to other factors that carry varying, context-dependent importance.

The four Factor Clusters we used to organise factors are consistent with real-world regulatory outcomes as illustrated by the following examples derived from product approvals and failures described in European Public Assessment Reports and withdrawal assessment reports. Our discussion focuses on key findings within each Factor Cluster.

Table 3. A summary of the objectives, key characteristics and factors identified by the assessed studies

Reference	Year of Publication	Objectives	Sample Size	Univariate or multivariate analysis	Factors Identified* (by Common Factor Terms)
4 (DiMasi)	2001	To analyse success rates for NCEs	671	Univariate	Clinical plan methodology
5 (Pignatti)	2002	To study the issues raised during MAA review and to identify predictors of outcome	111	Univariate and Multivariate	Clinical plan methodology Compound characteristics Deficient Preclinical plan Poor evidence of efficacy
6 (Motola)	2006	To determine whether therapeutic innovation prevails among non-biotechnological products	251	Univariate	Innovativeness Rare/serious disease; unmet medical need
7 (Heemstra)	2008	To identify predictors of successful marketing authorisation for OMPs	91	Univariate and Multivariate	Company size/sales Compound characteristics Disease prevalence Formulation Indication characteristic Innovativeness Prior approval/experience Rare/serious disease; unmet medical need
8 (Richey)	2009	To determine whether AA for oncology drugs facilitates rapid access; whether confirmatory trials are completed; whether safety concerns are identified after AA is granted	51	Univariate	FRPs Patient numbers Supportive Efficacy evidence
9 (DiMasi)	2010	To assess factors associated with clinical approval success rates and clinical development phase transitions	2,559	Univariate	Compound characteristics Compound source Indication characteristic

Table 3. (continued)

Reference	Year of Publication	Objectives	Sample Size	Univariate or multivariate analysis	Factors Identified* (by Common Factor Terms)
10 (Regnstrom)	2010	To identify factors associated with the outcomes of MAAs (with focus on scientific advice)	188	Univariate and Multivariate	Company size/sales Rare/serious disease; unmet medical need Scientific advice
11 (Heemstra)	2011	To determine crucial factors related to failure to achieve marketing authorisation for OMPs	56	Univariate	Company size/sales Compound characteristics Data quality Formulation Poor evidence of efficacy Prior approval/experience Rare/serious disease; unmet medical need Scientific advice
12 (Kesselheim)	2011	To define characteristics of approved OMP cancer drugs and their pivotal clinical trials versus non-OMPs	27	Univariate	Advisory Committee recommendation Endpoints Patient numbers Study design
13 (Putzeist)	2012	To investigate underlying factors of non-approved NCEs	68	Multivariate	Clinical plan methodology Poor evidence of efficacy Supportive Efficacy evidence

Table 3. (continued)

Reference	Year of Publication	Objectives	Sample Size	Univariate or multivariate analysis	Factors Identified* (by Common Factor Terms)
14 (Putzeist)	2012	To assess determinants of successful MAA for OMPs	114	Univariate and Multivariate	Company size/sales Compound characteristics Dose evidence Endpoints Indication characteristic Prior approval/experience Rare/serious disease; unmet medical need Scientific advice Study design Supportive Efficacy evidence
15 (Asada)	2013	To assess reasons for failure of NCEs to gain regulatory approval	53	Univariate	Data quality Dose evidence
16 (Wang)	2013	To determine whether characteristics of non-approved NCEs predict the likelihood of approval in subsequent review rounds	52	Univariate	Advisory Committee recommendation Company size/sales FRPs Indication characteristic Poor evidence of efficacy Safety concerns
17 (Hartman)	2013	To estimate for oncology NCEs the impact of regulatory decision-making on attrition rates; to identify determinants of successful outcomes	46	Univariate	Compound characteristics Endpoints Rare/serious disease; unmet medical need

Table 3. (continued)

Reference	Year of Publication	Objectives	Sample Size	Univariate or multivariate analysis	Factors Identified* (by Common Factor Terms)
18 (Getz)	2013	To build an algorithm for a probability of approval for oncology drugs that have completed Phase 2	61	Univariate and Multivariate	Clinical plan methodology Composite score Patient numbers Rare/serious disease; unmet medical need Supportive Efficacy evidence
19 (Moore)	2014	To assess development times, clinical testing, post-market follow-up, and safety risks for approved NCEs	20	Univariate	FRPs Patient numbers
20 (Malik)	2014	To identify characteristics and outcomes of published Phase 1 studies associated with regulatory approval	88	Univariate	Patient numbers Supportive Efficacy evidence
21 (van den Bogert)	2014	To investigate whether self-originated NCEs differed from acquired NCEs regarding MAA outcomes	171	Univariate	Company size/sales Compound source
22 (Ciociola)	2014	To describe the organisation and function of Advisory Committees	214	Univariate	Advisory Committee recommendation
23 (Belleli)	2015	To assess factors associated with the sustainability of drug development	257	Univariate	FRPs
24 (Liberti)	2015	To explore the relationship of three endpoints used in MAAs to regulatory outcomes for oncology products	50	Univariate	Endpoints Supportive Efficacy evidence
25 (Hofer)	2015	To investigate whether SA leads to changes in clinical trial design and whether the timing of and compliance with SA affects regulatory assessment and outcome	232	Univariate	Scientific advice

Table 3. (continued)

Reference	Year of Publication	Objectives	Sample Size	Univariate or multivariate analysis	Factors Identified* (by Common Factor Terms)
26 (DiMasi)	2015	To build an algorithm that assigns a probability of regulatory approval to oncology drugs that have completed Phase 2 testing and to compare the ease of use and accuracy of various predictive modelling technique	98	Univariate and Multivariate	Company size/sales Composite score Formulation Patient numbers Rare/serious disease; unmet medical need Supportive Efficacy evidence Trial duration

* A Common Factor Term may encompass multiple individual factors observed in a study.
AA: Accelerated Approval
FRP: Facilitated Regulatory Pathway
MAA: Marketing Authorisation Application
NCE: New Chemical Entity
OMP: Orphan Medicinal Product
SA: Scientific Advice from regulators

Evidentiary support: Having robust, supportive evidence of a clinical effect was the most common factor associated with a positive outcome; conversely, poor evidence of efficacy was the most common factor associated with a negative outcome.

Both the FDA http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf. [27] and European Medicines Agency (EMA) have provided guidance around standards for demonstrating efficacy of drugs, biologics including oncology products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/12/WC500119966.pdf. [28]. These guidance enabled sponsors to plan drug development programmes to be sufficiently robust to establish effectiveness without being excessive in scope and to bring greater consistency and predictability to the agency's assessment of efficacy. Importantly, following evidentiary guidelines has been linked with positive regulatory outcomes [24].

The product Giotrif (afatinib) is an example of the association of quality evidence derived from well-designed studies and a positive regulatory outcome. This product was granted marketing authorisation by the EMA for non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations. The recommendation for approval was based on a favourable benefit-risk profile supported by a progression-free survival (PFS) of 11.1 months ($p<0.001$ compared with alternative treatment) and an overall survival (OS) of 16.2 months (non-significant). The product was assessed using a broad range of endpoints; one hard endpoint (OS) and six surrogate endpoints. The reviewers concluded that "the magnitude of the benefit in terms of PFS demonstrated for afatinib over chemotherapy in treatment-naïve patients is statistically significant and clinically meaningful. In addition benefit was also shown in terms of symptom control. These data are considered robust" [29]. The magnitude of improvement, the statistical significance and the diversity of endpoints have been shown to be predictors of positive regulatory outcomes for oncology products [24].

By contrast, poor study design resulted in weak clinical evidence, which led to a major objection to the Erbitux (cetuximab) EMA marketing application, wherein the sponsor was seeking an extension of indication in combination with platinum-based chemotherapy for the first-line treatment of patients with advanced or metastatic non-small cell lung cancer with high EGFR expression. While the reviewers considered the endpoint (EGFR immunohistochemistry score) as a reliable predictive factor, the cut-off used by the sponsor was found to be in need of further validation. For this application, the lack of supportive efficacy evidence complicated by a poorly defined endpoint [30], were consistent with our observations, pointing to the likelihood of a failed regulatory outcome.

Product or indication characteristics: The studies in this cohort observed that having a therapy that addresses a serious or rare disease or which meets an unmet medical need has been associated with positive regulatory outcomes. Demonstrating robust product quality also was associated with positive outcomes; conversely, poor

product quality may lead to a negative outcome (Table 2) despite the product being developed for a high unmet medical need. In 2014, the initial marketing application to the EMA for faldaprevir for hepatitis C was withdrawn by the sponsor (Boehringer Ingelheim). At withdrawal, the Committee for Medicinal Products for Human Use (CHMP) was of the provisional opinion that the drug could not be approved because of "concerns regarding the starting materials used for the manufacture of the active substance and a problematic dissolution profile. Therefore, despite being developed for a serious illness, due to the concerns about quality, the benefits of faldaprevir did not outweigh its risks.

Social and regulatory factors: The field of factor assessment has evolved based on studies largely focused on readily measurable, historically observable evidence-based factors and less so on social (non-data driven factors). Although being difficult to quantify, social factors likely play an important role in characterising products wherein efficacy may be marginal or hard to measure, for which the safety profile is troublesome or the place in therapy is unclear [31,32]. These were the least studied factors in our cohort. More attention, therefore, needs to be given to these contextual and non-data driven social factors.

Several studies have begun to investigate the role of social factors in regulatory decision making. Regulators who participated in a "discrete choice" survey [33] to assess the benefits and risks associated with a hypothetical oral hypoglycaemic agent were found to value the major benefits and risks for an individual patient with diabetes similarly to a comparative cohort of doctors and patients; nevertheless, they exhibited some differences regarding the value of minor or short-term drug effects. While this study did not support the assumption that regulators have fundamentally different views from other stakeholders when valuing individual drug benefits and risks, it illustrated that differences may exist regarding the relative value of specific effects. In line with these observations, a survey of FDA and EMA reviewers [34] recognised that while evidence-based factors were the main drivers of most regulatory decisions, social factors (e.g., interactions with the industry, with clinical opinion leaders and patients) may contribute to divergent decisions observed between the agencies. Similarly, how European medical assessors perceive the benefits and risks of medicines has been related to social factors such as personality traits (e.g., how extraverted assessors perceived themselves) and gender [35]. More work is required in this field.

The use of novel accelerated pathways was associated with positive outcomes (4 instances)(Table 2), likely because these are often used for therapies for serious illnesses with unmet medical needs. In 2015, 61% of new active substances approved by FDA benefitted from at least one of the available facilitated regulatory pathways to expedite the regulatory process, as did 47% at the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), 44% at Swissmedic, 33% at Health Canada, 32% at EMA; the extent to which social factors play a role in these accelerated pathways should be studied further [36].

Company experience or strategy: We observed several factors within this Cluster that were associated with positive outcomes (e.g. having a prior approval and company experience; adhering to regulatory scientific advice; being a well-resourced company; and having a robust clinical development plan).

In July 2016, the novel agent Begedina (begelomab) was reviewed for a proposed use in the treatment of acute graft-versus-host disease. The negative opinion for this product was representative of the multifactorial nature of regulatory decisions. Importantly, the CHMP found that the clinical data provided were "insufficient to demonstrate a beneficial effect of Begedina" and that "the safety profile and the way the medicine was expected to work had not been sufficiently characterised." The CHMP also noted there were "deficiencies identified in the manufacturing process of the medicine." http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2016/07/WC500210883.pdf [37]. The sponsor withdrew the application. This product was developed by Adienne S.r.l., a small-to-medium enterprise, Swiss-based private company. At the time, the company had one approved drug.

Our study observed documented contributing factors associated with the negative decision for Begedina MAA: deficient preclinical plans that did not completely characterise the mechanism of action, poor supportive clinical evidence, quality (manufacturing) issues, small company size, a focus on rare diseases and a limited number of prior approvals. This recent failed application indicates that recognising *a priori* the multiple factors also identified in our review would likely have provided directional evidence that this MAA may have met with an unfavourable outcome.

Are some factors more important than others?

Experienced medicine developers and regulators may point to some of the factors as intuitively obvious; strong supportive evidence, adhering to scientific advice. But the cases illustrated herein indicate that while, the scientific evidence (e.g. the technical factors) provides an initial assessment basis, other factors tip the scale for or against a positive outcome. The impact of these intuitive, "imperative" factors (which are typically technical factors that appear as "obvious" to some) is therefore influenced and balanced by "compensatory" factors that play a balancing role; those addressing an unmet medical need, company experience, strength of the clinical plan methodology). Compensatory factors are often critical in changing how a positive benefit-risk balance is reached (e.g. demonstration and valuation of unmet medical needs, receiving and adhering to advice, procedural characteristics when there is considerable ambiguity about the strength of evidence between different experts and stakeholder groups and regulatory status such as orphan designation or fast track). For a particular decision therefore, compensatory factors may play a most critical role, particularly in difficult regulatory decisions.

An example of the multifactorial complexity of regulatory decision making can be seen in the evaluation of a medicine to address the challenge of malignant ascites

wherein clinicians are faced with limited treatment options. In 2009, the EMA approved Removab (catumaxomab) for use in patients with EpCAM-positive carcinomas where other treatments had failed. Despite a non-statistically significant increase in puncture-free survival versus paracentesis (from 11 days to 46 days), the occurrence of significant but manageable adverse events and the need for hospitalisation, the CHMP reached a favourable conclusion regarding the product's risk-benefit balance. The intuitive imperative factors would have suggested a negative opinion for this product. Numerous compensatory factors, therefore, appear to have contributed to the outcome more heavily than the limited evidence-based technical factors. These likely included factors such as the size and experience of the sponsor company (Fresenius Biotech GmbH a part of Fresenius with 2015 sales of €27.6 billion) a factor identified by van den Bogert et al [21]; that the sponsor took scientific advice on multiple occasions from the EMA regarding clinical aspects of the dossier and that most clinical studies were completed rapidly despite recruiting difficulties. These multiple factors associated with a positive outcome are consistent with factors in studies evaluated herein.

Opportunities for Further Study

None of the studies in our analysis assessed how stakeholders weighted or valued particular factors within the context of a product-specific decision, thereby providing an important opportunity for new research. Decision frameworks can help to more explicitly describe the value and relative importance of particular imperative and compensatory factors to the development of an innovative new medicine and to the associated regulatory decision [38]. Frameworks that document and contextualise the value of these factors could help to understand the basis for consistent or divergent decisions among regulatory agencies and individual regulators [34, 39]. These divergences may seem idiosyncratic, but describing the extent to which various factors are weighted to achieve the decision can provide transparency around the relative contribution of these factors [40].

Some factors may serve as proxies for other influencers and may not be directly brought into the individual decision-making process. These are often higher-level associations established on a population level (when comparing group of drugs). These associations point to abilities, prior experiences, extent of standardization etc. `For example, while several studies observed that larger company size was associated with a positive regulatory outcome, it is likely that sales or R&D volume alone were not the drivers of success. That these larger companies likely had greater financial resources to invest, may have had staff with more years and diversity of backgrounds, and more years of submission experience in a disease area, may have been factors underlying the aggregate "large company size" factor. These also had the ability to establish robust evidence and to navigate the complex regulatory landscape. Our

findings indicate that future work should focus on the role and added value of novel indirect and compensatory social factors.

It is clear that current development best practices need to address both the confluence of regulatory and access requirements. While none of the studies in this cohort identified factors associated with positive market access recommendations, it is likely that factors such as scientific advice, robustness of the clinical programme, the endpoints used, strength of the efficacy data and the target indication can all play a role in pointing toward positive access outcomes.

Our overall observations are directionally consistent with the consensus recommendations on regulatory predictability derived from two international workshops [2]; these identified a variety of key factors during product development that could contribute to predictability of a regulatory outcome: having agreed-upon surrogates and biomarkers; using clinically relevant dosages and forms; using regulatory validated assessment tools; having constructive interactions with regulators; selecting appropriate comparators; developing a realistic benefit-risk profile and demonstrating that the product can be clearly differentiated from other therapies and can address an unmet medical need.

Taken individually, some factors may potentially serve as predictors of regulatory outcome. But as observed from the above cases, these factors need to be assessed in a multidimensional milieu which has made it difficult to capture with simple metrics their individual value to a regulatory decision. Because of the heterogeneity we observed across these studies, the almost infinite permutations of factors indicates that the need for a new, holistic approach to understanding the relative contribution of both data-driven and social factors to development and regulatory decisions. Furthermore, because in some cases values are the critical influencers in decision-making, the question "what kinds of data are important?" may be better stated as "whose opinion regarding these data is valued?" This supports a "procedural adjustment" making regulatory assessments increasingly open to input from a wider range of stakeholders such as patients, healthcare professionals and health technology assessors.

Because of the multifactorial nature of these decisions, future research should assess the contribution of factors using multivariate models, as have some of the studies in this cohort. Our findings point towards the use of new comprehensive data sets and novel analytical techniques such as using machine learning for text mining and pattern recognition to provide more clearly defined factors that play a role in complex regulatory decisions. The integrated analysis of large public, private or consortium research and regulatory outcomes databases may offer novel regulatory science insights that can foster successful innovation and a more predictable regulatory process.

CONCLUSIONS

The variety of study designs and analytical techniques, viewpoints, and mixed hypotheses described in empirical studies to date have produced a heterogeneous mix of factors, with diversity across studies. Based on decades of individual reports, we confirmed a group of data-driven technical factors, today recognised as imperative, intuitive and self-evident, as the basis for regulatory decisions. However, we found that non-data driven social factors that often served as compensatory factors, play an important contributory role in determining the outcome of a product's review especially in cases where the benefit-risk profile is complex.

Based on these observations we conclude that no factor or cluster of factors alone provides the reason for submission success or failure but need to be considered holistically recognizing they carry varying, context-dependent importance. Drug developers who are not already working to identify the contribution of various factors to their product's probability of outcome profile in a dynamic way over time should incorporate such findings into their decision-making processes. More detailed holistic analyses of factors observed in this study could provide evidence to further enhance predictability of the regulatory outcome.

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chapter 4.3

FDA FACILITATED REGULATORY PATHWAYS: VISUALIZING THEIR CHARACTERISTICS, DEVELOPMENT AND AUTHORISATION TIMELINES

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Accessed at: http://journal.frontiersin.org/article/10.3389/fphar.2017.00161/abstract.

BACKGROUND

Patients have an expectation of rapid and efficient access to safe and effective, innovative new medicines. This has raised expectations around the speed of the development and regulatory review process. In the US, programs have sought to address these expectations, including the FDA's Critical Path Initiative which addresses the agency's strategy to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured. The US Food and Drug Administration (FDA) has taken a leadership role in implementing a variety of regulatory pathways that provide sponsors with flexible options to facilitate development, and for the agency to speed the regulatory review process without compromising standards for quality, safety and efficacy. Four expedited pathways for novel products for serious diseases or unmet medical need are available: Fast Track designation (FT), Breakthrough Therapy designation (BTD), Priority Review designation (PR) and Accelerated Approval pathway (AA). Their characteristics have been well described elsewhere [1].

We previously termed these expedited pathways as facilitated regulatory pathways (FRPs): regulatory pathways designed to speed the development, marketing authorisation and patient access to new drugs with a positive benefit-risk balance by providing alternatives to standard product development and regulatory review routes [2]. FRPs may increase the level of communication and commitment between the developer and the agency, can give a larger role to effects on surrogate end points, and may move some of the burden of evidence generation from the pre- to the post-authorisation phase. Since 2014, more than half of the new molecular entities approved by the FDA used one or more FRPs [3,4]. However, the extent to which the combined use of these programs affects the time taken in the regulatory review process remains unclear despite growing experience with the programs.

One of the expedited pathways (PR) specifies a shortened review timeline (six months) and FT and BTD have been designed to encourage interactions between the FDA and sponsors, thereby seeking to shorten development times. Therefore, we sought to determine to what extent these pathways influence development times and whether the combination of two or more FRPs influenced approval times compared to the use of PR alone. We undertook an analysis of products recently approved by FDA to assess the impact of the use of multiple combined FRPs on drug development and approval time. We also developed a simple methodology to illustrate the basic elements of these FRP and their influence on review times.

DISTINGUISHING ELEMENTS OF FDA FRPS

The four FDA programs can be distinguished by several specific characteristics [1], including their temporal implementation sequence during development and the nature of the minimally required supportive data: nonclinical evidence of

the potential to meet unmet medical need (FT); preliminary human experience suggesting a substantial improvement over available treatments based on a surrogate or intermediate clinical end point (BTD); demonstration of a meaningful therapeutic benefit over available therapies in clinical studies using a surrogate or intermediate end point (AA); and completed clinical trials that have demonstrated a significant improvement in safety and/or efficacy (PR). None of these programs are exclusive and any combination is permissible.

Three of these programs (FT, BTD, AA) have been designed to encourage and expedite development. A product in early development that is granted FT can be supported by early and frequent interactions with reviewers. This support is extended for products granted BTD through organisational commitment from senior agency leadership and the opportunity to receive additional intensive guidance beginning as early as Phase 1. FT and BTD encourage an expedited review by permitting the "rolling review" of sequentially submitted portions of the submission. Products approved via AA are balanced by rigorous post-authorisation study commitments. Importantly, PR decreases the statutory review time from ten months to six months.

Because outcomes of drug development are often difficult to predict, designations may be rescinded if products do not continue to meet defined criteria upon periodic reassessment. The FT designation may be rescinded at any time if the product no longer meets the qualifying criteria. Not all products assigned BTD will be shown to have substantial improvement over available therapies suggested by preliminary evidence; if clinical benefit is not supported by subsequent data or the non-completion of post-approval trials, the designation may be rescinded. Products with a PR designation must adhere to an integrated post-approval plan (the flexibility of which is determined by the product characteristics, seriousness of the condition and unmet medical need, manufacturing processes, sponsor quality systems, strength of risk-based quality assessment). Products approved via AA are subject to withdrawal if the post-authorisation confirmatory trials designed to verify and describe the anticipated effect do not confirm the expected outcomes.

Drug sponsors are required to submit formal requests to use FT and BTD but not for PR (determined by FDA upon start of the review) and AA (assigned by FDA at time of approval). From 2006 to 2014, the FDA Center for Drug Evaluation and Research received about 1,000 requests for FT and BTD [3].

OBSERVATIONS

We analysed new active substances (NAS) as previously defined [4] that received FDA approval between January 2013 and December 2015. Each was categorised as to the FRP(s) used. IND dates were obtained from public domain data and from the CRIB database (http://db.crib.wustl.edu). IND submission dates were typically reported in these sources. Where a specific day was not available, the 15th of the month was

used. IND dates were found for 68 products in this cohort. Times from IND date to assignment of FT or BTD and to NDA submission were calculated for each instance where dates were available. Time from NDA submission to approval date was calculated based on data obtained from the FDA website. This time in calendar days includes both agency review time and company response time.

We employed a "metro map" approach to illustrate the relationship between the key aspects of each FRP, the touch points and temporal relationship among them, and the length of the regulatory review times when these programs were employed. Figure 1 illustrates the key steps for each of the four programs, from pre-IND through to post-authorisation.

The process begins at the upper left region addressing factors related to acceptance and the product's characteristics. A product may then follow one of several pre-designation routes to a point at which a designation is assigned (a standard review is always an option and therefore is not illustrated here). The combination of FRP routes result in varying approval times, designated by the tracks in the Review Period sector. The relative length of the review period line corresponds to the median review time; the "node" size at the end of the line reflects the number of products that followed that route.

Among the 125 NAS approved during this period, 74 (59%) used one or more FRP. No products in this cohort used BTD alone, FT+BTD, BTD+AA, or FT+AA+BTD.

Development times (time from IND to NDA submission) were influenced by the FRP route (Figure 2). The median development time for products using any FRP was 2,377 days and for products not using an FRP (standard reviews) was 2,148 days. Products that used BTD+PR+AA had the shortest median development time (1,458 days). By contrast, products that were approved by FT or PR alone had the longest development time (2,620 and 3,515 days, respectively).

Poirier [5] observed that for non-oncology products and vaccines BTD had little impact on development timelines and that AA appeared to influenced timelines more than BTD. We observed that for this recent mixed product cohort, the provisions offered by FT and BTD resulted in shorter development times when used in combination with other FRPs. The underlying factors that influence development should be explored, as more products avail themselves of these designations throughout their research phase. The characteristics of the products, influence of unmet medical need, number and outcomes of advice meeting with the agency, nature of the clinical trials or other measures could provide insights into the influence of these FRPs on development programme efficiency. Similarly, an analysis of whether products that use an FRP during development stage are more likely to receive first cycle approval could point to what extent FRP use can be a predictor of more efficient regulatory processes.

In terms of regulatory review, the median approval time for the 74 products that used an FRP was 243 days compared to a median 365 days for the 51 products that

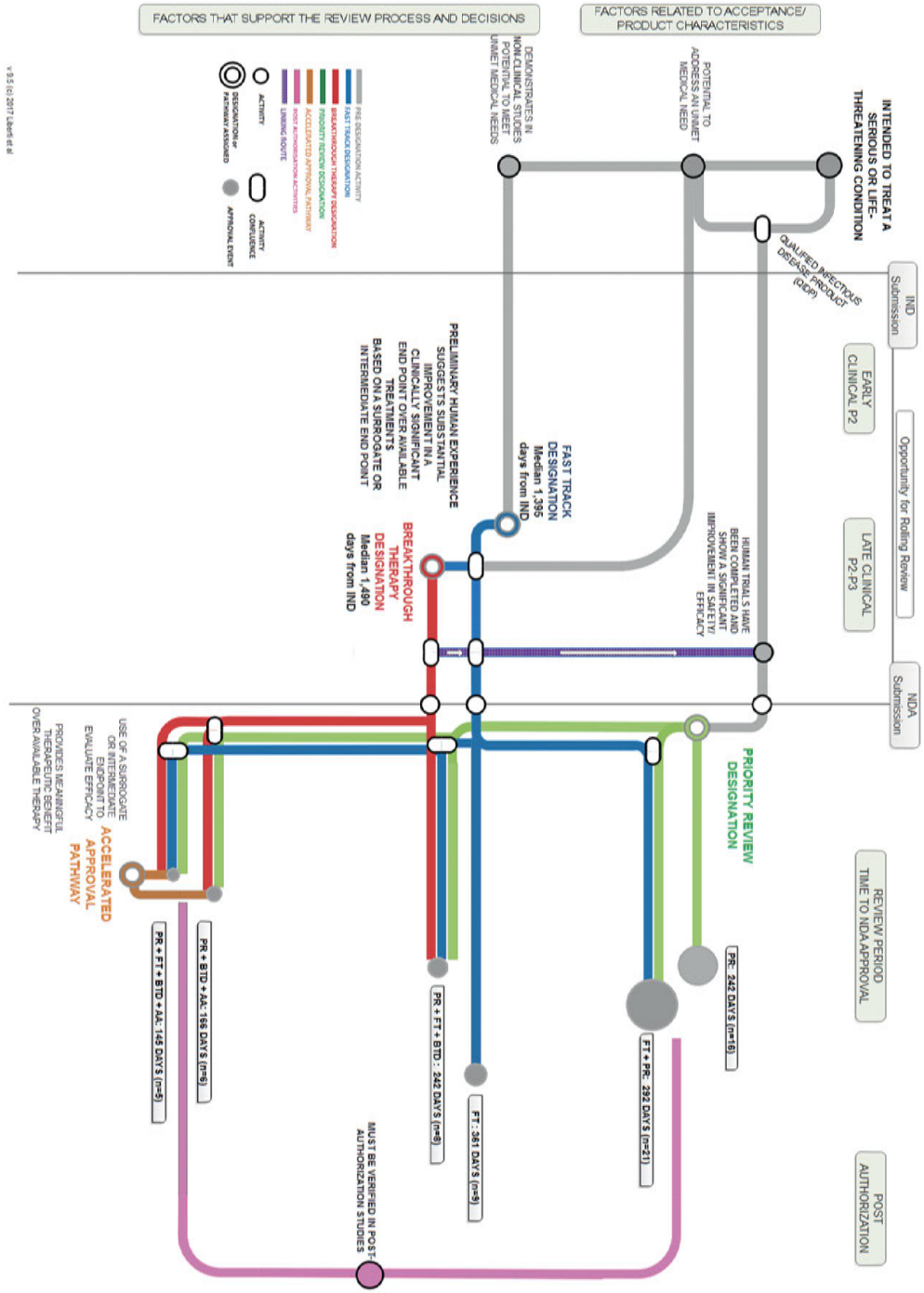

Figure 1. "Metro Map" analysis of FDA FRPs and influence on median approval times

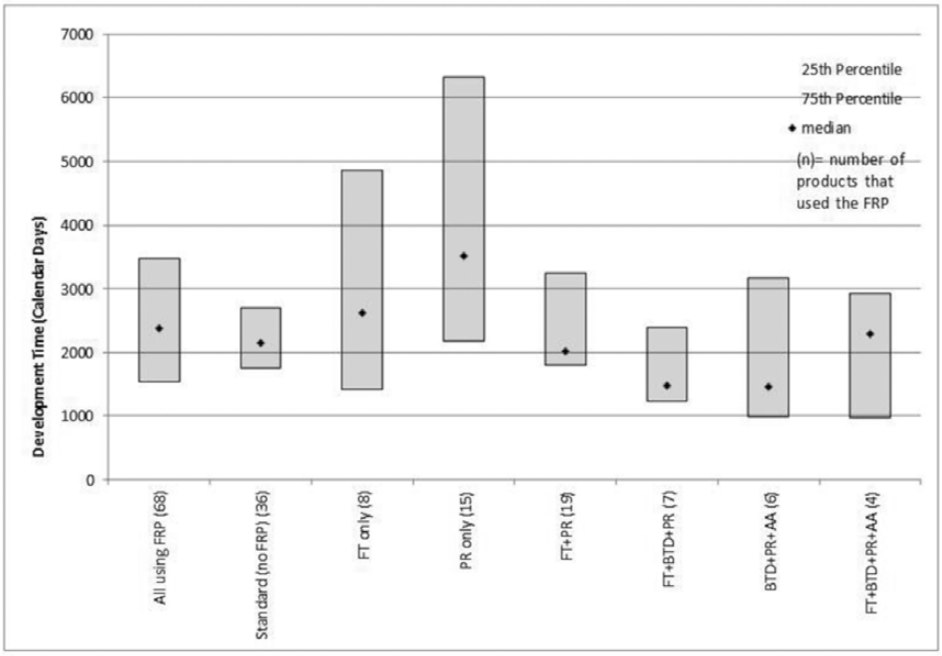

Figure 2. Median development times (IND to NDA submission) for products that followed one or more FRPs

did not use any FRP (standard reviews). PR alone had a median review time of 242 days. The most common FRP combination was FT+PR; the median approval time for the 21 products in this category was 292 days. The three fastest review times cohorts were PR+FT+BTD+AA (145 days), PR+BTD+AA (166 days), and PR+FT+BTD (242 days). The median approvals times and 25th -75th percentiles for FRPs used alone or in combination during the analysis time period used by 5 or more products are presented in Figure 3. The median approval times for FRPs used by the remaining products were AA (n=1; 1034 days), FT+AA (n=1; 304 days), PR+AA (n=2; 328 days), BTD+PR (n=3, 193 days) and FT+AA+PR (n=2; 543 days).

The median approval time for PR+FT+BTD was similar to that of PR alone suggesting that PR is a driver of shortened review time. The cohorts with the shortest review times also received AA. This program gives the agency the flexibility to approve products used for serious or unmet conditions (and with a positive benefit-risk profile) more rapidly on the basis of a surrogate or intermediate efficacy endpoints; expedited access is balanced against post-authorisation commitments of continuous assessment of the product's safety and efficacy linked to disengagement and withdrawal processes if the expected outcomes are not attained.

The use of all four FRPs together was associated with the fastest median approval time (145 days), and this likely reflected the critical importance of the products

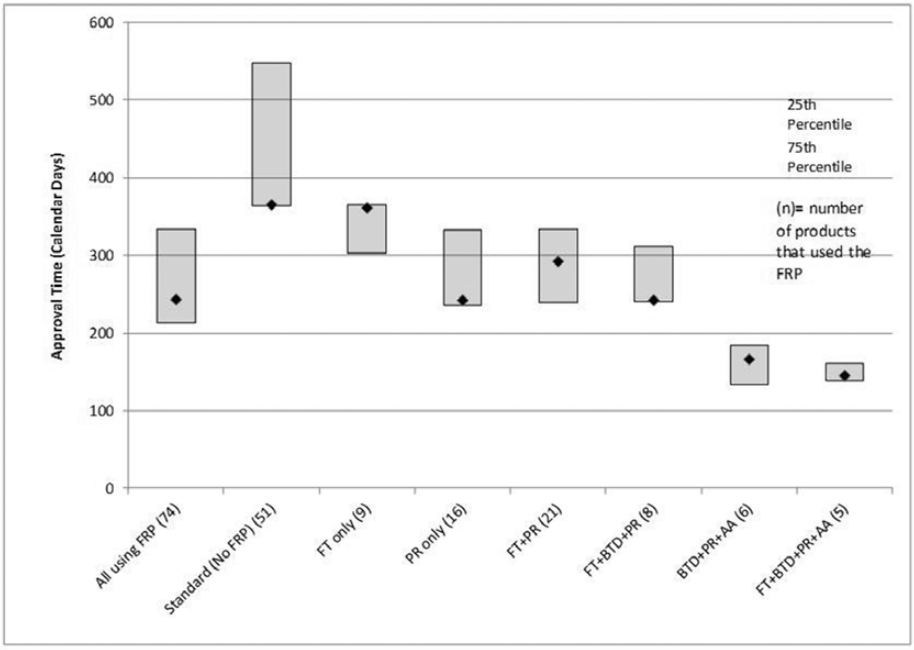

Figure 3. Median time for FDA approvals for products that followed one or more FRPs

assessed. All five products that qualified for use of all four FRPs (ibrutinib, idelalisib, nivolumab, osimertinib mesylate, daratumumab) are indicated for the treatment of serious oncologic conditions where there is a high unmet medical need.

When the median development and approval times were taken together, the time from IND to approval was 2,620 days for products that used an FRP and 2,513 days for those that did not use an FRP. Importantly, the shortest overall time from IND to approval was for the cohort of BTD+PR+AA (1,624 days). Combinations of FRPs contributed to faster overall times from IND to approval: FT+BTD+PR (1,720 days); FT+PR (2,308 days); FT+BTD+PR+AA (2,434 days). The longest times were FT alone (2,981 days) and PR alone (3,757 days).The FDA has worked closely with sponsors to manage adherence to post-authorisation commitments from FRPs. Where these are not fulfilled, the products may be withdrawn. In a recent example, the FDA approved lutropin alpha for use in infertile hypogonadotropic hypogonadal women under the AA pathway. Subsequently, the sponsor (EMD Serono) requested that FDA withdraw approval of the drug noting that it was not feasible to complete a trial that the company had agreed to at the time of approval; the application was withdrawn in 2016.

BTD has recently been shown to contribute to review times that were faster than target dates defined by PDUFA [6]. Because BTD was recently instituted (2012) many of the products in this cohort may not have been fully supported by the designation

throughout their development cycle; on-going assessments of new approvals will help define the contribution of BTD to the review timeline. Our findings support the value of the combination of FRPs for shortening review times beyond that provided by PR alone. These observations raise questions about the perceived market value of "Priority Review Vouchers (PRV)" wherein an eligible company can use the voucher to have any one of their drugs reviewed under PR.

APPLICATION TO OTHER FRPS

The nature of the data available during a product's development underpins the selection, sequence and confluence of FRPs. For example, not all products for serious or unmet medical need qualify for, or may find use of all FDA FRPs. However, the mapping approach presented herein can help illustrate how these programs fit into the overall product development and review process, the interconnections between the designations and pathway, and the relationship of their use to development strategies and approval times.

Similar research can be conducted to provide metrics around the use of novel FRPs in other ICH countries (e.g. Conditional Marketing Authorisation, Accelerated Assessment, Priority Medicines in the EMA, Early Access to Medicines Scheme in the UK, Sakigake at PMDA), and to assess the outcomes of activities associated with novel adaptive pathways. The utilisation of the metro map visualisation can serve as a platform to illustrate the requirements, touch points and influence on development, review and approvals times of these FRPs.

The metro map process can also assist in illustrating the routes and timings of specific FRPs often relied upon by maturing regulatory agencies (e.g. the WHO prequalification routes, EMA Article 58). Furthermore, this approach can provide transparency around FRPs being developed and implemented by maturing agencies and regional alignment initiatives around the world [2] and can help identify the different procedures and routes available to enable efficient outcomes through the appropriate application of FRPs.

ACKNOWLEDGMENTS

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chapter 5

POST-AUTHORISATION CONTROLS

chapter 5.1

POST-APPROVAL COMMITMENTS FOR DRUGS APPROVED BY THE FDA THROUGH EXPEDITED PATHWAYS

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*Poster presented at the Temple University Science Day, 17 February 2017**
To be submitted for journal publication
** This poster was awarded second place honours at this Science Day event*

INTRODUCTION

The approval of new medicines is regulated by agencies (i.e. FDA). Following their initial marketing authorization, many drugs require post-approval surveillance to confirm the findings from clinical trials. The FDA offers 4 pathways that expedite development or authorization of new medicines. These "facilitated regulatory pathways" (FRPs) encompass Fast Track (FT), Breakthrough Therapy designation (BTD), Priority Review (PR), and Accelerated Approval (AA).

Post-approval commitments (PACs) are set forth by the FDA as a condition of approval to better define a product's safety and efficacy profile. For the product to remain on the market, these PACs must be fulfilled by the manufacturers on scheduled deadlines. A variety of PACs have been designed to assure a product's efficacy, safety, and quality. Any shortcomings or failure to comply with these commitments can result in penalties, and even revoked drug approval. The extent to which these inform future knowledge about a medicine has been evaluated in both the US [1,2] and Europe [3,4]. However no study has look at the specific characteristics of the types of PACs put in place for products that have used an FRP in the US.

OBJECTIVES

The objective of this study was to assess the number, distribution, and characteristics of PACs imposed by the FDA on products that used FRPs. These products were stratified based on indication, type of study required, and the time needed to complete the PAC.

METHODS

During 2013-2015, we identified 74 drugs that were approved by the FDA using one or more FRPs. Data for these drugs were obtained through publicly available FDA websites (e.g. Drugs@FDA and the "Post-market Requirements and Commitments" search function at the FDA web site). Each drug was categorized based on type of FRP: FT, BTD, PR, or AA. A drug could have been assigned to more than one FRP category. Post-approval commitments were tallied and characterized as to whether the commitment was designed to further assess quality, efficacy, safety, or pharmacokinetics (usually in special populations or to assess food and drug interactions). PACs were also assessed by therapeutic areas (ATC codes). We used descriptive statistics to identify differences among cohorts. Because of the small numbers no formal statistical comparisons were conducted.

RESULTS

Overall, for this time period, 74 FDA approved drugs utilized one or more FRPs. For these 74 drugs, specific types of 735 PAC activities were requested by the agency.

SUMMARY

A total of 735 post-approval commitment types were observed across the 74 FDA products approved from 2013-2015 that used one or more FRPs. The most PACs were classified under ATC Codes L, Antineoplastic and Immunomodulating agents (n = 80) and J, Anti-Infectives (n = 28); because these are critical medicines for unmet medical need often approved based on minimal data to support safety and efficacy, it is reasonable that these categories would have the highest instances of PAC requirements. The most common types of PAC studies performed were those to investigate pharmacokinetics, safety, and efficacy, which are the key drivers of uncertainty at the time of approval. PACs were generally required to be completed in approximately 1200 days (from date of approval). Further analyses of PACs for these drugs approved through FRPs are being conducted.

Table 1. ATC Codes

Anatomical Therapeutic Class (ATC) Code	Therapeutic Drug Class
A	Alimentary Tract and Metabolism
B	Blood and Blood Forming Organs
C	Cardiovascular System
J	Anti-Infectives
L	Anti-neoplastic and Immunomodulating Agents
N	Nervous System
R	Respiratory System
S	Sensory Organs
V	Various

Table 2. Number of PACs by FRP and ATC code

		Number of Drugs By ATC Codes								
FRP	Number of PACs	A	B	C	J	L	N	R	S	V
FT	253	5	4	2	12	24	1	1		1
BTD	115	2			3	14		1		2
PR	279	7	1	4	13	28	2	1	1	5
AA	88		1			14	1			1
Total	735									

* Because a drug may have used more than one type of FRP, totals in any column may exceed 74.

Table 3. Number of drugs that used specific types of PAC study types by FRPs

FRP	Number of PACs	Number of Drugs By Types of Studies Performed					
		Efficacy	Efficacy + PK	Efficacy + Safety	PK	PK + Safety	Safety
FT	243	15	4	10	28	1	25
BTD	111	8	1	10	11		8
PR	269	19	2	18	30	2	31
AA	88	12		8	11		10
Total	711						

* A drug may have been required to comply with more than one type of PAC
* Details were not identifiable for 24 PACs

Table 4. Time given to complete PAC

FRP	Days (Average)	Minimum	Maximum
FT	1293	25	5879
BTD	1025	25	3555
PR	1359	25	5879
AA	1126	45	2859

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chapter 6

A GLOBALLY APPLICABLE FRP FRAMEWORK

chapter 6.1

A PROPOSED FRAMEWORK FOR A GLOBALLY APPLICABLE PRAGMATIC APPROACH TO USING FACILITATED REGULATORY PATHWAYS (FRPs)

A manuscript derived from this chapter will be submitted for publication

BACKGROUND

All regulatory agencies for medical products have come under pressure to address the timely review of important medicines. Because of an expanding workload of new and generic medicines, and limited by the constraints of institutional, technical and human resources, their capacities and expertise are challenged to keep up with the growing diversity of products.

The World Bank Sustainable Development Goal 3.8 seeks to achieve universal health coverage, with access to safe, effective, quality and affordable essential medicines and vaccines for all by 2020 [1]. The Lancet Commissions[2] confirmed the critical importance of making quality essential medicines available through the actions of effective medicines regulatory authorities. Many countries, however, lack agencies that can undertake a full independent dossier review to ensure safe and effective quality products enter their markets.

At an international level, duplication of regulatory evaluations of medical products and audits and inspections of clinical sites, manufacturers and suppliers create inefficiencies, time delays, and additional costs. While medicine regulators have a diverse set of responsibilities, the assessment of products to determine their suitability for use by a country is arguably among the most important functions. In part driven by resource constraints, there is increasing awareness of the need and value of implementing alternative regulatory pathways to expedite the assessments of new medicines particularly by emerging national regulatory agencies (NRAs).

Consequently, opportunities are available to mature and emerging agencies to accelerate the review of medicines by adopting alternatives to a standard review [3]. We characterise these expedited pathways as facilitated regulatory pathways (FRPs): regulatory pathways designed to accelerate product development, the submission of market authorisation applications, and regulatory reviews. The goal of FRPs is to speed patient access to new drugs with a positive benefit-risk balance, especially for serious diseases or where there is an unmet medical need. FRPs may increase the level of communication and commitment between the sponsor and the agency, can give a larger role to effects on surrogate end points, and may move some of the burden of clinical benefit and safety evidence generation from the pre- to the post-authorisation phase. Importantly some FRPs are designed to encourage reliance on or recognition of prior decisions made by reference authorities, thereby reducing regulatory duplication and the burden of review (see Chapter 1, General Introduction).

FRPs fall into two distinct categories: *Primary* FRPs are those used by a stringent regulatory authority (SRA) to(https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf) speed the development, review and initial approval of a product and may be alternately termed *mature, advanced or reference NRAs. Secondary* FRPs (those used by NRAs or regional regulatory initiatives (RRIs) wherein their decisions can be expedited by the reliance on or recognition of prior reviews) [4].

Table 1. Examples of Primary FRPs in selected SRAs

Program Focus	Agency and Primary FRP Program Name
Increased level of communication and commitment between regulator and sponsor	FDA Fast Track designation FDA Breakthrough designation PMDA Sakigake EMA PRIME programme
Faster Review	FDA Priority Review EMA Accelerated Assessment PMDA Priority Review Health Canada Priority Review (proposed) TGA Priority Review (proposed)
Give a larger role to surrogate or intermediate clinical endpoints	FDA Accelerated Approval – subject to confirmatory trials EMA Conditional Marketing Authorization
Approval on limited data; moves burden of evidence generation to post-authorisation period	FDA Accelerated Approval – subject to confirmatory trials EMA Marketing Authorization under Exceptional Circumstances Health Canada Notice of Compliance with conditions (NOC/c) Health Canada Accelerated Authorisation (proposed) TGA Provisional Approval (proposed)
Waivers or Incentives	FDA orphan designation EMA orphan designation FDA priority review vouchers

Primary FRPs are often described by terms such as *expedited, accelerated authorisation, priority review, and conditional authorisation*, among others (Table 1) [3]. Even those agencies that offer some form of primary FRP could benefit from the availability of multiple flexible pathways. However, as all reviews are labour-intensive, reliance- or recognition-based FRP approaches are now being considered to minimize duplicative effort and optimize resource use.

Secondary FRPs rely on or recognise a SRA or reference agency decision or on assessments conducted through a mutually aligned regulatory process (e.g. through an RRI). Furthermore, decisions may be based on the outcomes of an initial "altruistic" review, such as those conducted through the EMA Article 58, the PEPFAR (US President's Emergency Plan for AID Relief) process, the FDA Certificate of Pharmaceutical Product (CPP) for unapproved products (for drugs) or Certificate of Exportability (for biologics and devices) (https://www.fda.gov/RegulatoryInformation/

Guidances/ucm125789#vi), Swissmedic's Marketing Authorisation for Global Health products (MAGHP) and medicines reviewed through the WHO Collaborative Prequalification of Medicines Programme (PQP)[5]. Their role in accelerating medicine assessment will be illustrated in more detail in the sections that follow. Secondary FRPs are applied when the quality of the product under review has been verified to an appropriate standard.

Because of the flexibility offered by FRPs, diverse types of medicines can be reviewed through these pathways. Primary FRPs have been considered as most relevant for the assessment of medicines to treat serious conditions, where there is an unmet medical need or for those that demonstrate an important innovation [6]. Secondary FRPs, which can accelerate the review process by relying on or recognising prior decisions,widen the scope of FRP uses and evaluation of include generics, biologics, and vaccines among others. A single FRP cannot address the accelerated review of all medicines. These conditions have resulted in the development of numerous country- and region-specific pathways to expedite regulatory reviews [7].

LIMITATIONS OF AND OPPORTUNITIES FOR THE CURRENT FRP ENVIRONMENT

A pragmatic approach to using FRPs should provide regulatory flexibility and the selection of an appropriate FRP should be based on a logical framework. Emerging NRAs and RRIs have implemented diverse approaches to meet their respective public health mission [8,9]. This heterogeneity, coupled with a relative lack of transparency about the review process, complicates the ability of sponsors to effectively use FRPs in a coordinated manner. Although these pathways provide flexible approaches, their processes and goals vary, there is little standardisation and an opportunity exists to identify and implement best practices across them.

When considering the review of a marketing authorisation application (MAA), an agency must clearly define how its activity "adds value" especially when prior reviews have been conducted with positive recommendations by SRAs or reference agencies. To address this issue, a risk-stratification approach has been implemented by many agencies. However, there is no common or single approach to this stratification process. More appropriately referred to as *benefit-harms-uncertainty stratification* a product can be categorised by a variety of factors: the risk to the population by not making the product available while an unmet medical need exists; its expected benefit-risk profile; the uncertainty around the nature and results of the supportive evidence; the trust level in agencies that have conducted prior assessments and the strengths and limitations of relying on that decision.

One approach that is gaining acceptance among a growing number of NRAs is a process in which a three-tier review strategy is used to stratify reviews, commonly referred to as verification, abridged and full review options. Based on the assessment of risks, an agency can determine the best use of two types of FRP routes: *verification*

or *abridged*. These routes are characterised by the extent to which the agency relies on prior decisions, the details of the review, and timing of the review process. By using verification or abridged FRPs, an agency can ensure the quality, safety and efficacy of their products while relying on reviews and assessments previously conducted by reference authorities. Where the agency has the capability and capacity, it can maintain the option for a full independent dossier review.

Formally codified and implemented by Singapore, this approach can rely on prior decisions, provides regulatory flexibility, the ability to allocate resources to key dossier reviews, the jurisdictional sovereignty to reach a locally relevant benefit-risk decision, and the ability to speed the review of important new medicines. The characteristics of this model are illustrated in Figure 1.

Importantly, an abridged review requires that the NRA has the competency to "translate" the experience of the SRA to the NRA's jurisdiction. Recently Saudi Arabia and Egypt have implemented pathways based on this model. Indonesia has instituted a multi-path regulatory assessment approach that also tiers the risk associated with products for reviews based on product type and prior assessment history.

Despite the on-going trend towards global regulatory convergence, no formal guidelines or best practices have been promulgated that describe the elements of

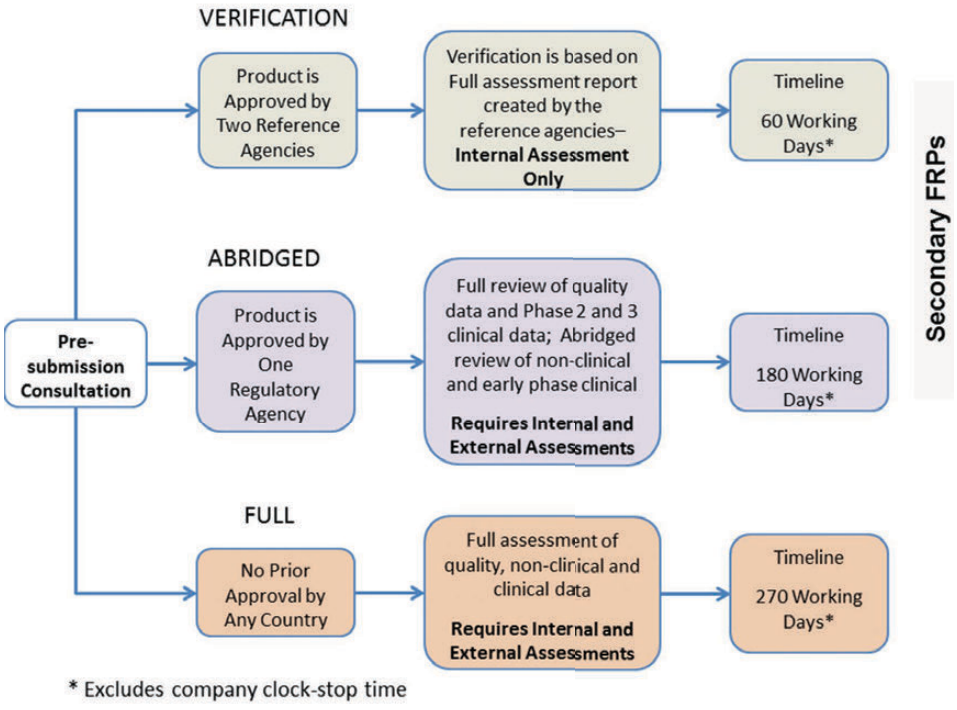

Figure 1. A model for risk-based stratification of regulatory reviews determined by a product's prior review experience (based on Singapore HSA criteria)

or conditions needed to select a particular accelerated regulatory review pathway. Diversity of FRPs creates confusion across stakeholders, with uncertainty about how to accelerate the review and differences in processes across jurisdictions resulting in patients questioning the timing or divergences in access to important medicines.

Deciding which route is best suited for a particular agency requires guidance offered through a framework approach. Because of the limited guidance available, an opportunity therefore exists to promulgate a framework for the use of FRPs that ensures that the work conducted by an agency adds value to the process. To this end, we propose herein a pragmatic approach to a framework for the effective use of FRPs that could serve as the evidentiary basis for a formal guidance on this topic. The approaches described herein have been designed to provide solutions to questions regarding the use of FRPs by NRAs: what conditions should be in place in a jurisdiction and agency for an FRP to be used effectively; what should be the basic characteristics of an FRP; what decision criteria can be used to guide a balanced regulatory decision; how can a risk-based stratification approach be used to maximise the use of prior regulatory decisions while ensuring that any additional review effort by a specific jurisdiction adds value to the prior decision?

BUILDING STRUCTURE INTO FRPS

The foundation for implementing and effectively using an FRP is the use of a framework to identify the most relevant FRP approach for the NRA. Addressing a spectrum of underlying considerations ensures that the appropriate systems are in place to provide the context for the use of specific types of FRPs. A logical framework identifies and aligns key characteristics of process predictability across locally implemented FRPs. It permits a pragmatic approach to determining how prior regulatory decisions can inform subsequent reviews. Applying a framework to understand the capabilities and processes used by other agencies to reach a regulatory decision builds confidence in and reduces uncertainties regarding their decision.

The Framework described here guides a pragmatic process for selecting review option pathways to accelerate regulatory reviews by assessing an agency's capabilities and environment and optimizing use of prior regulatory decisions. Importantly, following the Framework illustrates how an agency can rely on prior decisions and limit duplicative effort and add value to the process.

In their proposal for optimizing authorisations in emerging NRAs, Ahonkhai et al [10] identified three key strategies: a move to decrease the complexity of an individual agency's activities through regional alignment; the enforcement of international quality standards; and a focus on conducting value-added activities that minimize repetition, maximize the use of the WHO PQP, and build on NRA accelerated review programmes. Our framework addresses these strategies.

It is not our intention to describe the characteristics of each of the accelerated pathway options cited in this work. Rather, we have provided an holistic overview of how agencies can identify and implement the most appropriate FRP using supportive criteria based on evidentiary factors consolidated from the findings of a variety of research sources.

THE BUILDING BLOCKS OF AN EVIDENCE-BASED FRP FRAMEWORK

We propose a 4-step framework approach to determine diverse underlying factors contribute to the efficient implementation and use of primary and secondary FRPs. We have informed our framework through observations about factors that give confidence to a regulatory decision. This pragmatic framework is based on the consolidation of observations derived from primary research, international workshops, surveys, literature, regulatory capability categorisation analyses, and practical experience. We do not make recommendations for new alternative review pathways, but our recommendations provide guidance for the effective use of currently available approaches, which we believe offer ample flexible options.

Step 1: FRP Environment Preparedness

A regulatory environment is a reflection of a jurisdiction's political, social and legal policies. In a global survey [3], 80 respondents from 50 diverse pharmaceutical-related organisations provided their insights as to the environment and opportunities for the use of FRPs. More than half of the respondents believed that the following criteria were important social determinants for successful use of FRPs: having an enabling regulatory environment (proper laws and regulations including intellectual property protections); stakeholder support for and understanding of the benefits and uncertainties associated with an FRP-approved medicine; and agreement on appropriate evidentiary requirements (i.e., clinically relevant endpoints, patient reported outcome, etc).

Our observations from this and other studies point towards several consistent characteristics that underlie the effective use of an FRP. As detailed in Table 2 the characteristics fall into four domains of FRP environment preparedness: the social and regulatory environment (that encourage the use of a bona fide pathway); capacity and competency (agency ability to conduct the relevant form of review); decision-making tools (those that help conduct a consistent, predictable and transparent decision process); and post-authorisation activities (those that can add certainty to the initial decision).

The characteristics within each domain provide an ideal scenario; no jurisdiction would be expected to have all of these elements in place. For example, a WHO assessment of 26 sub-Saharan regulatory agencies found wide disparities in resources

Table 2. Step 1: Assessing the four domains of FRP Environment Preparedness (n=33)

Social and Regulatory Environment	Capacity and Competency
Country has a legal provision requiring health services and medicine registration [13]	Standards for the submission of a fit-for-purpose dossier are transparent [11]
Fit-for-purpose governmental regulatory enforcement infrastructure[13]	Standards for the assessment of the dossier are transparent
Political will to implement an enabling environment for FRPs	Ability to apply aligned diseases-specific guidances to assess products [11]
Agency commitment to FRPs	A formal policy recognises and encourages the adherence to Good Regulatory/Review Practices [4]
Country has memorandum of understanding or other legal structures with other NRAs	The agency maintains a well-trained professional staff [12]
Mechanisms are available to base a decision on regulatory reviews from other agencies	Best practices ensuring the review adds value to previously conducted assessments [12]
Opportunity for early stakeholder engagement [6]	There are mechanisms to effectively use non-agency specialists/advisors to support the review [11,12]
Ability to identify an "unmet medical need" [11]	The agency serves as a regional Center of Excellence
Consensus on "innovativeness" or societal impact of the product	A transparent project management/status tracking system is used
Impact of local requirements is transparent (e.g. bridging studies, local trials) [11]	
Societal agreement on benefit-risk and uncertainty tradeoffs associated with FRPs [6]	
Integration of patients voice/expectations [6,11,12]	
Opportunities to obtain stakeholder feedback on the FRP process [11]	
Opportunities for inter-agency shared learnings and with collaborating parties [11]	
Established sanctions for infringement of standards by regulated parties [13]	
Decision Making Tools	**Post-Authorisation Activities**
Acceptance of inspections by other NRAs or PIC/S	Use of globally validated risk-management tools [11]
Acceptance of clinical data from other regions	Has formal access to national, regional or global pharmacovigilance databases
Acceptance of relevant comparators from other jurisdictions [11]	Has a transparent mechanism to manage post-approval manufacturing and labeling changes
Routine use of decision-making frameworks (e.g benefit-risk assessment tools)	Having defined withdrawal and disengagement strategies [6]
Acceptance of validated surrogate efficacy markers [11]	

FRP= facilitated regulatory pathway; NRA=national regulatory authority; PIC/S= Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme

Table 3. Step 2: Process Criteria for FRPs (n=27)

Agency Assistance and Acceptance Criteria	Elements of the Review process	Decision Criteria	Post-Authorisation and Disengagement Activities
A dedicated team/office is available at the agency for interactions/advice	An SOP on the review process and criteria is available to the reviews (or publicly)	General Criteria are considered (e.g.):	A public assessment report describing the rationale for the decision is available
An SOP/guidance for submitting the dossier and managing the submission is available	The review target time is defined by the agency (e.g. between 60 and 90 days)	Well-defined indication	A risk management plan may be established as a condition of approval
Product Selection criteria are defined (e.g.):	A "rolling review" can be conducted	Sponsor experience	A sponsor commitment to conduct post-authorisation follow-up may be established (on an as-needed basis)
Treatment of a serious disease	When Non-agency experts participate in the review of the dossier, their response time is defined (e.g. within 30-90 days; specific meeting participation etc)	Extent/nature of prior interactions with the agency	Post-approval variations are addressed in a timely manner
Address an unmet medical need	Company response time to questions is defined (e.g. 30 days); triggers a clock-stop for the review	A decision can be based on a prior approval by an SRA, RRI, or reference agency	A periodic re-approval is undertaken (e.g. every 1-2 years)
Biologic or vaccines	GMP inspections can be based on other reference authority decisions; PIC/S	WHO PQP status is recognised	A mechanism to identify the cohort that benefits the most from the therapy is available.
Generic products	Requirements for quality and sample analysis are defined	Prior marketing experience of the product helps to define the product benefit-risk profile	There is a defined mechanism to consider the product for restricted use or withdrawal if it does not meet port-authorisation criteria or if indicated by international findings
Orphan drugs	Stability requirements adhere to international standards	Clinical assessment criteria:	
Are considered Essential medicines		Use of relevant endpoints has been verified	
Where preliminary clinical evidence indicate potential for improvement of a clinically relevant endpoint		Clinically important improvement in endpoints and other efficacy parameters are defined	
The agency should respond to the request for use of an FRP in a timely manner (e.g. 30 days)		CPP requirements are defined and met	
An application processing fee may apply		Local data are not required for approval	
MAA can be filed electronically		Quality of product has been well characterised	
Relevant sections of the CTD to be submitted should be agreed upon with sponsor			

CPP=certificate of pharmaceutical product; CTD=common technical document; FRP=facilitated regulatory pathway; GMP=good manufacturing processes; MAA=marketing authorisation application; NRA=national regulatory authority; SRA=stringent regulatory authority; PIC/S= Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme RRI=regional regulatory initiatives; SOP=standard operating procedure; WHO PQP=World Health Organization Collaborative Prequalification of Medicines Programme

and capabilities. While the majority of countries had in place a legal basis for registering medicines, the guidelines and procedures were typically administrative rather than technical [14]. This was consistent with broader findings from our survey of FRPs from 29 geographically diverse emerging NRAs where more than twice as many procedural characteristics were described in guidances compared with substantive characteristics that supported decision making [6].

Therefore, implementing the characteristics that are within the current regulatory and technical scope of an agency provides a solid step towards regulatory process strengthening in particular as related to FRPs and addresses the questions of "to what degree does the environment in which my agency works prepare it to be fit-for-purpose to effectively use an FRP?"

Step 2: Process Criteria for FRPs

Once an agency has assessed its environment preparedness, it must consider to what extent it has or can address specific criteria that are relevant to assessments conducted via a FRP. Step 2 (Table 3) provides a detail of internal process activities derived from a review of FRPs in SRAs [15] and a survey of FRPs in emerging NRAs [6].

The activities are organised according to four key process steps an agency follows when using an FRP: the type of pre-submission assistance provided and the dossier acceptance criteria; the review process; the criteria upon which the regulatory decision is made; and post-authorisation and disengagement activities. Therefore, an agency's internal processes must align with the type of reviews it plans to conduct.

Step 3: Self-assessment of readiness and capacity

The increasing importance of ensuring efficient, fit-for-purpose regulatory processes has highlighted the underlying diversity in structure and capabilities across regulatory agencies. Because a variety of factors will influence the ability of an agency to follow a particular FRP pathway, a classification methodology can help agencies determine their state of readiness to undertake specific regulatory review activities.

We propose stratification criteria based on these and other experiences and have illustrated these in Table 4. Our schema allows an agency to classify itself into one of 3 tiers. An agency can be classified as Tier 1: fully prepared to implement primary and secondary FRPs; Tier 2: have the capacity to implement some FRPs or Tier 3: do not have the capacity to implement an FRP.

Tiers 1 and 2 are further classified based on the extent to which an agency can implement a primary or secondary FRP. Based on their self-assessment, an agency can identify the Tier Stratification Class by which it is best described. These classes are: A (mature); B (maturing); C (realizing); D (evolving) and E (foundational). Tier 3 agencies are considered in Class F (ill-equipped). RRIs may comprise agencies that span the three tiers and therefore must assess the collective capabilities to identify

Table 4. Step 3: A tier-based agency self-assessment approach to establish readiness to implement an FRP process

Stratification Class	State of Development	WHO Maturity Level	Number of Elements from Step 1 (Table 2)	Number of Elements from Step 2 (Table 3)	Percentage of Elements from the PAHO Assessment Scheme Table 5
Tier 1. Prepared to Implement Primary and Secondary FRPs					
A- Mature	Fully mature review capabilities	Class 5: Fully integrated; initiative-taking; autonomous regulatory system	20 or more	20 or more	75% -100%
B- Maturing	Have most of the review capabilities of a Mature agency	Class 4: Proactive, well-resourced regulatory system; continually improving functions	12 to 19	12 to 19	75%-100%
Tier 2: Have the capacity to implement some FRPs					
C- Realising	Transitioning from Evolving to Maturing	Class 3: Systematic regulatory approach; functions with essential capacity	8 to 12	8 to 12	50%-74%
D- Evolving	Implementing basic review processes and structures	Class 2: Reactive and/ or responsive regulatory system	4 to 8	4 to 8	25%-49%
E- Foundational	Identifying basic review processes and structures	Class 1: Some elements of regulatory systems	4 to 8	4 to 8	1%-24%
Tier 3: Do not have the capacity to implement an FRP					
F- Ill-equipped	No formal review process in place	Class 1: Some elements of regulatory systems exist	3 or fewer	3 or fewer	none

CPP= Certificate of Pharmaceutical Product; FRP=facilitated regulatory pathway; MAA=Marketing Authorisation Application; NA=not applicable; PAHO=Pan American Health Organization; PV=pharmacovigilance WHO=World Health Organization

the most applicable overall tier to enable the utilisation of FRPs that ensure efficient regulatory reviews.

We described ten categories of criteria an agency should use to determine its readiness to use an FRP in Table 4. In line with some other regulatory capacity-building initiatives, such as that promulgated by the Pan American Health Organization (PAHO),

Resources for Reviewing MAAs	Serves as a Formal Reference Agency	Relies on CPP	Transparency of Submission Requirements	Comply with WHO Minimum requirements for a functional PV system	Applies Good Review Practices and Decision Frameworks	Staff Training
Diverse and well-resourced providing ability to conduct full reviews of all product types	Yes	No	Consistently well documented and readily available	Yes	Well-documented and consistently embedded in practice	Well structured; comprehensive; required participation
Diverse and well-resourced providing ability to conduct full reviews of most product types	Yes	Varies by country	Generally well documented and readily available	Yes	Generally well-documented; inconsistently embedded in practice	Well structured; comprehensive; inconsistent participation
Fit-for-purpose resources	No	Yes	Generally well documented but availability is inconsistent	Yes	Being developed; opportunities to improve embeddedness	Fit-for-purpose; under development; required participation
Under-resourced for some regulatory activities	No	Yes	Poorly documented; Limited availability	Possibly	Being developed; inconsistently implemented	Being developed; inconsistent participation
Under-resourced for most regulatory activities	No	Yes	Limited or no documentation	Possibly	Conducting needs assessment; not implemented	Conducting assessment of training needs
Limited or no resources	NA	Yes	NA	No	NA	NA

for the number of elements from Steps 1 and 2, and the PAHO assessment scheme, we have made recommendations for specific numbers of process criteria that in this case, should be in place for the effective use of an FRP. These serve as a guide to key elements agencies should consider when addressing a risk-based review. While it would not be expected that any agency would be in a position to implement or

Table 5. PAHO Indicators for the assessment of national regulatory systems

Organization and structure

5000. Pharmaceutical regulation is under the jurisdiction of the Ministry of Health and other organs (institutions, agencies, regulatory authorities) at the same or different levels of government.

5001. The responsibilities, functions, organization, powers, and structure of the organization(s) responsible for pharmaceutical and health-technology regulation are clearly defined in legal documents and supplementary documents, in particular as relates to the competencies and objectives associated with the pharmaceutical regulation that it/they control(s), such as categories of regulated products and regulatory functions.

5002. Legislation defines the institutions involved in the pharmaceutical regulatory system, their authority, functions, roles, responsibilities, and powers.

Legal basis

5003. Legislation defines the creation of the NRA, its mission, and its terms of reference, as well as its scope, functions, and responsibilities.

5004. The Regulatory Authority responsible for implementing and enforcing the regulations involved in developing them.

5005. During the process of developing legislation and regulations, there are mechanisms through which various sectors of civil society are involved, such as NGOs, health sector representatives, industry, consumers, patients, and other stakeholders.

5006. The legislation and regulations are publicly available for the stakeholders to whom they apply, and adequate means and channels of communication are available to make the legislation and regulations known.

5007. The legislation gives the NRA authority to bring in experts and create committees, and to define their functions and the situations in which they are to be brought in or created.

Administrative model

5008. The organizational structure of the NRA includes a governing board, executive staff, and administrative committee or organ responsible for creating and/or adopting the strategic development plan.

Institutional development

5009. The NRA has an institutional development plan that is implemented and up to date.

5010. The general objectives of the NRA are established and have been broken down into specific objectives, with timeframes for the different regulatory functions.

Quality management system

5011. The NRA has implemented a quality management system (QMS) for all regulatory processes.

5012. The quality management system is based on or recognizes reference standards (WHO, PIC/S, ISO, etc.).

5013. The documentation system needed to establish, implement, and maintain the QMS has been created (quality manual, records, policies, quality procedures, operational procedures).

Funding of the NRA

5014. The sources of funding for the NRA to carry out all its regulatory functions have been established.

5015. The rates, fees, charges, or costs that must be paid for the NRA's services are published. 0

5016. The NRA has the authority to collect funds and to use them internally.

Human resources management

5017. There is an organizational chart of the NRA's structure.

5018. The obligations, functions, and responsibilities of key staff are set forth in their job descriptions.

Table 5. (continued)

External committees and experts

5019. The NRA has an Advisory Committee (which may include in-house specialists and external experts) that is involved in the NRA's regulatory processes.

5020. There is a written policy/procedure for selecting and bringing in external experts, in which candidates are selected by a panel or jury whose final decision is made public.

5021. There is a general policy on potential conflicts of interest that applies to external experts brought in on an ad hoc basis as well as to members of the Advisory Committee.

5022. The NRA participates in a global network with recognized scientific associations and professional groups.

Transparency and confidentiality

5023. Legislation includes requirements to ensure confidentiality and transparency in the work of the NRA.

5024. There is a documented policy on public access to information, with defined exemptions/exceptions.

5025. Information on legislation, regulation, procedures, and guidelines is available to the public on websites and through other mechanisms that ensure that such information is satisfactorily available and up to date.

5026. Information on decisions is available to the public on a timely basis, and includes negative decisions on specific cases (when legislation so allows).

5027. The NRA holds meetings regularly with stakeholders and creates opportunities for consultation with the general public, such as days when it is open to the public.

Independence and impartiality

5028. There is a documented code of conduct for staff members involved in regulatory functions.

5029. There is an internal policy/established mechanism regarding potential conflicts of interest that applies to members of the staff and is updated with appropriate frequency.

5030. The NRA maintains independence from researchers, producers, distributors, and drug wholesalers.

Infrastructure

5031. The NRA's spaces, work environment, and room for filing documentation are adequate.

5032. The NRA has the appropriate equipment for conducting its regulatory functions.

Monitoring and control

5033. Regulatory functions and processes are monitored and reviewed regularly and systematically to identify problems, gaps, weaknesses, and inconsistencies within the NRA.

Information management system

5034. The NRA uses computer systems to manage data efficiently so that the information is collected, entered into a database, and put in reports where it can be consulted.

5035. The NRA has its own website, or has an agreement to use another institution's.

ISO=International Organization for Standardization; NGO=non-governmental organization; NRA=national regulatory authority; PAHO=Pan American Health Organization; PIC/S= Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme [16] and http://www.paho.org/hq/index.php?option=com_content&view=article&id=1615%3A2009-sistema-evaluacion-autoridades-reguladoras-nacionales-medicamentos&catid=1267%3Aquality-drug-regulation&Itemid=1179&lang=en

integrate all of these activities into their FRP process, an agency that works to address these will be moving towards building a robust, transparent, consistently applied, efficient FRP process.

The WHO is beginning to apply a set of standards to the evaluation of the maturity level of regulatory agencies based on ISO 9004; this assessment allows a categorization from 1 (no formal approach to the issue) to 5 (best-in class performance) [13]. As this approach is under development and has not been incorporated into our Framework pending further experience, we have noted in Table 4 the WHO maturity level classification terminology that we believe is congruent with our Framework

Categorizing agencies as to their structure, capacity, and resources has also been undertaken by the PAHO. PAHO has developed basic indicators to assess regulatory capacity http://www.paho.org/hq/index.php?option=com_content&view=article&id=1615%3A2009-sistema-evaluacion-autoridades-reguladoras-nacionales-medicamentos&catid=1267%3Aquality-drug-regulation&Itemid=1179&lang=en). Based on the percentage of 36 critical indicators (Table 5) that have been implemented agencies are categorized from Level 1 (where offices for the health institutions fulfil certain basic health regulation functions for medicines, 0-24% implementation) to Level 4 (in which the NRA that is competent and efficient in performance of the health regulation functions and serves as a Regional Reference Authority, 75% to 100% implementation). We believe that the PAHO assessment scheme is a validated tool to evaluate the readiness of an agency to conduct medicine regulations, can be extrapolated to other agencies and therefore, forms part of this Framework.

We would expect all Tier 1 agencies will meet minimum requirements for a functional national pharmacovigilance system as promulgated by the WHO [17],

Table 6. Step 4: Types of risk-stratified reviews that could be implemented by agencies based on their tier stratification

Tier Stratification Category	Primary FRPs		Secondary FRPs	
	Full (Standard)	Full (expedited)	Abridged	Verification
Tier 1. Prepared to Implement Primary and Secondary FRPs				
A (Mature)	YES	YES	YES	YES
B (Maturing)	YES	POSSIBLY	YES	YES
Tier 2: Have the capacity to implement some FRPs				
C (Realising)	POSSIBLY	POSSIBLY	YES	YES
D (Evolving)	NA	NA	YES	YES
E (Foundational)	NA	NA	POSSIBLY	YES
Tier 3: Do not have the capacity to implement an FRP				
F (Ill-Equipped)	NA	NA	NA	NA
Regional Regulatory Initiatives (RRIs)				
RRIs	POSSIBLY	POSSIBLY	YES	YES

FRP=facilitated regulatory pathway; NA: Not applicable

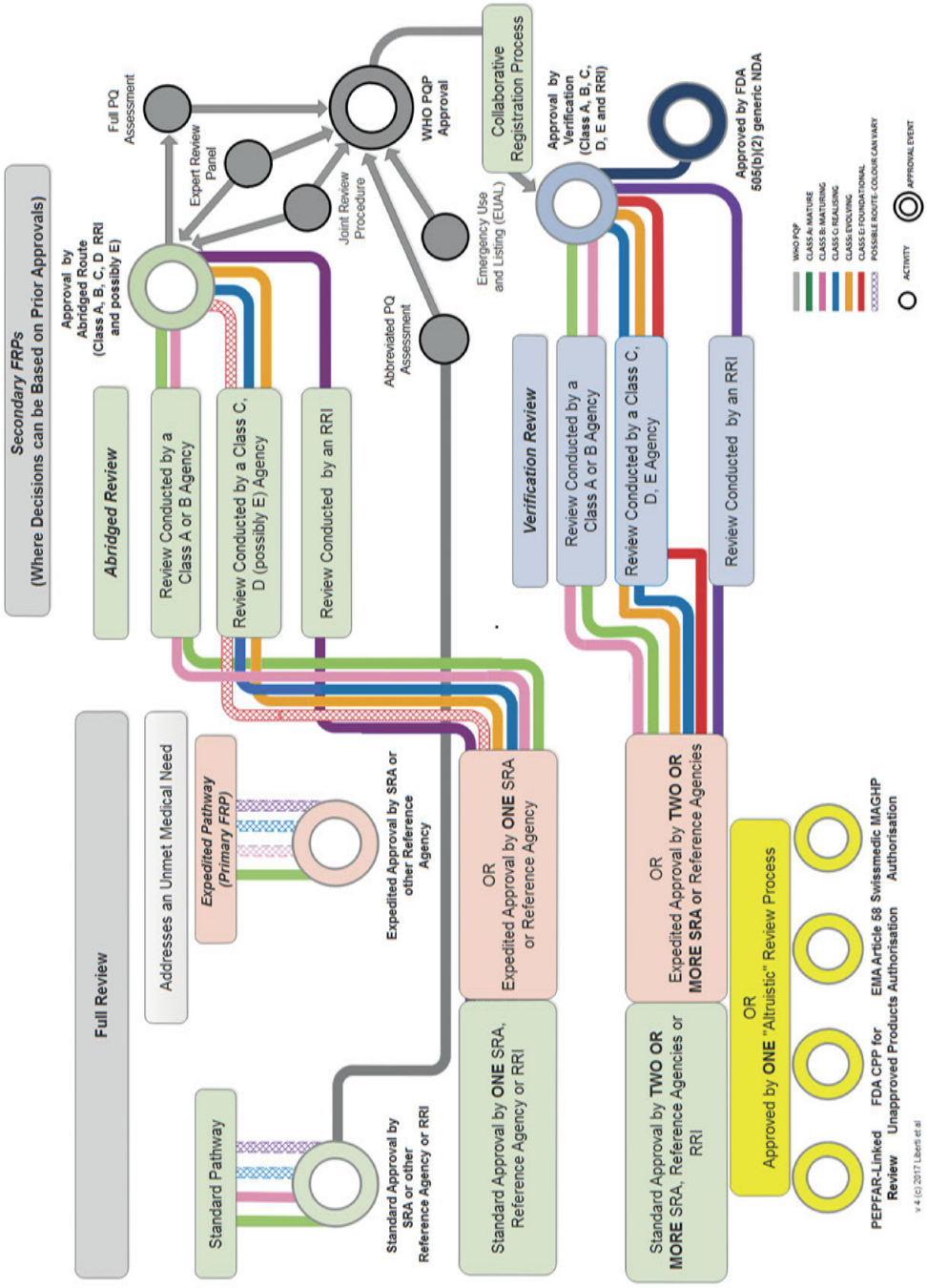

Figure 2. Step 4 Metro Map. An integrated Framework for the use of Primary and Secondary FRPs

Table 7. Proposed information requirements and agency activities for risk-based FRP reviews

Criteria	Full Review	Abridged Review
Product Quality		
Formulation, manufacturing process and dosage form are identical or substantially similar to a prior approval		
CPP or other proof of quality (e.g.PIC/S) is required		☑
Full stability data report is required		☑
Indication, Dosage, Strength, Labeling		
Are identical or substantially similar to a prior approval		
Prior Regulatory Reviews		
Standard: Approved by one SRA, reference agency or RRI OR Expedited: Approved by one SRA or reference agency		☑
Standard: Approved by two or more SRA, reference agencies or RRI OR Expedited: Approved by two or more SRA or reference agencies		
Product is being made available through an NGO or aid programme or has been reviewed by WHO PQP		
Documents and CTD sections (noted parenthetically) to be submitted by the sponsor	Full CTD for Quality, Non-Clinical and Clinical.	Quality Summary (2.3), Non-clinical Overview (2.4) and Tabulations/Summary (2.6), and Clinical Overview (2.5).
Agency actions required to add value to the assessment	Agency conducts a full, independent assessment of findings of each CTD section and Assesses benefit/risk. Prepares Comprehensive internal report and PAR	Full review of 2.3 Quality Assessment of Country (programmatic) suitability. Summarizes key aspects of observations and assesses implications of benefit/risk for local population. [Prepares PAR]

CTD=Common Technical Document; FRP= facilitated regulatory pathway; PAR=Public Assessment Report
NGO=non-governmental organization; NRA=national regulatory authority; QIS- Quality Information Summary
PIC/S= Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme
RRI=regional regulatory initiative; SRA=stringent regulatory authority

Verification Review	Pro-forma Registration
☑	
☑	
☑	
☑	
☑	
	☑
PARs from SRA/Reference agencies Quality Summary (2.3) Or PQ QIS	PARs from SRA/Reference agencies PQ QIS
Full review of 2.3 Quality or of the PQ QIS Review "Desk Audit" of PARs for Non-Clinical and Clinical. Assessment of Country (programmatic) suitability. Statement indicating verification review has been conducted. [Prepares PAR]	"Desk Audit" of PQ QIS. Pro-forma confirmation product registration.

although not all Tier 2 agencies will be in this position. The following are the minimum WHO requirements that should be met in any national pharmacovigilance system. 1. a pharmacovigilance centre with designated staff collaborating with the WHO Programme for International Drug Monitoring; 2. a spontaneous reporting system; 3. a database for managing reports; 4. a pharmacovigilance advisory committee; 5. a clear strategy for routine and crisis communication.

The value of this classification framework is that it helps an agency determine whether its capabilities are fit for purpose for conducting a full review or whether their added value is best applied to the type of FRP it selects through Step 4. Importantly an NRA can be considered "functional" even if relying on others for certain regulatory activities.

Step 4: Determining the most relevant FRP

The basis of the approach we promulgate is that any activity conducted by an agency following an initial assessment of a product by a SRA, RRI or reference agency, must add value to the prior review. Our focus on reducing duplicative efforts, building process efficiency and effectively allocating scarce agency resources by selecting FRPs that are appropriate for each Tier Class is consistent with the WHO focus on the related concepts of reliance and recognition.

Several FRP options are available to regulatory agencies with the appropriate competencies to use these effectively. Based on the experience of countries such as Singapore and Saudi Arabia and supportive research [3,6,18,19,20] we propose a Framework that can be readily implemented by emerging NRAs in Tiers 1 and 2 to identify the most relevant risk-based stratification pathway for a particular MAA review.

Simplified, a proposed approach to the type of review each Class could best implement is presented in Table 6.

Table 7 proposes the type of data to be submitted by the sponsor or obtained by the agency, and identifies the "added value" activities we propose be conducted by the reviewing agency using FRPs. Agencies have often requested complete dossiers even in the absence of a procedure or capabilities to review all sections; these proposed submission components should therefore be negotiated as part of Step 2 (see Table 3; Agency Assistance and Acceptance Criteria).

However, we illustrate a flow approach for determining the most appropriate review pathway to be used by a specific agency (Figure 2). This approach is based on the "metro map" concept previously used to describe primary FRPs at the FDA [20] and consolidates all of the major primary and secondary FRP review pathways. Based on its class, an agency can determine its options for using a secondary FRP and relying on predicate decisions or whether it can pursue a more comprehensive expedited initial review (primary FRP).

Tier 3 countries will not have the capabilities to benefit from the use of verification or abridged reviews. However, when medicines are made available through non-

governmental organisations or aid agencies, some form of importation license or other formal recognition of the receipt of the product needs to be available. In these cases we suggest the use of a "pro-forma registration" in which a desk audit of the PQ quality information summary is conducted and a confirmation of registration is maintained on file (Table 7).

As with any other regulatory intervention with great potential impacts, measures aimed at recognising other regulator's decisions require an understanding of the other's system and requirements, an analysis of the impact of these decisions before they are applied, and the design of the best strategy and regulatory option to be followed [4]. Our framework steps build a platform of trust based on allowing agencies to understand the readiness and capability levels of agencies upon which reliance or recognition can be based.

Pharmacovigilance, post-authorisation and disengagement procedures

Decisions made by an SRA about products that have undergone review via an FRP may be based on more limited clinical experience than products that have undergone a standard development programme. Primary FRPs may shift the burden of data collection and activity verification to the post-authorisation period. In SRAs, post-authorisation pharmacovigilance can be robust and is a tested approach to confirming authorisation decisions. At the FDA, post-approval commitments for products approved via an FRP have been found to vary by therapeutic area with most focusing on further assessments of pharmacokinetics, followed by safety and efficacy issues [21].

When emerging NRAs use secondary FRPs based on prior decisions made via standard or expedited pathways, these decisions have likely been made without representation of local populations. Therefore, the opportunity for appropriate post-authorization monitoring of the product by the RRI or NRA to build certainty around the local benefit-risk-uncertainty decision remains.

However, even basic pharmacovigilance may be a long-term goal for many regions. An assessment of systems in India, Uganda and South Africa found that all three countries faced similar barriers: lack of sufficient funding, limited number of trained staff, inadequate training programs, unclear roles and poor coordination of activities. Although South Africa has a legal requirement for pharmacovigilance, these countries uniformly were found to lack adequate capacity to monitor medicines and evaluate risks according to the minimum standards promulgated by the WHO [22].

Fortunately, the growing access to global pharmacovigilance databases (e.g. VigiBase [23], VigiMine and VigiFlow from the Uppsala Monitoring Centre (UMC); http://www.who-umc.org/graphics/28464.pdf) and the FDA's Sentinel programme provides regulators with speedy access to important changes in the safety status of approved products and can play key roles in jurisdictions with limited pharmacovigilance capabilities. In addition, alerts from pharmaceutical companies and web posting from SRAs and reference agencies regarding safety labeling updates can provide insights

into safety changes. With support from the UMC, approximately 60 % of African countries were full or associate members of the programme by 2010 signaling an increasing recognition of the importance of post-authorisation pharmacovigilance monitoring an important sign of the importance on collaborative safety assessments [24].

Other approaches to informing a post-authorisation assessment include activities such as those of Pharmacovigilance sans Frontiers (PVSF), a group of African consultants with interest in pharmacovigilance whose focus is on drug safety issues in the African setting and the establishment of a WHO Collaborating Centre for Advocacy and Training in Accra, Ghana; these represent important advances towards consolidating the initial gains made in the establishment of pharmacovigilance in developing regions [24].

A jurisdiction that uses a secondary FRP should have the ability to periodically re-assess the product's safety. We observed that 78% of FRPs from emerging NRAs assessed [6] required some level of commitment from the sponsor to conduct post-authorisation studies (these were not specifically indicated to be done in the local jurisdiction).

In concert with routine pharmacovigilance assessment there is a need to have well-defined product withdrawal and exit strategies. Approximately three-quarters of FRPs assessed from emerging NRAs described the need to establish post-authorisation control procedures [6]. These may span from updating cautions and implementing new warnings in the labeling, to narrowing the use of the product to specific patient groups or through selected prescribers, to full withdrawal. In each of these cases, it is critical to ensure that even if faced with a reduction in access, responding patients can continue to receive the medicine. However the onus of managing post-authorisation lifecycle variations on resource-constrained NRAs must be considered and the WHO has developed guidance on best practices and initiatives such as these can reduce some of the burden on agencies [25].

Can realistic recommendations be made for target FRP timelines?

Whether to use a verification, abridged or full review pathway as the route to a regulatory decision will be based on the capacity of the agency, a risk-based assessment of the product and other factors associated with the legal and regulatory environment. These decisions therefore may be subject to inefficiencies or delays.

Several factors will affect the speed at which a product is reviewed by an FRP. Initially, agencies and sponsors should reach a timely agreement as to whether the submission is appropriate for review via an FRP and that the submitted dossier meets the expected content requirements. Our survey of emerging NRA FRPs found that most commonly, agencies with FRPs strive to respond to a request for an FRP designation within 30 days of the sponsor request [6]. We believe this is an appropriate

response target that allows prioritisation of products to be identified as being eligible to proceed through the Framework described in Figure 2.

In theory, the use of FRPs can reduce review time by both SRAs and emerging NRAs. In an assessment of products approved in 2015 by six SRAs, products that benefitted from an expedited FRP (e.g. priority or accelerated review) had an overall median approval time (agency plus company time) of 265 days compared with 407 days for standard reviews [26].

The Singapore and Saudi models set agency timelines, excluding clock stops during which the sponsor responds to agency queries, as follows: Verification review- Singapore 60 days; Saudi 30 days. Abridged review- Singapore 180 days; Saudi 60 days. The Egyptian Decree 820, which describes a 3-option risk-based registration process, commits to timelines ranging from 1 month to 6 months. An analysis of review times for emerging NRAs as determined by CIRS for the period of 2011 to 2015, based on industry-provided data (internal data set, CIRS) indicated that overall median total review time (agency plus industry clock stop time) was 251 days for products assessed by a verification route (57 products assessed by 2 countries) and 421 days for products that were assessed by an abridged route (315 products assessed by 9 countries). Individually for the countries assessed, the total review times ranged from 245 to 256 days for verification reviews and from 282 to 892 days for abridged. Among 98 products approved by the WHO CRP by 2015, 57 were approved within 3 months, and 77% within 4 months; the median time was 89 days [27]. In our review of guidelines for FRPs in 29 emerging NRAs, the most common agency target time cited for a priority/accelerated review pathway was 61 to 90 days [6].

These observations suggest that for agencies that wish to implement a verification FRP pathway, the target time of up to 120 calendar days for agency or RRI time, excluding clock stops for sponsor responses, is a practical goal. An abridged review could be completed in 180 calendar days (excluding clock stops). If the NRA must further approve the product for use in its jurisdiction following approval by a RRI, this should occur within 60 calendar days of notification of the RRI decision. In order to ensure that these FRPs meet their mandate, agencies should simplify the process used to communicate requests to companies and companies should seek to respond in a timely manner.

However, agencies should only request additional information when the questions add value to the review (e.g. to clarify a benefit-risk profile for the local population, where stability data cannot be extrapolated to a local jurisdiction); if the questions have been addressed in previous reviews by other agencies and the assessing agency has access to previous evaluation reports and list of questions, redundant requests should not be made of the sponsors. Where specific data (e.g. manufacturing data or zone-specific stability) are requested by an agency or RRI conducting a review, these requests should be in alignment with international reference standards (e.g.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH]) and if not, a clear explanation should be given as to why prior data cannot be extrapolated and why the new data or analyses are required.

For processes described in Figure 2 that use a secondary FRP, delays may occur resulting from waiting for the completion of the review by the appropriate SRAs, WHO, or altruistic reviewers. Where an NRA must indicate acceptance/rejection of an RRI decision, additional time will enter the process.

The use of a CPP was initially acknowledged as a useful tool in accelerating drug approvals if the receiving countries make their decision in a timely manner after receipt of the documentation [28]. In practice, obtaining a legalized CPP can delay a secondary FRP approval. Determining from which country a CPP must be obtained (e.g. the location of manufacture, the location of the production of the raw material, the approving country) can add delays. Although reviews by SRAs will ensure a relevant assessment of safety and efficacy and appropriate inspection reports will verify quality, we recognise that some agencies will require legalized proof of these activities by regulation and that the CPP will therefore continue to play a documentation role in secondary FRPs; therefore, this is a component of Step 3.

Reliance on a WHO PQP may also incur delays. In 2010, for products that relied on a WHO PQP certification, the median time to prequalify an innovator product was 4.3 months, and 31.6 months to prequalify a generic product [29]; however, the process can typically take 18 to 24 months [30]. This timing needs to be factored into RRI and individual NRA times when seeking to use a PQP-related process described in Figure 2.

STRENGTHS AND LIMITATIONS OF THE FRP FRAMEWORK

The proposed FRP Framework is the first to use an holistic, pragmatic approach to determining how agencies can most effectively use FRPs. While relevant to any agency, this Framework has been developed with a particular focus on emerging NRAs, our Tier 2 agencies. The framework is based on a 4-step process, each with its strengths and limitations.

Step 1 requires an agency to assess the regulatory environment of their jurisdiction based on four domains of Preparedness (Table 2). While these elements have been derived from surveys and international consensus workshops and represent a consolidation of observations primarily from regulators and sponsors, other readiness elements could be identified that support the Preparedness domains. A growing database of experience with RRIs, further experience with categorizing agencies through the initiatives such as the PAHO PRAIS initiative (Regional Platform on Access and Innovation for Health Technologies; http://prais.paho.org/rscpaho/#/home), the WHO Maturity Level Classification programme and experience derived from the expected increase in the use of existing FRPs now in place in some emerging

NRAs will provide further insights into the refinement of the most practical and relevant elements of Preparedness domains.

Step 2 (Table 3) guides an agency as to the process criteria that are key to implementing FRPs. The four categories address essential activities in the FRP assessment process. All Tier 1 and 2 agencies are likely to be able to consider addressing many of these criteria. Some may be less important to implement immediately (e.g. the ability to accept an "electronically filed" dossier) while others should be available at all agencies (e.g. an SOP/guidance for submitting the dossier; a defined target review time; flexibility around post-authorisation follow-up commitments).

We suggest seeking concordance on the use of appropriate "imperative" evidentiary criteria to inform a decision, based on our observations associated with positive and negative regulatory outcomes (i.e., has a mix of relevant endpoints been assessed, did these demonstrate clinically important improvements, were these statistically significant, were they relevant on the balance of unmet medical need) and factors associated with positive regulatory outcomes [19,31]. Despite our findings of consistency observed in the value of some imperative characteristics to predict regulatory success (evidentiary support, sponsor experience and development strategy, relevant product indications and clear characteristics, social and regulatory environmental factors) [31], other "compensatory" characteristics that add value to the review process have been observed (e.g. demonstration and valuation of unmet medical needs, receiving and adhering to advice, procedural characteristics when there is considerable ambiguity about the strength of evidence between different experts and stakeholder groups and regulatory status such as orphan designation or fast track) and need to be explored in the context of how they contribute to the basic criteria that inform the benefit-risk regulatory decision for products being assesses via FRPs.

Step 3 (Table 4) helps agencies build on the first two steps based on their readiness to implement an FRP process; this is done by conducting an introspective assessment of an agency's activities. Agencies can follow these criteria to identify the Class that best characterises their capacity. Based on this assessment, an agency can determine its preparedness to conduct a verification or abridged assessment relying on prior agency decisions, or to conduct a full review.

As with other steps, only selected criteria need to be in place for an agency to consider itself fit-for-purpose. Within CARICOM countries, an analysis of PAHO basic indicator data shows that much of the region (Central America and Latin Caribbean, North America, and South America sub-regions) has achieved 90% or more of these criteria. Not all agencies, however, have attained Level 4 recognition. And the Non-Latin Caribbean lags significantly behind in these capacities having implemented 39% of the basic indicators. These countries often show poor capacity in core functions, including marketing authorization, pharmacovigilance, and post-

market surveillance, among others. For example, only 55% have a legal provision requiring marketing authorization of pharmaceutical products [32,33]. We believe that the PAHO assessment scheme is an important tool in evaluating the readiness of an agency to conduct medicine regulations and can be easily used by other agencies.

A limitation to this classification process is that an agency could exhibit some characteristics of multiple classes. In these cases, this Framework opts for the simplest class and pathways, in which the prior decisions are the driver for a timely review and where the added value of additional work conducted by the agency must clearly contribute to the knowledge base of the application. This step provides the foundational elements for a classification process and should be refined with further experience or expansion to more detailed criteria being developed by organisations such as the WHO. The International Council for Harmonisation could also serve as a platform for developing a guidance on the topic of implementing FRPs.

Step 4 (Table 6 and Figure 2) provides a process for agencies to then identify the most appropriate FRP option based on their tiering. This process is based on the concept that Tier 1 agencies will be best prepared to conduct a full dossier review that may follow a standard route or a primary FRP. Importantly, Tier 1 agencies will in theory have the capacity and competency to also conduct verification or abridged reviews based on the recognition of decisions made by other reference agencies if appropriate legal structures were to be in place. Tier 2 agencies have numerous secondary FRP options upon which to rely on. Despite these options, being influenced by their legal mandates, manpower and skill capacity, volume of reviews, and the need to address both speed and quality of the regulatory decision, some Tier 2 agencies will be limited in their ability to make use of specific FRPs.

Although relying on a prior decision is an important aspect of secondary FRPs, potential reluctance to rely on a predicate decision has been observed in some emerging NRAs; consequently, the need to encourage a cultural shift in an organisation to develop the confidence in another's decision cannot be underestimated. Some countries prefer reviews by FDA or EMA, while others prefer WHO-PQP [29,34]. Skepticism about the value of decisions made by SRAs is reflected in the 2010 WHO survey of sub-Saharan African countries in which of 18 countries assessed, only 2 explicitly relied on prior regulatory decisions made by SRAs or other reference authorities [14]. The fees charged by Article 58 may deter the use of this avenue in contrast to WHO-PQP and PEPFAR-linked review.

While FRPs are typically used for medicines that fulfil an unmet medical need, defining this need can be a challenge. Where possible, concordance on definitions is needed between regions on products that will benefit from an FRP to support a single global development plan.

In some jurisdictions, which FRP to use is a decision arrived at jointly by the sponsor and the regulator. Because of specific issues associated with a local application (e.g.

different indications from a prior approval; changes in packaging), a verification route may not be the best option, shifting the weight of workload to abridged processes.

While providing numerous potential benefits (shared workload, joint learning opportunities, expedited reviews), effectively using RRIs may be limited by the lack of memoranda of understanding or other legal agreements among participants, differences in the capabilities of the participating agencies, or limited funding to build the necessary infrastructure and processes to centralise the results or monitor the effectiveness of the initiative. The public documentation available describing another agency's prior decision may be insufficient to inform a secondary FRP decision [35] and access to more detailed confidential evaluation reports or lists of questions may be limited by the lack of legal structures for information sharing and the time needed by the first agency to prepare such documentation.

Although opportunities are presented by RRIs, evidence demonstrating their value in reducing work burden for individual agencies and return on investment for governments and funders, improving efficiency of reviews and shortening dossier assessment times are only now being collected. Implementing RRIs is not without difficulties [36] but none of the barriers observed to date appear to be insurmountable. Some agencies will appropriately seek to balance the use of reliance mechanisms with opportunities to strengthen the internal regulatory knowledge and capabilities of their staff.

The lack of basic pharmacovigilance systems in many emerging NRAs is a challenge to addressing the post-authorisation aspects of secondary FRPs. Reliance on regional pharmacovigilance hubs, on safety notices from SRAs and from alerts from organisations such as the WHO UMC provide alternatives to help address the post-approval monitoring of products approved via an FRP. Reviewing and implementing timely post-approval manufacturing and labeling changes remain a burdensome challenge for most emerging NRAs and sponsors.

Many emerging NRAs are challenged to ensure that quality medicines are being introduced into their countries focussing on protecting their constituents from falsified and adulterated medicines. Basing their decisions on prior PQP assessments and on good manufacturing assurances through organisations such as Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) can help to efficiently address these concerns without duplication of inspection efforts [37].

The impact of FRPs on stakeholders other than the sponsor and agency must be considered where possible. If health technology assessment (HTA) agencies or payers are not involved in a country's FRP process (agreeing on the FRP route, agreeing on products that should undergo an FRP because they address societal needs) a mechanism should be considered to engage these bodies if they exist within the jurisdiction. Having an enabling HTA/payer environment (where these stakeholders

support accelerated market access in concert with accelerated regulatory review) was ranked as a key aspect of implementing FRPs by slightly more than half (53%) of the respondents in one international survey [3].

Ultimately it is the patient for whom medicines are made available. While patient input is more commonly observed in primary FRPs in SRAs for products that address an unmet medical need, the patient voice is playing a growing role in all countries. This is particularly important where medicines need to address therapeutic areas in which no or poor alternatives exists or may be as basic as ensuring that essential medicines are available in a timely and affordable manner for acute and chronic diseases especially those emerging as societies modernise.

ONGOING REFINEMENT OF THE FRP FRAMEWORK

Because of the rapidly growing interest in and need to accelerate the quality assessment of new medicines especially in emerging NRAs, the work in this field needs to continue and evolve to identify ways to make the use of FRPs as efficient as possible. The ongoing work on good regulatory practices [1], good review practices [38,39] and the proposed WHO good reliance practices must address the role FRPs.

The extent to which emerging NRAs can efficiently implement FRPs must be further explored. A standardized assessment approach should be a two-way activity: information collected from participating agencies about their FRPs readiness and processes needs to be fed back to key stakeholders in a comprehensive, collaborative manner, where shared learnings support the transparent use of efficient FRP options. Organisations must continue to map and characterise the types of FRPs processes used, assess capabilities and manpower allocated to FRPs, and provide performance assessments [e.g. the number of products that have followed those pathways, the efficiency and timeliness of the reviews (addressing both agency and company time), and the nature of the elements that facilitate the process or create barriers]. When conducted in a standardized manner across agencies and RRIs globally, best practices can be identified, recommended and ultimately, implemented. In this manner, a truly consensus-driven, standardized, pragmatic framework for a globally applicable approach to using FRPs will evolve.

CONCLUSIONS

The growing need to expedite the review of medicines provides the opportunity for all agencies to explore the use of FRPs. In SRAs, primary FRPs are used to accelerate the primary review of critical new medicines. In emerging NRAs, secondary FRPs offer the ability to apply a risk-stratification approach to determine when to conduct a verification or abridged review thereby maximising the efficient use of resources. The four-step framework described here promotes a pragmatic approach that reliance

on or recognition of prior decisions can form the basis of using secondary FRPs when the appropriate regulatory environment exists, when the agency readiness and capacity are appropriate and where the agency has the ability to base its decisions of a formal set of process criteria. This Framework makes recommendations for the constituent elements of each step from evidence derived from a variety of research-based activities. The growing experience with FRPs will provide the opportunity for the continuous refinement of the Framework with the goal of informing a globally applicable approach to implementing FRPs in all agencies.

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chapter 7

GENERAL DISCUSSION

SUMMARY

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GENERAL DISCUSSION

All national regulatory agencies (NRAs) for medical products have multiple responsibilities ranging from approving new clinical trials to assuring the quality of health products. Among these responsibilities is the review of medicines for safety and efficacy. Agencies have come under increasing pressure to address the timely review of important medicines. Because of an expanding workload of new and generic medicines and limited by the constraints of institutional, technical and human resources, their capacities and expertise are challenged to keep up with the growing diversity and number of products to be assessed. In a world where production and distribution of medical products are global endeavours, regulatory oversight is no longer limited to a single NRA; all play some role in this endeavour.

The need for international regulatory cooperation has long been recognised and to encourage this engagement, a country's regulatory requirements should be aligned with those of other countries. Without this alignment, inefficiencies and the local costs of regulatory compliance will rise – perhaps out of proportion to the potential returns in that market. Such conditions may discourage the investment needed to bring appropriate and affordable products to that market. Most importantly, at an international level, duplication of regulatory evaluations of medical products and audits and inspections of suppliers create inefficiencies, time delays, and additional costs [1].

The past 20 years have seen the advent of important new medicines for serious diseases and for unmet medical needs. Novel approaches for HIV, malaria and cancers and recently Ebola, have highlighted the need for clear pathways for expedited regulatory review and approvals. In response to the need to expedite the review of new therapies that address unmet serious public health needs, many NRAs around the world have implemented expedited review pathways that provide an alternative to a standard process. However, the implementation of these facilitated regulatory pathways (FRPs) has been fragmentary and these could benefit from greater international convergence.

Although international regulatory activities are quickly moving toward alignment, the way to best coordinate the landscape for FRPs has not been well explored. In this concluding chapter we discuss insights into the state of play, observations on activities in this field and ultimately, our recommendations for a pragmatic way forward for the use of FRPs.

DIVERSITY OF FRPS

The growing number of new innovative medicines together with an explosion in generic products has resulted in an ever-growing workload for all regulatory agencies. Facing practical resource limitations, it is becoming increasingly challenging for many agencies to conduct timely reviews of all of the submitted dossiers. All stakeholders

are affected: sponsors may encounter lengthy intake queues and review times; reviewers are faced with a burdensome workload and often a resultant backlog of applications; and patients experience delays in access to medicines.

A response to these issues has been the development of country-specific pathways to expedite the regulatory review of important medicines. They may be applied to small molecules or biologics with prior approvals by multiple stringent regulatory authorities (SRAs), those with limited prior approvals or divergent regulatory decisions, those that may have been granted World Health Organization (WHO) prequalified status, generics, or products with no prior approval. No single FRP is appropriate for the accelerated review of all of these medicines. Therefore, a variety of approaches have been explored to expedite regulatory reviews while maximising the efficient use of local resources. Herein we present a practical approach to the use of FRPs to accelerate the review of new medicines.

Primary FRPs, used by SRAs, are generally reserved for medicines to treat serious conditions, and that demonstrate an important innovation or where there is an unmet medical need. Similarly, in a survey we conducted of FRPs implemented in emerging NRAs [2], 86% of assessed FRPs focused on serious or unmet medical needs. We agree that expedited pathways should be applied to these critical categories.

However, when considering that secondary FRPs can accelerate the review process by relying on or recognising prior decisions, the scope of FRP use becomes wider. Medicines that can be reviewed through these mechanisms are diverse: they can be new molecular entities, vaccines, anti-infectives, follow-on drugs and generic products, some of which may form part of an Essential Medicines listing. Secondary FRPs can be applied when the quality of the product under review has been verified (having been found to be identical or equivalent to a prior approved product); assessments can be based on a mutually aligned regulatory process, for example, through a regional regulatory initiative (RRI) for conducting collaborative work-sharing reviews or where an agency can use a formal process to accept the outcomes of another reference agency's review. Furthermore, decisions may be based on the outcomes of a primary "altruistic" review, such as those conducted through the EMA Article 58, the PEPFAR (US President's Emergency Plan for AID Relief) process, the FDA Certificate of Pharmaceutical Product (CPP) for unapproved products (for drugs) or Certificate of Exportability (for biologics and devices) (https://www.fda.gov/RegulatoryInformation/Guidances/ucm125789#vi), Swiss Medic's Marketing Authorisation for Global Health products (MAGHP) and medicines reviewed through the WHO Collaborative Prequalification of Medicines Programme (PQP).

Secondary FRPs share some common elements but nevertheless have evolved from different needs and, therefore, reflect an uncoordinated approach to expedited medicines review. Several strategies have been suggested to codify these accelerated assessment pathways.

Duggal et al [3] proposed that economically efficient review processes for niche markets could be based on the wider implementation of "fast track" approaches. For generics, this could include the broader use of biowaivers and reliance on the FDA 505(b)(2) NDA process in which an application contains assessments of safety and efficacy but where some of the information is derived from studies not conducted by the applicant or on WHO PQP assessments.

Through the PQP the WHO carries out a comprehensive, scientific evaluation of a product to ensure drug quality [4]. While initially focused on medicines for treating HIV/AIDS, malaria and tuberculosis, the programme has been expanding to other pharmacologic classes. The WHO Collaborative Registration Process (CRP) is a collaborative programme that leverages the work of the WHO PQP to support decisions by NRAs. This initiative seeks to facilitate and accelerate national regulatory approvals through the confidential sharing of specific results of the dossier assessment by the WHO Prequalification Team (PQT) with an NRA reviewing the same dossier for registration. Participation in the CRP is voluntary for manufacturers and NRAs and is not in conflict with national decision-making processes already in place. The CRP programme can also rely on decisions made by SRAs. To engage in the process, interested NRAs agree to confidentiality, commit to following the principles of the process, and attempt to make a decision on the registration of a product within a target timeline of 90 days [5]. The success of this programme is reflected in the fact that as of November 2015, 98 registrations were made using CRP (with 54 pending a decision) in 15 participating countries [6]; by 2016, 27 countries were participating and 100 products had been approved through this mechanism [7].

Saidu and colleagues identified core elements of a broadly applicable regionally aligned regulatory review framework, proposing elements of the key aspects of the submission and validation process, the scientific assessment procedure, sample analysis and the approval event [8]; this model was derived from an overview of established RRIs such as the Association of Southeast Asian Nations (ASEAN); Gulf Central Committee (GCC); The Pan American Network for Drug Regulatory Harmonization. (PANDRH) and the Southern African Development Community (SADC) but its recommendations were not based on empirical observations of the characteristics of FRPs used in these emerging markets or on the decision making criteria that underlie effective regulatory outcomes.

The Bill and Melinda Gates Foundation have proposed a 3-step review process for a new generic drug wherein the first registration is conducted by a SRA or by a reference NRA, followed by a quality assurance review (such as the WHO PQP), followed by the local registration of the product by a NRA, based on reliance on the prior steps [9].

One procedure that builds on reliance on prior regulatory decisions to inform a local recommendation considers the use of a risk-stratification process based on the types of prior approvals and enables an agency to allocate constrained resources

more efficiently [10]. As discussed in the General Introduction (**Chapter 1**), many factors can be used to assess the "risk" associated with a product for review. A more general view of risk is addressed by the Organisation for Economic Co-operation and Development (OECD) which views risk-based regulation as the development of decision-making frameworks and procedures to prioritise regulatory activities and deploy resources based on an assessment of the risks that regulated firms pose to the regulator's objectives. In risk-based approaches, the focus is not on the potential risks that individuals or the market economy may face from the actions of firms per se, but on the risks the regulator faces in failing to achieve its objectives. Risk-based regulation thus requires regulators to explicitly define their regulatory objectives and to translate their statutory mandates into operational objectives [11]. These themes are congruent with the risk-stratification approaches to medicine review, as they relate to the selection of various FRP routes used in our FRP Framework (**Chapter 6.1**).

These concepts can also be readily identified in a regulatory review risk-stratification approach that is gaining acceptance among a growing number of NRAs, a process formally codified and implemented by Singapore in which a three-tier review strategy is used to stratify products for review. Commonly referred to as *verification, abridged* and *full review* options, this approach is based on the nature of prior decisions, provides regulatory flexibility, the ability to allocate resources to key dossier reviews, the jurisdictional sovereignty to reach a locally relevant benefit-risk decision, and the ability to speed the review of important new medicines.

A growing number of agencies are moving to implement some form of this risk-based approach. In an analysis of the regulatory pathways used by the Saudi FDA compared with Australia, Canada and Singapore [10], the authors recommended that the Saudi agency consider implementing a risk-based stratification review approach. This approach was codified in regulation in late 2016 by the Saudi FDA. Recently, the Egyptian Minister of Health and Population issued Decree 820 (2016) describing a three-option registration process committing to the following registration times: for products approved by both the FDA and EMA, 1 month; for products approved by one of those agencies; 2 months; and for products that submit a common technical dossier (CTD) for full review, 6 months. Indonesia has had a multi-path regulatory assessment approach that similarly tiers the risk associated with products for reviews in place; Path V represents a secondary FRP wherein reliance on a prior decision is used.

WHAT ARE THE LIMITATIONS OF THESE APPROACHES?

While all regulators share a common mission to ensure that quality, safe and effective medicines reach their constituents in a timely manner, the practicalities of designing and enacting FRPs to help attain this goal may limit their widespread use, especially by emerging NRAs. Barriers vary across jurisdictions. When considering

using FRPs, agencies must assess their mission and legal responsibilities, available regulatory routes, professional experiences and capabilities, and ability to allocate manpower to accelerated regulatory reviews. The degree to which there is sustained institutional support for FRPs will influence their uptake and outcome. Importantly, how a jurisdiction's legislation is written describing the requirements and processes that can be undertaken to approve a product can have a major impact on whether (or which types of) FRPs can be used by an agency.

Other factors that may limit an agency's ability to implement FRPs include: uncertainty as to how to make a decision for products for which there is no or only limited product exposure or experience; difficulty in extrapolating the relevance of clinical findings from other jurisdictions where the product has been approved; limited ability to address the safety risks associated with uncontrolled distribution or prescription, coupled with limited post-approval assessment mechanisms for effectiveness and safety; and being challenged with inadequately defined processes for removing the product or curtailing its use in the event of an emergent post-authorisation issue.

Delays may occur resulting from waiting for the completion of the initial review by the appropriate SRAs, WHO, or altruistic reviewers. Where an NRA must make a decision to accept or reject an RRI decision, additional time will enter the process. If a jurisdiction requires the use of the Certificate of Pharmaceutical Product (CPP), inspection reports or reliance on the WHO PQP, additional time may be added to the review component.

Importantly, limited reviewer resources may contribute to regulatory delays [12]. Not all jurisdictions have the social and regulatory framework to appropriately implement an FRP and there is skepticism as to the importance of having these pathways in place. In our international survey of perceptions of FRPs (**Chapter 2.1**), less than 1% of respondents cited having a "well-defined regulatory pathways in emerging countries for important therapies for which there is no prior reference agency approval" as an important factor in accelerating patient access [13].

SECONDARY FRPS CAN HELP RESOURCE-CONSTRAINED AGENCIES

Equitable access to medicines is a right of all patients. For products for which safety and efficacy have been confirmed, patients in other jurisdictions should expect timely access facilitated by the regulatory process.

Many countries lack NRAs that can undertake a full independent dossier review to ensure safe and effective quality products enter their markets. Indeed, according to a report by the World Health Organization (WHO 2010), many WHO member states—particularly developing nations—lack the capacity to effectively regulate medicinal products in their jurisdictions. Limited human and material resources, regulatory

experience and training, and political will to implement robust regulatory policies curb the capabilities of these emerging agencies. As countries develop their regulatory capacity, it is important that their regulatory systems be science based, respect international standards and best practices and adopt an approach that focuses on what can be done by an NRA and leveraging the work of other trusted agencies and regulatory networks for the rest. When considering the review of a medicine dossier, the agency must clearly define how its activity adds value, especially when prior reviews have been conducted with positive recommendations by SRAs or reference agencies. This added value may be a local jurisdictional confirmation that the new product meets the required quality standards or that the safety profile is appropriate for the local population. But where decisions cannot readily be extrapolated from prior assessments, a more detailed review may be required.

In part driven by resource constraints, there is increasing awareness of the need and value of implementing alternative regulatory pathways to standard full reviews to expedite the review and approval of new medicines, particularly by emerging NRAs. In all cases, the evidentiary standards for expedited pathways remain the same as those of standard pathways; that is, substantial and compelling evidence in clinically meaningful endpoints and showing an acceptable benefit-risk balance is required for approval, even with smaller study populations and clinical trial challenges associated with assessing products for unmet needs. Product quality must similarly be ensured. An FRP should allow a robust assessment of a product's benefits and risk with appropriate risk mitigation plans to ensure the safe use of quality, effective medicines.

Consequently, emerging NRAs have implemented diverse FRP approaches to meet their respective public health mission [12]. A growing number of emerging NRAs have published details of codified primary and secondary FRP routes that provide simple, yet flexible approaches to accelerated medicine review in their jurisdictions (**Chapter 2.2**) [2]. Although these FRPs share several common elements (e.g., a focus on medicines for unmet medical need, an accelerated approval target timeline, the ability to use surrogate markers to support a regulatory decision) there remains great diversity. This heterogeneity, coupled with a relative lack of transparency about the processes, complicates the ability of sponsors to effectively use FRPs in a coordinated manner.

Despite their proliferation, there is no consensus or international guideline for the definition, basic elements or best practices for using FRPs. Diversity of FRPs creates confusion across stakeholders, with uncertainty about how to accelerate the review and differences in processes across jurisdictions, resulting in patients questioning the timing or divergences in access to important medicines. Because no formal internationally developed guideline for the implementation and use of FRPs exists, there is an opportunity to promulgate a framework for the use of FRPs that provides transparency and process predictability to sponsors and ensures that any additional work conducted by an agency adds value to the process.

The learnings derived from this thesis form the building blocks for a globally applicable FRP framework with the goal of improving equitable access to medicines across all jurisdictions.

APPLYING THE FRP FRAMEWORK

Because of the lack of aligned consensus, we observed an opportunity to provide recommendations to stakeholders (SRAs, NRAs, sponsors) as they move to create, implement and use FRPs. To this end, we have proposed a pragmatic framework for the effective use of FRPs that could serve as the evidentiary basis for a formal guidance on this topic. The approaches described herein have been designed to provide solutions to questions regarding the use of FRPs by NRAs.

The foundation for implementing and effectively using an FRP is the use of a framework to identify the most relevant FRP approach for the NRA. Addressing a spectrum of underlying considerations ensures that the appropriate systems are in place to provide the context for the use of specific types of FRPs. A logical framework identifies and aligns key characteristics of process predictability across locally implemented FRPs. It permits a pragmatic approach to determining how prior regulatory decisions can inform subsequent reviews. Applying a framework to understand the capabilities and processes used by other agencies to reach a regulatory decision builds confidence in and reduces uncertainties regarding their decision.

The framework approach described in this thesis provides a roadmap to guide the decision process for selecting review option pathways to accelerate assessment by optimising use of prior regulatory decisions and applying the appropriate use of local resources. Importantly, following the framework illustrates how an agency can rely on prior decisions, limit duplicative effort, and add value to the process.

THE BENEFITS OF COLLABORATION

However, as all reviews are labour-intensive, a reliance- or recognition-based FRP approach should be considered in the first instance to minimise duplicative effort and optimise resource use while informing a sovereign decision.

The World Health Assembly recognised the value in collaborative approaches to regulatory activities [15]. To this end, the WHA Resolution 67.20 emphasized the need for NRAs to engage in global, regional and sub-regional networks, recognising the importance of collaboration to pool regulatory capacities to promote greater access to quality, safe, efficacious and affordable medical products. The resolution also noted the benefits of promoting appropriate international cooperation for collaboration and information sharing.

Several RRIs have been exploring the benefits of partnering amongst nearby regulatory agencies to maximise the efficient use of each jurisdiction's resources while striving to expedite the review of medicines [16]. Developing countries have

implemented diverse approaches to meet their respective public health mission [12]. These include: the activities sponsored by the African Union's African Medicines Regulatory Harmonisation Initiative [5,17] in the East African Community; the ZaZiBoNa Collaborative Medicines Registration Initiative (supporting the Southern African Development Community-SACD nations through work-sharing from the resources provided by Zambia, Zimbabwe, Botswana, and Namibia) (http://www.mcaz.co.zw/index.php/latest-news/16-zazibona-collaborative-medicines-registration-process); the broader African Medicines Agency initiative; the Caribbean Regulatory System (CRS) under the auspices of PAHO, the Caribbean Public Health Agency (CARPHA) and Caribbean Community (CARICOM) [18]; the ASEAN Pharmaceutical Product Working Group (ASEAN-PPWG) joint review initiative lead by Malaysia; the GCC for Drug Registration (GCC-DR); the Eurasian Economic Union; and the alignment initiatives promoted by PANDRH.

It may be difficult for an agency to determine whether it has a robust reliance process in place; to this end, the framework described in Chapter 6.1 and new efforts by the World Health Organization to develop Good Reliance Practices, can provide needed guidance.

Although flexible approaches to regional needs exist, processes and goals vary across these initiatives; there is little standardisation with an opportunity to identify and implement best practices across them. The framework described in this thesis provides the substantive building blocks to support a flexible approach to using FRPs, applicable to all medicines regulatory agencies.

THE WAY FORWARD

By providing supportive evidence for the building blocks of FRP best practices, we believe the approaches detailed in this thesis can form the basis for aligning the wide variety of review programmes that are in place or that are being promulgated for the accelerated assessment of important medicines.

We have assessed the fundamental elements that form the four buildings blocks that support our proposed pragmatic FRP framework, and have provided a pathway for agencies to identify and implement the most appropriate FRP for their jurisdiction. Much can be learned from the shared experience of FRPs used by SRAs, maturing NRAs and RRIs. We cannot miss the opportunity to collaborate with these initiatives to validate new FRP approaches, to test the framework developed here, and translating their experiences into best practices.

We look to organisations such as The International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the WHO to continue their efforts to bring continuity to the use of pragmatic regulatory review approaches, and trust that the work presented here can serve as the basis for international policies for efficient medicines reviews that can contribute to the equitable access to medicines.

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SUMMARY

Equitable access to medicines is a right of all patients and they may have great expectations of rapid and efficient regulatory processes that contribute to accelerated access to safe and effective innovative new medicines. However, the use of expedited regulatory review pathways and authorisations must ensure that a benefit-risk decision appropriate to the local population supports the timely availability of quality safe and effective medicines.

A variety of approaches have been developed to accelerate the regulatory review of medicines. We characterise these various expedited pathways as facilitated regulatory pathways (FRPs): regulatory pathways designed to accelerate product development, the submission of market authorisation applications, and regulatory reviews. The goal of FRPs is to speed the assessment of new drugs with a positive benefit-risk balance, often for serious diseases or where there is an unmet medical need. But FRPs may be applicable to a broader group of products, including the assessment of generics, biologics and vaccines among others. FRPs may increase the level of communication and commitment between the sponsor and the regulatory agency, can give a larger role to medicines effects on surrogate endpoints and may move some of the burden of clinical benefit and safety evidence generation from the pre- to the post-authorisation phase. Importantly, some FRPs are designed to encourage reliance on or recognition of prior decisions made by reference authorities, thereby reducing regulatory duplication and the burden of review.

In spite of the on-going trend towards global regulatory convergence, no internationally relevant guidelines or best practices have been promulgated that describe the elements or conditions needed to implement an accelerated regulatory review pathway. The diversity of FRPs found across high-, middle- and low-income countries creates confusion for stakeholders, with uncertainty about the accelerated review requirements and processes across jurisdictions; this results in patients questioning the timing or divergences in access to important medicines. No single FRP represents the most appropriate route for the accelerated review of all medicines.

Therefore, we conducted this research to identify and characterise the key building blocks that provide context and support for the efficient use of FRPs. We hypothesised that through the methodical assessment of four key themes (stakeholder support and the regulatory environment; processes that contribute to predictability in regulatory decision making; use and interpretation of evidence associated with regulatory outcomes; post-authorisation assessments) we would be able to characterise a globally applicable pragmatic framework for the use of a diverse set of currently available FRPs. Herein we present our observations, based on these building blocks, that support our proposal for a globally applicable approach to using FRPs.

This thesis, which is focused on the constituent elements required to develop a pragmatic approach to implementing FRPs, builds on a body of prior work that has

laid the groundwork for our research. This thesis contains eight studies organised into four sections that reflect the four blocks upon which the proposed FRP framework described in Chapter 6.1 is constructed. Each of the chapters represents a building block that supports the development of the proposed pragmatic framework for FRPs.

Chapter 2 focuses on describing the stakeholder support and regulatory environment needed to be in place for FRPs to be used effectively. Despite the growing interest in accelerated pathways, no research had assessed stakeholder perceptions of currently available FRPs and for the potentially transformative *adaptive licensing* pathways (these latter are not addressed in this thesis). Therefore, we conducted a study to characterise stakeholder impressions of these pathways, to understand opinions about the key elements, to recognise the barriers to implementing these pathways and to seek recommendations for overcoming these challenges (Chapter 2.1). Fifty (56%) of 90 invited organisations responded; 80 (32%) of 252 individual responses were returned (a single consolidated response was received from 8 organisations). Respondents were from 14 countries and reflected a diversity of stakeholders; pharmaceutical company regulatory and outcomes research/access departments, regulatory agencies, HTA agencies, patient groups and others. FRPs at the FDA were generally considered fit-for-purpose (63% respondents) as were specific FDA programmes: Priority Review (54%), Accelerated Approval (50%), Breakthrough Therapy (42%) and Fast Track (33%). In contrast, FRPs available at EMA and the Japanese PMDA were rated as fit-for-purpose by 13% and 7%, of respondents, respectively. A majority (65%) felt that companies were using FDA FRPs appropriately and this was perceived by 61% as reducing time to license. However, just 29% of respondents thought EMA FRPs reduced licensing time. This limitation was reflected in that 74% of respondents saw a need for alternative pathways at the EMA compared with 55% for the FDA. These observations indicated that FRPs could be designed to meet the intended goals, but the perceptions of the respondents also pointed to the need to further understand the characteristics and roles of FRPs, define and build on the elements of successful FRPs, and determine optimal approaches to FRP implementation in a global context. This provided guidance for our next research activities.

Unlike FRPs being used or piloted by SRAs, no one had systematically reviewed and assessed formal FRPs implemented by emerging NRAs. Therefore, to understand the diversities and similarities, we undertook a descriptive study of FRPs used by more than two dozen emerging NRAs (Chapter 2.2). Characteristics of 33 FRPs used in 29 countries around the world were compared using a list of 27 FRP characteristics. We categorised characteristics as procedural or substantive and based them on five sequential regulatory activities. The regions with the characteristics most extensively described by their FRPs were Middle East/North Africa and Eastern Europe while the FRPs that were least specific in described characteristics were in Sub-Saharan Africa.

All FRPs addressed at least twice as many procedural as substantive characteristics reflecting the overall mix assessed. Among the most common characteristics were: the availability of a guidance or standard operating procedure for submitting the FRP dossier; that the product should address a serious condition or unmet medical need; that non-agency experts could be enlisted to assess the dossier; that efficacy could be based on the use of surrogate endpoints; and that the sponsor would be required to conduct post-authorisation follow-up assessments. We felt that this research would inform our development of characteristics for a globally applicable approach to FRPs; could help standardise approaches to accelerated medicine reviews; and would provide international organisations with evidence to help focus their regulatory strategies to increase capacity within emerging NRAs.

Having an appropriate regulatory environment is a key to encouraging the development and authorisation of both innovative and follow-on products. Therefore, we investigated the processes that can be put in place to provide confidence in a regulatory decision.

In Chapter 3.1 we assessed approaches to global development and simultaneous submissions. Challenges and opportunities to facilitate the regulatory process were assessed during a comprehensive workshop, the results of which were described in this chapter. Activities that could expedite reviews and align expectations included the use of enhanced clinical designs and the use of tools such as biomarkers and appropriate surrogate endpoints. These concepts are evolving rapidly and may result in greater predictability in the pharmaceutical development process and improved targeted therapies with better benefit-risk profiles resulting in the minimisation of divergent regulatory outcomes. The use of standardised benefit-risk assessment tools, the use of validated endpoints and patient-focused outcomes, and the mitigation of cultural differences in the development and review process are approaches companies can take to implement best practices that support efficient and transparent regulatory decision making, especially when using an FRP.

In Chapter 3.2, we explored these concepts further to make recommendations as to how good review practices can facilitate transparent, timely, procedurally predictable and good-quality evaluations of new medicines. Regulators are seeking ways to ensure that they are not only undertaking a good quality review process but also making a good-quality regulatory decision. We focused on the elements of good decision making. Training in the use of decision tools was found to be imperative. These tools included the recognition of the importance of and use of elements broadly encompassed by Good Review Practices, including using a systematic benefit-risk assessment framework and a structured decision making and documentation framework. Importantly, we recognised that quality decisions were best made with the input of diverse stakeholders (e.g., the sponsor, healthcare professionals, patients and regulators).

FRPs are often used to assess important medicines where there is an unmet medical need. In these cases, the data set upon which a decision is made may be smaller or more time-limited than observed with a product undergoing a standard review. Consequently, in **Chapter 4** we sought to understand how the use and interpretation of evidence was associated with regulatory outcomes in these special cases and to extrapolate these observations to decision making in support of FRPs.

The basis for the approval of a new medicine is a favorable benefit-risk profile: the demonstrability of efficacy together with an acceptable safety profile. The regulator is challenged with balancing the need for rapid market access to novel therapies with an acceptable level of benefit-risk uncertainty. The combination of hard and surrogate efficacy end points provides researchers and assessors with tools to characterize a new therapy's profile of clinical activity. However, using common end points and the magnitude of their outcomes are not always determinants of a successful regulatory submission. In **Chapter 4.1** we explored the association of three key endpoint properties (type of endpoint [hard/surrogate], magnitude of an endpoint outcome and its statistical significance) with oncology product authorisation outcomes to determine the extent to which these were associated with a positive or negative regulatory outcome at the EMA. We explored the relationship of the three endpoint properties to regulatory outcomes by assessing 50 oncology marketing authorization applications reviewed from 2009 to 2013. Overall, 16 (32%) had a negative outcome. The most commonly used hard endpoints were overall survival (OS) and the duration of response or stable disease. OS was a component of 91% approved and 63% failed MAAs. The most commonly used surrogate endpoints were progression-free survival (PFS), response rate, and health-related quality of life assessments. A mean of slightly more than four surrogate endpoints were used per approved MAA compared with slightly more than two for failed MAAs. Longer OS and PFS duration outcomes were generally associated with approvals, often even when not statistically significant. The approved cohort was associated with a preponderance of statistically significant ($p < .05$) improvements in primary endpoints ($p < .0001$ difference between the approved and failed groups). Notwithstanding the contribution of unique disease-specific circumstances, the three endpoint characteristics we assessed were associated with a predictable positive outcome for oncology MAAs.

These observations led to the broader question of whether there were specific factors that were associated with positive or negative regulatory outcomes. Based on a comprehensive literature survey, we assessed 23 articles published between 2001 and 2015 that sought to determine relationships between certain factors and positive or negative regulatory outcomes and which met our inclusion criteria (**Chapter 4.2**). These articles were heterogeneous in nature, with diverse objectives, hypotheses, methodologies and cohorts assessed. Nevertheless, we identified 151 factors that we categorised into four "Factor Clusters": evidentiary support (52; 34%) followed

by company experience or strategy (46; 31%), product and indication characteristics (45; 30%), and social and regulatory factors (8; 5%). We observed a heterogeneous mix of technical factors (e.g., study designs, clinical evidence of efficacy) and less studied "social" factors (e.g., company-regulator interactions); we confirmed factors known to be of relevance to drug approval decisions (imperative) and a cohort of less understood (compensatory) social factors. We evaluated the public assessment reports for several recent approvals and negative regulatory outcomes for products assessed by the EMA and observed that the factors we detailed in our study were recognisable in each of the cases described. Our observations illustrated the multifactorial nature of regulatory decision making. Because no single factor was consistently associated with a positive or negative regulatory outcome, we concluded that factors need to be considered holistically because they have varying, context-dependent importance for both development and regulatory outcomes. These factors, together with the three endpoint factors we assessed in **Chapter 4.1**, would become important components of our proposed FRP Framework to establish how agencies can use evidence to make a regulatory decision. An important observation from this study was that special regulatory pathways (i.e. accelerated pathways, orphan designations, etc.) could have a positive impact on regulatory outcome. This led us to question to what extent FRPs influenced development and regulatory times.

Therefore, in **Chapter 4.3** we sought to determine to what extent the combination of two or more FRPs influenced development and approval times. We developed a "metro map" to illustrate FRP elements and their influence on review times and used this map as the basis for the map used in our FRP Framework in **Chapter 6.1**. The FDA has four FRPs: Fast Track (FT), Breakthrough Therapy (BTD), Priority Review (PR) and Accelerated Approval (AA). Only PR specifies an expedited review timeline (6 months). We focused on a cohort of products that had been approved by the FDA through specific FRPs and compared their development and regulatory review times to products that used the standard route. We assessed 125 new active substances (approved January 2013 - December 2015) 74 of which used one or more FRPs. For these 74, development times ranged from 1,458 (BTD+PR+AA) to 3,515 days (PR). PR alone had a median approval time of 242 days. The most common combination was FT+PR (median approval 292 days, n=21). The fastest approval times were for PR+FT+BTD+AA (145 days) and PR+BTD+AA (166 days). Our findings not only confirmed shortened development and review times for certain FRPs and combinations but also provided the experience to create a novel "metro map" approach to illustrating FRP pathways.

Because a more rapid decision made using an FRP may seek to more fully understand the product's benefit-risk profile by shifting the burden of evidence collection to the post-authorisation period, in **Chapter 5.1** we conducted a preliminary assessment of the types of post-approval commitments (PACs) sought by the FDA for

products that were recently approved through an FRP. A total of 735 post-approval commitments were observed across the 74 FDA products approved from 2013 to 2015 that used one or more FRPs. The most PACs were classified under ATC Codes L, antineoplastic and immunomodulating agents and J, anti-Infectives. These are critical medicines for unmet medical need often approved based on minimal data to support safety and efficacy; therefore, it is reasonable that these categories would have the highest instances of PAC requirements. The most common types of PAC studies performed were those to investigate pharmacokinetics, safety, and efficacy, which are the key drivers of uncertainty at the time of approval. PACs were generally required to be completed in approximately 1,200 days (from date of approval). These findings provided evidence for our FRP framework that post-authorisation assessment commitments are important to confirm the observations upon which an FRP decision is made.

As regulatory agencies are coming under increased pressure to rapidly review medicines of critical importance to facilitate equitable access, the benefits of using expedited review pathways as alternatives to standard dossier reviews are being explored by many countries around the world. These FRPs provide a variety of options for the accelerated review of a medicine. Stringent regulatory authorities (SRAs) use *primary* FRPs to help accelerate development or to shorten review time. Some emerging national regulatory authorities (NRAs) can implement primary FRPs but are more likely to use *secondary* FRPs that rely on or recognise a SRA or reference agency decision, the WHO Collaborative Prequalification of Medicines Programme (PQP), "altruistic" reviews, or collaborative work-sharing decisions made through regional regulatory initiatives.

Despite availability of these FRP options, there is no formal guideline or consensus for the definition, basic elements or best practices associated with FRPs. Therefore, in Chapter 6.1 we integrated the findings from the previous chapters and presented a 4-step pragmatic framework approach designed to help agencies of all maturity levels determine how best to address the use of FRPs. Step 1 assesses four domains of the environment preparedness, Step 2 offers process criteria that should be in place to effectively use an FRP, Step 3 tiers agencies through a self-assessment of readiness and capacity, and Step 4 provides a pathway for agencies to determine the most relevant FRP for their use.

This framework represents the first endeavour to holistically address the multifaceted aspects that should be considered for the effective use of an FRP through the integration of all of the elements explored in this thesis. It offers process transparency to address the needs of sponsors and suggests timelines that address the practical considerations of sponsors and agencies and the expectations of patients. By providing supportive evidence for the building blocks of FRP best practices, we believe the approaches detailed in this thesis can form the basis for aligning the wide variety of review programmes that are in place or that are being promulgated for

the accelerated assessment of important medicines. We trust that the work presented here can serve as the basis for international policies for efficient medicines reviews that can contribute to the equitable access to medicines worldwide.

The studies presented in this thesis were conducted under the supervision of Prof. dr. H.G.M Leufkens and Prof. dr. Sir A.M. Breckenridge together with Dr. P. Stolk and Dr. J.A.N. McAuslane. These studies contribute to a larger body of research in regulatory science developed under the auspices of the Utrecht-WHO Collaborating Centre for Pharmaceutical Policy and Regulation based in the Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands.

SAMENVATTING

Breed toepasbare en gefaciliteerde regulatoire routes om de rechtvaardige toegang tot geneesmiddelen te verbeteren

Een rechtvaardige toegang tot geneesmiddelen is een recht voor alle patiënten. Zij mogen daarom de verwachting hebben dat de regulatoire routes die bijdragen aan de versnelde toegang tot veilige en effectieve geneesmiddelen snelwerkend en efficiënt zijn. Echter, het gebruik van zulke versnelde regulatoire routes en de daaropvolgende markttoelating moet ertoe leiden dat een besluit over de balans tussen werkzaamheid en veiligheid, passend voor de lokale patiëntenpopulatie, de tijdige beschikbaarheid van kwalitatief goede, veilige en effectieve geneesmiddelen ondersteunt.

Diverse benaderingen zijn ontwikkeld om de regulatoire beoordeling van geneesmiddelen te versnellen. Wij karakteriseren deze verschillende versnelde routes als facilitated regulatory pathways ('gefaciliteerde regulatoire routes' of FRPs): regulatoire routes die ontworpen zijn om de ontwikkeling van producten, de indiening van handelsvergunningsverzoeken en de regulatoire beoordeling te versnellen. Het doel van een FRP is om de beoordeling van nieuwe geneesmiddelen met een positieve werkzaamheid-veiligheidsbalans, veelal voor ernstige ziekten of daar waar een medische behoefte is, te versnellen. Maar FRPs zijn mogelijk ook toepasbaar voor een bredere groep producten, waaronder voor de beoordeling van generieke of biologische geneesmiddelen en vaccins. FRPs kunnen de communicatie en wederzijdse binding tussen de sponsor en het regulatoire agentschap vergroten, kunnen de rol van surrogaateindpunten versterken, en kunnen de last voor het onderzoeken van de klinische werkzaamheid en veiligheid verplaatsen van de periode pre-markttoelating naar de periode post-markttoelating. Een belangrijk punt is dat sommige FRPs zijn ontworpen om het vertrouwen in, of de erkenning van, eerdere beslissingen door referentie-autoriteiten aan te moedigen, waarmee regulatoire duplicatie wordt vermeden en de werklast voor de beoordeling wordt verminderd.

Ondanks de beweging naar regulatoire convergentie bestaan er geen relevante internationale richtlijnen die de noodzakelijke elementen of condities beschrijven waaronder een versnelde beoordelingsroute kan worden geïmplementeerd. De diversiteit aan FRPs die gevonden wordt in hoge-, midden- en lage-inkomenslanden veroorzaakt verwarring voor belanghebbenden, met als gevolg onzekerheid over de voorwaarden voor versnelde beoordeling en het verloop van het proces in verschillende jurisdicties. Dit heeft ook tot gevolg dat patiënten vragen stellen bij verschillen in de timing en mate van toegang tot belangrijke geneesmiddelen in verschillende landen. Echter, er is niet één bepaalde FRP die als meest passend beschouwd kan worden voor de beoordeling van elk geneesmiddel.

Om deze reden hebben wij dit onderzoek uitgevoerd om de belangrijkste bouwstenen die de context en het fundament voor het efficiënt gebruik van

FRPs vormen te identificeren en karakteriseren. Onze hypothese was dat wij door de methodische beoordeling van vier belangrijke thema's (steun van belanghebbenden en de regulatoire omgeving; processen die bijdragen aan de voorspelbaarheid van regulatoire besluitvorming; gebruik en interpretatie van het bewijs dat geassocieerd is met regulatoire uitkomsten; beoordelingen na de markttoelating) in staat zouden zijn om een wereldwijd toepasbaar raamwerk te beschrijven dat gebruikt kan worden voor de FRPs die op dit moment beschikbaar zijn. In dit proefschrift presenteren we onze observaties, gebaseerd op deze bouwstenen, die ons voorstel voor een wereldwijd toepasbare benadering voor het gebruik van FRPs ondersteunen.

Dit proefschrift, dat zich richt op de elementen die benodigd zijn om een pragmatische benadering te ontwikkelen voor het implementeren van FRPs, is gebaseerd op een corpus van eerder werk dat het fundament voor ons onderzoek vormt. Dit proefschrift bevat acht studies en is verdeeld over vier secties die de vier bouwstenen reflecteren waarop het voorgestelde raamwerk voor FRPs, zoals beschreven in Hoofdstuk 6.1, is gebaseerd. Elk hoofdstuk representeert een bouwsteen die de ontwikkeling van het voorgestelde pragmatische raamwerk voor FRPs ondersteunt.

Hoofdstuk 2 richt zich op de steun van belanghebbenden en de regulatoire omgeving die aanwezig moet zijn om FRPs effectief te kunnen gebruiken. Ondanks de groeiende belangstelling voor routes voor versnelde toelating is er nog geen onderzoek gedaan dat de percepties van belanghebbenden op de huidig beschikbare FRPs en op mogelijke, meer transformatieve, adaptive pathways heeft geëvalueerd (deze laatste worden in dit proefschrift niet onderzocht). Om deze reden hebben wij een studie gedaan om de impressies van belanghebbenden met betrekking tot deze regulatoire routes te karakteriseren, om hun mening over de belangrijkste elementen te begrijpen, om de barrières voor implementatie te identificeren en om aanbevelingen te formuleren om deze uitdagingen te adresseren (Hoofdstuk 2.1). Vijftig (56%) van de 90 uitgenodigde organisaties hebben aan onze uitnodiging gehoor gegeven; 80 (32%) van de 252 uitgenodigde individuen hebben geantwoord (van 8 organisaties werd een geconsolideerde respons ontvangen). Respondenten waren afkomstig uit 14 landen en representeerden een diverse groep van belanghebbenden: afdelingen regulering en uitkomstenonderzoek/markttoelating binnen farmaceutische bedrijven, nationale agentschappen, HTA organisaties, patiëntenorganisaties en overige soorten organisaties. FRPs van de FDA werden in het algemeen als passend gezien (63% van de respondenten), ook specifieke FDA-programma's werden als zodanig beoordeeld: Priority Review (54%), Accelarated Approval (50%), Breakthrough Therapy (42%) en Fast Track (33%). In contrast hiermee werden de FRPs van de Europese EMA en de Japanse PMDA als passend gezien door respectievelijk 13% en 7% van de respondenten. Een meerderheid (65%) was van mening dat bedrijven

FDA FRPs op een passende manier gebruikten en 61% was van mening dat dit de tijd tot markttoelating reduceerde. Echter, slechts 29% van de respondenten was van mening dat de FRPs van de EMA de tijd tot markttoelating reduceerden. Deze vermeende tekortkoming is ook gereflecteerd in het feit dat 74% van de respondenten een noodzaak zien voor alternatieve routes bij de EMA, in vergelijking met 55% bij de FDA. Deze observaties geven aan dat FRPs weliswaar kunnen worden ontworpen om beoogde doelstellingen te bereiken, maar dat de percepties van de respondenten de noodzaak aangeven om de karakteristieken en de rollen van FRPs beter te begrijpen, de elementen voor succesvolle FRPs te definiëren en de optimale benadering voor de implementatie van FRPs in een wereldwijde context te bepalen. Dit hoofdstuk heeft richting gegeven aan ons vervolgonderzoek.

In tegenstelling tot FRPs die gebruikt of getest worden door Stringent Regulatory Authorities (SRAs, als gedefinieerd door de Wereldgezondheidsorganisatie), is het gebruik van FRPs door opkomende National Regulatory Authorities (NRAs) nog niet op systematische wijze onderzocht. Om de verschillen en overeenkomsten op dit vlak te onderzoeken hebben we een beschrijvende studie naar de FRPs gebruikt in 29 opkomende NRAs uitgevoerd (**Hoofdstuk 2.2**). Drieëndertig FRPs die in 29 landen gebruikt zijn werden vergeleken aan de hand van 27 FRP karakteristieken. We hebben de karakteristieken geclassificeerd als procedureel of inhoudelijk en gebaseerd op vijf volgordelijke regulatoire activiteiten. De regio's waarbij de karakteristieken van de FRPs het meest uitvoerig zijn beschreven zijn het Midden-Oosten/Noord-Afrika en Oost-Europa. De regio's waar de FRPs het minst gedetailleerd beschreven zijn was in Sub-Sahara Afrika. Alle FRPs beschreven ten minste tweemaal zoveel procedurele als inhoudelijke karakteristieken. De meest voorkomende karakteristieken waren: de beschikbaarheid van richtsnoeren of standard operating procedures voor het indienen van een FRP dossier; het gegeven dat het product bestemd moet zijn voor een ernstige conditie of onbeantwoorde medische behoefte; dat experts van buiten de autoriteit bij de beoordeling van het dossier betrokken kunnen zijn; dat de werkzaamheid ook gebaseerd kan worden op surrogaateindpunten en dat sponsors verplicht zijn studies na de markttoelating te doen. Wij waren van mening dat deze studie ons verder zou informeren over de identificatie van eigenschappen voor een wereldwijd toepasbare benadering voor FRPs, ons kon helpen bij het standaardiseren van benaderingen voor de versnelde beoordeling van geneesmiddelen en voor internationale organisaties de informatie zou leveren om hun regulatoire strategie te bepalen om de capaciteit van NRAs in opkomende landen te versterken.

Het beschikbaar hebben van een passende regulatoire omgeving is cruciaal voor het stimuleren van de ontwikkeling en markttoelating van zowel innovatieve als 'vervolg' producten. Om deze reden onderzochten we de procedures die opgezet kunnen worden om meer zekerheid in een beslissing te bieden.

In **Hoofdstuk 3.1** beoordeelden we de benaderingen voor de wereldwijde ontwikkeling en gelijktijdige indiening. De uitdagingen en mogelijkheden om regulatoire processen te ondersteunen werd beoordeeld in een uitgebreide workshop, waarvan de resultaten in dit hoofdstuk beschreven zijn. Activiteiten die de beoordeling zouden kunnen versnellen en de verwachtingen met elkaar in lijn kunnen brengen bestonden, onder meer, uit het gebruik van geavanceerde ontwerpen voor klinische studies en het gebruik van gereedschappen zoals biomarkers en passende surrogaateindpunten. Deze concepten ontwikkelen zich momenteel snel en zouden kunnen leiden tot een grote voorspelbaarheid van het geneesmiddelontwikkelingsproces en meer doelgerichte therapieën met een betere balans tussen werkzaamheid en veiligheid en het minimaliseren van verschillende uitkomsten van het regulatoire proces. Het gebruik van gestandaardiseerde instrumenten om de balans tussen werkzaamheid en veiligheid te beoordelen, het gebruik van patiëntgerichte uitkomsten en het beperken van de culturele verschillen in het ontwikkel- en beoordelingsproces zijn benaderingen die bedrijven kunnen kiezen om best practices te implementeren die een efficiënte en transparante besluitvorming ondersteunen, in het bijzonder wanneer van FRPs gebruik gemaakt wordt.

In **Hoofdstuk 3.2** verkenden we deze concepten in meer detail om zo aanbevelingen te kunnen doen voor hoe goede beoordelingspraktijken een transparante, voorspoedige, voorspelbare en hoogkwalitatieve beoordeling van nieuwe geneesmiddelen kan ondersteunen. Autoriteiten zijn op zoek naar manieren om te borgen dat ze niet alleen een goed proces voor de beoordeling hebben, maar ook een uitkomst van goede kwaliteit krijgen. We richtten ons op de elementen van goede besluitvorming. We concludeerden dat training in het gebruik van besluitvormingsinstrumenten essentieel is. Deze instrumenten bestonden onder meer uit de erkenning en gebruik van de elementen die onderdeel uitmaken van Good Review Practices, waaronder het gebruik van systematische raamwerken voor de beoordeling van de balans tussen werkzaamheid en veiligheid en een gestructureerd raamwerk voor besluitvorming en documentatie. Een belangrijke bevinding was dat hoogkwalitatieve besluitvorming het best tot stand kwam met de inbreng van diverse belanghebbenden (zoals de sponsor, zorgprofessionals, patiënten en beoordelingsautoriteiten).

FRPs worden regelmatig gebruikt om belangrijke geneesmiddelen voor een onbeantwoorde medische behoefte te beoordelen. In deze gevallen is de data waarop men een beslissing baseert mogelijk kleiner of beperkter in de tijd dan bij een product dat een standaardprocedure doorloopt. In **Hoofdstuk 4** hebben we getracht te begrijpen hoe het gebruik en de interpretatie van bewijs gerelateerd was aan regulatoire uitkomsten in deze bijzondere gevallen en hebben dit geëxtrapoleerd naar besluitvorming om FRPs te ondersteunen.

De basis voor de markttoelating van een nieuw geneesmiddel is een positieve balans tussen werkzaamheid en veiligheid: het aantonen van positieve effecten

tezamen met een aanvaardbaar veiligheidsprofiel. De autoriteit wordt uitgedaagd om de balans te vinden tussen de noodzaak voor snelle toelating tot de markt voor nieuwe geneesmiddelen en de noodzaak voor een beperkte mate van onzekerheid over de balans tussen werkzaamheid en veiligheid. De combinatie van harde en surrogaateindpunten voor werkzaamheid biedt onderzoekers en beoordelaars de mogelijkheid om het profiel van een nieuw geneesmiddel te karakteriseren. Echter, het gebruik van gangbare eindpunten en de grootte van het gemeten effect zijn niet altijd determinanten voor een succesvolle aanvraag voor markttoelating. In **Hoofdstuk 4.1** onderzochten we de associatie tussen drie eigenschappen van eindpunten (type [hard/zacht], grootte van het gemeten effect en statistische significantie) en uitkomsten voor markttoelatingsaanvragen voor oncologieproducten. We onderzochten in welke mate deze eigenschappen geassocieerd waren met een positieve of negatieve uitkomst bij de EMA door 50 oncologische geneesmiddelen te analyseren die tussen 2009 en 2013 beoordeeld zijn. In totaal hadden 16 producten (32%) een negatieve uitkomst. Het meest gebruikte harde eindpunt was overall survival (OS) en de duur van de respons of stabiele ziekte. OS werd gebruikt bij 91% van de toegelaten en 63% van de afgewezen verzoeken tot markttoelating. Het meest gebruikte surrogaateindpunt was progression free survival (PSF), de mate van response en kwaliteit van leven. Gemiddeld werden iets meer dan vier surrogaateindpunten gebuikt per toegelaten product en iets meer dan twee bij de afgewezen producten. Langere OS en PFS waren in het algemeen geassocieerd met markttoelating, zelfs als deze niet statistisch significant waren. Het cohort van toegelaten geneesmiddelen was geassocieerd met statistisch significante ($p < .05$) verbeteringen in de primaire eindpunten ($p < .0001$ verschil tussen de toegelaten niet afgewezen verzoeken). Niettegenstaande de bijdrage van unieke ziektespecifieke omstandigheden, zijn de drie eindpunten die we onderzocht hebben geassocieerd met een voorspelbare positieve uitkomst voor een verzoek tot markttoelating in de oncologie.

Deze observaties leidden ons tot de bredere vraag of er specifieke factoren zijn die geassocieerd zijn met positieve of negatieve regulatoire uitkomsten. Gebaseerd op een uitgebreid literatuuronderzoek evalueerden we 23 artikelen, gepubliceerd tussen 2001 en 2015, die als doel hadden om de relatie tussen specifieke factoren en positieve of negatieve regulatoire uitkomsten te karakteriseren en die voldeden aan onze inclusiecriteria (**Hoofdstuk 4.2**). De geselecteerde artikelen hadden een heterogeen karakter, met verschillende doelstellingen, hypotheses, methoden en cohorten. We hebben 151 factoren in de artikelen gevonden en hebben deze verdeeld in vier Factor Clusters: ondersteunend bewijs (52;34%), ervaring of strategie van het indienend bedrijf (46;31%), product- en indicatie-eigenschappen (45; 30%) en sociale en regulatoire factoren (8; 5%). We vonden een heterogene mix van technische factoren (zoals studie-ontwerp, klinisch bewijs van werkzaamheid) en

minder bestuurde sociale factoren (zoals interacties tussen het bedrijf en de autoriteit). Met onze studie bevestigden we de relevantie van een aantal bekende factoren en onderzochten we de minder bestudeerde sociale factoren. We evalueerden de publieke beoordelingsrapporten voor verschillende recente positieve en negatieve beoordelingen door de EMA en vonden dat de factoren die we in onze studie hebben bestudeerd herkenbaar waren in de verschillende casus. Onze bevindingen illustreerden het multifactoriële karakter van regulatoire besluitvorming. Omdat niet één bepaalde factor consistent geassocieerd was met een positieve of negatieve uitkomst hebben we geconcludeerd dat de factoren op een meer holistische wijze beschouwd moeten worden omdat zij een verschillend, contextafhankelijk belang hebben voor zowel de geneesmiddelontwikkeling als de regulatoire uitkomsten. Deze factoren, in combinatie met de drie eindpuntfactoren die we hebben onderzocht in **Hoofdstuk 4.1** zijn belangrijke componenten geworden van ons voorgestelde FRP raamwerk om vast te stellen hoe agentschappen bewijs kunnen gebruiken om tot een beslissing te komen. Een belangrijke constatering uit deze studie was dat speciale regulatoire routes (zoals de versnelde toelating, de weesgeneesmiddelenindicatie etc.) mogelijkerwijs een positief effect kunnen hebben op de regulatoire uitkomst. Dit leidde ons tot de vraag hoe FRPs de tijdslijn voor ontwikkeling en markttoelating van een geneesmiddel beïnvloeden.

Om deze reden hebben we getracht om in **Hoofdstuk 4.3** te bepalen in welke mate een combinatie van twee of meer FRPs de ontwikkelings- en toelatingstijd van geneesmiddelen beïnvloedt bij de FDA. We hebben een 'metrokaart' ontwikkeld om de FRP elementen en hun invloed op beoordelingstijd te visualiseren en hebben de kaart gebruikt voor ons FRP raamwerk in **Hoofdstuk 6.1.** De FDA heeft vier FRPs: Fast Track (FT), Breakthrough Therapy (BTD), Priority Review (PR) en Accelerated Approval (AA). Alleen PR specificeert een tijdspad voor de review (6 maanden). We richtten ons op een cohort van producten dat is goedgekeurd door de FDA via een specifieke FRP en hebben hun ontwikkel- en beoordelingstijd vergeleken met producten die gebruik maakten van de standaardroute. We hebben 125 nieuwe werkzame stoffen beoordeeld (goedgekeurd tussen januari 2013 en december 2013), waarvan 74 een of meer FRPs gebruikten. Voor deze 74 producten verschilde de ontwikkeltijd van 1458 (BTD+PR+AA) tot 3515 dagen (PR). Alléén PR had een mediane beoordelingstermijn van 242 dagen. De meest voorkomende combinatie was FT+PR (mediane beoordelingstermijn 292 dagen, n= 21). De snelste mediane beoordeling vonden we voor PR+FT+BTD+AA (145 dagen) en PR+BTD+AA (166 dagen). Onze bevindingen bevestigden niet alleen de kortere ontwikkelings- en beoordelingstermijn voor bepaalde FRPs en combinaties hiervan, maar gaven ons ook de mogelijk om de 'metrokaart' te gebruiken om FRP routes te visualiseren.

Omdat snellere besluitvorming via een FRP tot gevolg kan hebben dat activiteiten om de balans tussen werkzaamheid en veiligheid te begrijpen van de pre- naar

de post-markttoelatingsfase verplaatst worden, hebben wij in **Hoofdstuk 5.1** een eerste beoordeling gemaakt van de van de soorten post-approval commitments (PACs) die de FDA vraagt voor producten die recent tot de markt zijn toegelaten via een FRP. In totaal zijn 735 PACs gevonden voor 74 producten toegelaten tussen 2013 en 2015 die gebruik maakten van een of meer FRPs. De meeste PACs worden gevonden onder ATC Code 'L', antineoplastische en immuunmodulerende stoffen, en 'J', anti-infectie middelen. Dit zijn kritische geneesmiddelen voor een onbeantwoorde medische behoefte, veelal toegalaten op basis van een beperkte hoeveelheid data om veiligheid en werkzaamheid te ondersteunen; het is daarom redelijk om te verwachten dat deze categorieën de meeste PACs zullen hebben. Het meest voorkomende type PAC zijn diegene die bedoeld zijn om de farmacokinetiek, veiligheid en werkzaamheid te onderzoeken. Dit zijn de belangrijkste oorzaken voor onzekerheid op het moment van markttoelating. In het algemeen werd vereist dat de PACs binnen 1200 dagen van het moment van markttoelating voltooid zijn. De bevindingen verschaften steun voor ons FRP raamwerk waarin PACs van belang zijn om de bevindingen waarop een FRP beslissing gestoeld is te bevestigen.

Autoriteiten staan onder toenemende druk om nieuwe geneesmiddelen die als van groot belang worden gezien snel te beoordelen om zo een rechtvaardige toegang te faciliteren. Om deze reden worden de mogelijke voordelen voor het gebruik van versnelde beoordelingsroutes (FRPs) als alternatief voor standaardroutes onderzocht op vele plaatsen in de wereld. Deze FRPs bieden verschillende mogelijkheden om een versnelde beoordeling van geneesmiddelen te bewerkstelligen. Stringent Regulatory Authories (SRAs) maken gebruik van primaire FRPs om de ontwikkelings- of beoordelingstijd te versnellen. Sommige opkomende National Regulatory Authorities (NRAs) kunnen hun eigen primaire FRPs inrichten, maar het is meer waarschijnlijk dat ze gebruik maken van secundaire FRPs die zich baseren op de beoordeling van een SRA of ander agentschap, de WHO prekwalificatie procedure (PQP), 'altruïstische' reviews, of werkdeling via regionale samenwerkingsverbanden.

Ondanks de mogelijkheden voor verschillende FRPs, is er geen formele richtlijn of consensus voor de definitie, constituerende elementen en best practices voor FRPs. Daarom hebben wij in **Hoofdstuk 6.1** de verschillende bevindingen uit de voorgaande hoofdstukken samengebracht en een pragmatisch raamwerk bestaande uit 4 stappen ontworpen om alle soorten regulatoire autoriteiten te assisteren bij het bepalen welke toepassing van FRPs het meest passend is. In Stap 1 worden vier aspecten van de geschiktheid van de omgeving beoordeeld. In Stap 2 worden procescriteria geformuleerd die aanwezig moeten zijn voor het effectieve gebruik van FRPs. Stap 3 geeft autoriteiten de gelegenheid zichzelf te classificeren voor wat betreft gereedheid en capaciteit. Stap 4 geeft een route om te bepalen welke FRP het meest geschikt is voor hun situatie.

Dit raamwerk is de eerste poging om op een holistische manier de verschillende aspecten van FRPs die in ogenschouw moeten worden genomen om deze routes

effectief te kunnen gebruiken samen te brengen. Het raamwerk biedt transparantie voor het proces dat doorlopen moet worden en tracht de behoeftes en verwachtingen van verschillende groepen belanghebbenden te adresseren. Door ondersteunend bewijs te bieden voor de bouwstenen voor best practices op het gebied van FRPs, menen wij dat de benadering beschreven in dit proefschrift kan helpen om meer lijn te brengen in de variëteit aan FRPs die zijn geïmplementeerd of worden voorgesteld. We hopen dat dit proefschrift als inbreng kan dienen voor internationale beleidsdiscussies ten behoeve van een efficiënte beoordeling van geneesmiddelen en kan bijdragen aan een rechtvaardige toegang tot geneesmiddelen, wereldwijd.

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LIST OF PUBLICATIONS

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Lawrence Liberti has worked in the fields of pharmaceutical regulatory affairs, communications and clinical R&D for the past 38 years. He began his career at Wyeth Laboratories working in Product Development, then as a regulatory writer in Clinical R&D, and Manager of Safety Surveillance in Medical Affairs. He served as the Editorial Director for the North American operations of ADIS international after which he founded PIA Ltd, a company specializing in regulatory writing and consulting; he co-founded Astrolabe Analytica under which he helped develop, patent and commercialize the Astrolabe Message Mapping System™. Since 2009 he has served as the Executive Director of CIRS (the Centre for Innovation in Regulatory Science, Ltd). He has been actively involved in promulgating best practices in the regulatory aspects of medicines development, especially in the emerging markets.

Mr. Liberti received both his bachelor of science in pharmacy and master's degree in pharmacognosy from the Philadelphia College of Pharmacy and Science (now the University of the Sciences in Philadelphia). He attained the status of Regulatory Affairs Certified (RAC) with the Regulatory Affairs Professional Society and was awarded an honorary Doctor of Science by his alma mater. He is a Fellow of the American Medical Writers Association and is a recipient of their Golden Apple award for excellence in teaching. He is a co-founder of the Erudee Foundation, a non-profit dedicated to supporting local post-secondary educational opportunities for students in Latin America and Africa.