SCENDEA

The Importance of Regulatory Strategy

Authors

Lumanity
Sébastien Geneve PharmD

Scendea
Dr James Parsley, Dr Jens Van Wijngaarden,
Dr Natalie Thomas, Harriet Thomasson, Dr Hannah Lewis

Introduction.

> **Those who don't know history are destined to repeat it.**
>
> - Edmund Burke

Getting a new drug to the patient involves numerous stakeholders that are part of a multi-faceted regulatory framework. This framework has evolved over time and proceeds from drug discovery to development to regulatory evaluation.

Ideally, these aspects form the integral parts of a dynamic cycle, where the latest scientific innovations are incorporated and to which the framework adapts and reshapes itself. This evolutionary concept comes from an inherent driver to prevent history repeating. In short: it has learned from its past mistakes.

The European regulatory framework is a prime example of successful EU harmonisation but it did not fall into place in an instant. In 1953, the company Grünenthal obtained a patent for a new agent that would prove to be a blockbuster in its era: thalidomide. Without the backing of clinical trials and thought to be completely non-toxic, Grünenthal began marketing of thalidomide in 1957 as a morning sickness agent and it soon became readily available as an over-the-counter product. Once apparent that thalidomide was related to congenital malformations in newborns, the drug was withdrawn from the market. Legislation was developed which reinforced the FDA's responsibilities, and in Europe, the first pharmaceutical EC Directive 65/65/EEC1 was implemented. The aim of this legislation was to ensure that no medicinal product should ever again be marketed in Europe without prior authorisation and to establish a framework for the protection of public health.

Since then, the regulatory framework has evolved dramatically. Two key principles of the framework have however remained the same.

The first is that 3 key stakeholders are involved: the patient (generating a need), a drug developer (driving a new development with the incentive of patient benefit and financial stimulus), and a competent authority (safeguarding quality, safety and efficacy of medicinal products).

The second is the ability of the framework to adjust itself to scientific innovation in pharmaceutical development.

The aforementioned ability to adjust to scientific developments is based on several factors. Regulatory authorities issue guidance on specific product related developmental issues. The need to further develop guidance arises from questions from developers which are not covered in existing guidance, or from flaws identified in the application of existing guidance. When related questions are raised by developers requesting scientific advice from one of the competent authorities and appear indicative of a particular lack of guidance, competent authorities may identify the need to address this through updated or new guidance.

It is understood that scientific innovation spurs the need for new regulatory guidance and given the latest developments, one can only expect more to follow. Now, more than 2 decades into the 21st century, through progress in cell biology, genetics, molecular and systems pharmacology, the next paradigm shift in drug research is unfolding. The adoption of 'biological network transduction models', evaluating drug effects as the result of multiple interactions in a biological network, has yielded the potential for targeted therapy.

Following the rapid expansion of regulatory guidance and pharmaceutical law, it has become increasingly important to map out a regulatory strategy pathway for pharmaceutical development. A sound and robust strategy will facilitate efficient development strategy and reduce the attrition rate. This Whitepaper further elaborates on the need for such a strategy and highlights some important aspects to consider.

Overview.

A regulatory strategy is core to a future product's market success. It combines regulatory requirements and company objectives to allow access to patients and meet their medical needs. **It helps define the key elements to achieve these, including:**

- The Target Product Profile.
- Major regional considerations.
- Medicinal product classification.
- Paediatric and rare disease considerations.
- Available regulatory framework and programmes to enhance or accelerate development.
- Agency Interactions.

Regulatory Strategy, What it Comprises.

GLOBAL DEVELOPMENT

When developing a regulatory strategy, it is important to consider the key intended markets well before the start of clinical trials. This allows the best approach to accommodate the specific regional regulatory requirements.

Addressing regional regulatory requirements in parallel instead of in a sequential manner will obviously accelerate time to market, however, this approach also facilitates patient access and avoids superfluous data generation such as unnecessary, or inadequate clinical trials. The most obvious example of this is designing a study program that meets both applicable regional regulatory standards, where existing differences result in specific regulatory challenges, such as inclusion and choice of comparator arms, observational versus controlled trials, acceptance of surrogate endpoints and estimates of clinical relevancy. Considering these issues early in development helps smooth the development pathway.

PLANNING FOR AGENCY INTERACTIONS

Agency interactions, including pre-IND, Innovation Task Force (ITF), scientific advice, pre-submission meetings, etc may be of significant importance during drug development. Starting a dialogue with the regulatory authorities can help address certain issues that come forward during development and validate a company's approach. Sometimes, existing gaps in standing guidance may hinder development and an official communication from a competent authority can set a company on the right path and avoid future discussion during the marketing application submission. There are multiple ways to interact with the competent authorities and it is vital to make an informed decision on the when, who and how to drive the regulatory programme.

While sometimes not considered an important aspect of the product development, the market access strategy should be taken into account prior to Phase 3 entry for prescription medicines intended for payers' reimbursement. The payer's hurdle has become, and will continue to be, a critical step to enable patient access to new therapies and market success. Hence, it is advisable to plan for HTA meetings early enough during the product development. These allow exchange of information between the payers and the health technology developers for a given health technology. They also facilitate the generation of evidence that meets the likely evidence requirements of a subsequent payer's assessment on that health technology.

CONSIDERATIONS FOR THE RARE DISEASE SPACE

In response to the high number of serious and/or life-threatening rare diseases with marked unmet need, major regulatory authorities introduced incentives to stimulate development of medicinal products in inherently small populations. Development in these orphan indications can present unique challenges owing to their often-complex biology, a limited knowledge of the natural history/course of disease, and a need to consider innovative clinical trial designs owing to the low prevalence of the patient population. In both the US and EU, successful authorisation of medicinal products intended for orphan diseases confers multiple benefits, including a period of market exclusivity.

For developers of medicinal products in the pre-authorisation space, pre-market orphan designation can offer incentives including fee reductions on scientific advice in the EU, as well as a regulatory validation of the potential therapeutic value of a medicinal product in the target indication; this can be particularly important for small companies seeking external investment to progress towards later stage clinical development.

Orphan designation requirements in the EU and US are broadly aligned, with the Sponsor having to demonstrate medical plausibility of activity in the target disease and prevalence data meeting the threshold for definition of orphan (< 200,000 in the US and < 5 in 10,000 in the EU). In the EU, the sponsor should also show potential for significant therapeutic benefit over approved medicinal products in the target indication, if applicable.

Regulatory teams can use precedent designations as an initial guide as to whether diseases of interest are likely to meet the prevalence criterion for designation. The regulatory team should interact with the non-clinical development team in pre-clinical development to ensure that pharmacology studies are undertaken in appropriate disease models, with relevant comparators (if applicable) included as treatment groups. This will ultimately increase the likelihood of a successful orphan application. Early clinical development should incorporate pharmacodynamic assessments where possible, to provide further support for potential activity in the target disease in support of pre-market orphan designation.

Companies should expect that the chemistry, manufacturing and control (CMC) and non clinical data expectations for products with orphan designation are fully aligned to products intended for indications in larger patient populations. Recognising the complexities outlined above with respect to orphan diseases, however, regulatory bodies are routinely considering novel approaches to clinical development to expedite time to market in these challenging indications. Engagement of patient organisations and specialist treatment centres early in clinical development can ensure inclusion of highly relevant clinical outcome measures, facilitate patient recruitment and improve clinical trial design. In addition, regulatory professionals working in the rare disease space should plan for early regulatory engagement in key jurisdictions through advice procedures, as global harmonisation of regulatory expectations for approval is key to success.

CONSIDERATIONS FOR PAEDIATRIC DEVELOPMENT

Historically, the development of paediatric medicines had been somewhat neglected, with off label use of adult medicines in dosage forms unsuitable for children often being the only option available.

In recent years, regulatory authorities have developed stringent requirements for drug developers to ensure the availability of medicines that have been specifically developed for the paediatric population. As such, timely development of a robust paediatric strategy is fundamentally important to the success of a development programme.

In the EU, the Paediatric Medicine Regulation (PMR) mandates that a Paediatric Investigation Plan (PIP) be agreed with EMA. The PIP must outline the planned paediatric clinical studies and paediatric formulation development, to ensure sufficient data is obtained for approval of use in children. Compliance with the agreed PIP is a requirement for validation of a marketing authorisation application (MAA). In certain cases, such as where a disease does not occur in children, a waiver or deferral may be granted for all or part of the paediatric population, exempting the Sponsor from the requirement to include paediatric clinical data at time of MAA. EMA recommends that Sponsors should agree a PIP shortly after completing Phase 1 clinical studies to ensure their development program is aligned with agency requirements. EMA does offer some incentives to developers of paediatric medicines, including a 6-month extension of the supplementary protection certificate (SPC) and an additional 2 years of market exclusivity for paediatric orphan medicines. EMA also offers free scientific advice on questions relating to paediatric development.

Typically, the UK MHRA aims to take agreed EMA PIPs into account when commenting on UK PIPs. As such, a sensible strategy for Sponsors is to seek agreement of a PIP with EMA, followed by a UK PIP, enabling a clinical development programme that is aligned across Europe.

The US FDA has adopted a similar approach to the EMA via the Paediatric Research Equity Act (PREA), which requires Sponsors of a marketing application for a new active ingredient, indication, dosage form or regimen, or new route of administration to submit an initial paediatric study plan (iPSP). However, unlike the EMA, the US FDA, waives this requirement for medicines with orphan drug designation except for certain paediatric cancer targets. An iPSP must be submitted no later than 60 days after the End of Phase 2 (EOP2) meeting, or before initiation of phase 3 studies where an EOP2 meeting has not been held. Waivers and deferrals can be requested as part of an iPSP, although there are slight differences in eligibility criteria to the EU.

PREA does not confer any benefits to sponsors. However, sponsors of products not required to submit an iPSP under PREA can voluntarily agree a paediatric development strategy with FDA under the Best Pharmaceuticals for Children Act (BPCA) to obtain an additional 6 months of exclusivity upon approval.
Given the extent of the legislation in place in the EU, UK and US, it is a clear that the development of safe, effective paediatric medicines in an age-appropriate formulation is a priority for EMA, MHRA and FDA. To ensure compliance with regulatory requirements, Sponsors should consider their paediatric development strategy as early as possible. This approach allows Sponsors to make the most of incentives during development, and well-considered waiver or deferral requests (where eligible) can ultimately enable earlier submission of a marketing application.

EARLY ACCESS PROGRAMS AND EMERGENCY USE APPROACHES

Depending on unmet medical need related to the intended indication and the benefit impact of the product in development for patients, there might be the opportunity to request a fast-track review process or an early access/emergency use conditional approvals. Traditionally, such approaches were restricted to oncologists and rare disease indications. However, with the advent of COVID-19, agencies and innovators alike had to launch into somewhat unknown territory, utilising and developing the existing framework for the rapid yet safe advancement of vaccines and medication to tread COVID-19. Now, nearly all regulatory professionals have heard of emergency use authorisation, conditional approval, and Article 5(3) opinions. Japan has Special Approval For Emergency (SAFE), and Canada has the Interim Order. Further discussion of approaches to accelerated approval and early access are discussed below.

PLANNING FOR DESIGNATIONS AND ACCELERATED APPROVAL PROGRAMMES

A comprehensive regulatory strategy should proactively assess opportunities and optimal timings for interactions with incentivised regulatory procedures across the global stage, for any given product type, or target indication. The advantages of such incentives range from increased and tailored interactions with regulatory bodies, exemption from fees for regulatory procedures, and even accelerated assessment at the time of MAA.

A selection of such schemes, in the context of the progressing development phases, are highlighted here. To take advantage of all opportunities, Sponsors should build a strategy that is forward looking based on the availability of promising data. For example, considerations for US Orphan Drug Designation can begin as early as pre-clinical development, when an application can be submitted based on positive pre-clinical data supporting the scientific rationale that the product has the potential to treat a given indication (see section above on considerations for rare diseases). Moreover, pre clinical data can also be leveraged to request US Fast Track Designation at the time of original IND submission, to benefit from enhanced Agency communication and input from the beginning of the clinical programme (the data should demonstrate the potential to address unmet medical needs in the treatment of serious or life threatening conditions). The UK MHRA have developed innovative and unique procedures to support early patient access to medicines for life threatening or seriously debilitating conditions. During early development (based on supportive pre-clinical data), the Innovative Licensing and Access Pathway (ILAP) utilises UK multi-agency input (i.e., National Institute for Health and Care Excellence [NICE], Scottish Medicines Consortium [SMC]) to aid Sponsors in the development of a product-specific roadmap towards patient access in the UK. Examples of such tools are adaptive inspections and continuous benefit/risk assessment integrating real world evidence.

During clinical development, Sponsors should begin considering whether initial (including interim) clinical data could be supportive of an application for the Priority Medicines (PRIME) initiative (EU), or Breakthrough Therapy Designation (US). These designations are intended to enhance support for medicines for the treatment of unmet medical needs. Notably, for PRIME, as the EMA recognises the specific challenges faced by academics and smaller businesses, a company with Micro, Small and Medium-Sized Enterprise (or SME) designation and applicants from the academic sector can apply at an earlier stage than a larger company (i.e., proof of principal/mechanism compared to proof of concept stage) on the basis of compelling non-clinical data and tolerability data from initial clinical trials.

Due to the incentives offered (including the potential for Accelerated Assessment), attaining access to these programmes is competitive; the timing of applications should therefore be carefully considered to allow demonstration of a meaningful clinical effect, at an appropriate stage in development, to be able to fully benefit from Agency input on the development plan.

In the light of compelling data from pivotal studies, focus should turn to expedited approval (for MAANDA/BLA. The pathways for such advances include Accelerated Approval (US) and Conditional Marketing Authorisation (EU); considerations for such should be built into the clinical development plan and/or regulatory strategy.

Approaching MAA, regulatory procedures should be considered in the context of the MAA/NDA/BLA review timeline; Accelerated Assessment (as mentioned above) and Priority Review offer a fast track review of the respective marketing application in the case of products presenting major advances in treatment or intended for unmet medical needs. In the US, specific to the oncology space, the FDA has also developed the Real-Time Oncology Review (RTOR) programme, allowing reviewers to identify data quality and potential review issues earlier, with the overall aim to enable patient access as early as possible.

In the UK, a similarly patient-focussed approach has been taken with the MHRA's Early Access Medicines Scheme (EAMS). The Promising Innovative Medicine (PIM) designation provides a gateway to the scheme, enabling multi-stakeholder advice meetings and the opportunity for patients to receive treatment prior to marketing authorisation.

DEVELOPMENT OF EU PHARMACEUTICAL LEGISLATION

As outlined in the introduction of this Whitepaper, an adaptive regulatory framework is key for the latest scientific innovations to be incorporated into pharmaceutical development. Law and policy makers fulfil an important driver in shaping the right environment for sound pharmaceutical development. Ideally, the law addresses existing or emerging patient needs, innovative developments and gaps identified in standing law or policy. One interesting example that is fast approaching is the anticipated new EU pharmaceutical legislation.

EU law is dynamic and rapidly changing. This is not surprising and a direct consequence of the political landscape in Europe. In the EU, policy makers are taking their decisions within a framework of legal regulations at national and European level. They must relate to the political and social context of their country, while at the same time considering European and international developments.This system alone would be complex to navigate but is further influenced by the diverse interests of other stakeholders such as prescribers, regulators, pharmacists, payers, industry and patients. From 2020 onwards alone, several significant revisions in law have been adopted and implemented, such as the new Medical Devices Regulation (Regulation (EU) 2017/745, MDR) and the Clinical Trials Regulation (Regulation (EU) No 536/2014, CTR). In addition, by the end of 2022 a full review of the general EU pharma legislation as well as a revision of the orphan and paediatric medicines regulations is expected.

The main goals of the anticipated revisions have been made public by the European Commission in the published Pharmaceutical Strategy for Europe in 2020. This includes four key pillars that the new legislation builds from:

- Ensuring access to affordable medicines for patients and addressing unmet medical needs;
- Supporting competitiveness, innovation and sustainability of the European Union's pharmaceutical industry and the development of high quality, safe, effective and greener medicines;
- Enhancing crisis preparedness and response mechanisms, diversified and secure supply chains, and addressing medicine shortages;
- Ensuring a strong EU voice in the world, by promoting high quality, efficacy and safety standards.

The success of the new legislation will depend on the coordination amongst Member States as well as between the European Commission and the Council. The priorities will also depend on the dynamic created by the ongoing pandemic. The fact that this will prove a complex task has been corroborated by a recent publication of APM Health Europe as published on the 3rd of May.

This publication reports of a workshop as led by consultants retained from the EC on the proposed legislative changes. It speaks of widespread dissatisfaction, both on quality, scope and management. This is indicative of the complex environment and task the EC is currently facing in all pending reforms.

Keeping track of the upcoming changes in the regulatory framework is a challenging task, both for the EU as well as the US and illustrated by the above. It is imperative that clients monitor and incorporate the necessary legislative changes in their ongoing drug developments. One way of achieving this is to have a sound regulatory strategy in place that is revisited for amendment on a regular basis.

Conclusion.

Defining an effective regulatory strategy can be a game changer for companies, enhancing potential revenue, reducing product failure rates and bringing much needed therapies to patients.

Whether an SME or large corporation, **the benefits of a clear regulatory strategy include accelerating timelines, cost incentives and the chance to partner with regulators to ensure a smooth development programme**. However, a regulatory strategy set early in development is unlikely to be flawless as the demands and challenges faced throughout the development programme are likely to require continual adaptation. These may arise from new science, changing or new regulatory guidance, a changing treatment paradigm or even untoward changes forced through the results of nonclinical and clinical data.

Planning is key, and a good understanding of the regulatory framework is paramount to ensure appropriate milestones are met, such as paediatric plans and notified body opinions for combination products. At the heart of all the planning and adaptation is communication. A regulatory strategy cannot be left to a small group of regulatory staff, but must encompass all stakeholders including, for example, clinical operations, toxicologists, formulators, manufacturers, and commercial.

Without a continuous flow of information across all stakeholders and a clear vision, encompassed in the strategy or development plan, a project is likely to face additional challenges causing delays and potentially failure. The importance of a regulatory strategy cannot be underestimated, ultimately accelerating development of beneficial medications and enabling patient access.

SCENDEA

www.Scendea.com
Contact@Scendea.com

Lumanity

www.Lumanity.com
ClinicalandRegulatory@Lumanity.com

HEAD OFFICE.

Scendea Ltd
20 The Causeway
Bishop's Stortford, Hertfordshire,
CM23 2EJ
United Kingdom
Tel: +44 (0)1279 656 305

US / HEAD OFFICE.

67 E Park Place
Morristown, NJ 07960
USA

EU OFFICE.

Scendea B.V
De Cuserstraat 93
1081 CN Amsterdam
The Netherlands
Tel: +31 (0)208 949 169

EU OFFICE.

Lumanity GmbH
Grundstrasse 12
6343 Rotkreuz
Switzerland

US OFFICE.

Scendea (USA) Inc.
Suite 110
5764 Pacific Center Blvd.
San Diego, CA 92121
USA

Tel: 001-619-793-4511