The Role of Regulatory Agencies in New Drug Development: A Global Perspective

Regulatory agencies worldwide play a critical role in healthcare as independent reviewers and approvers of applications made by sponsors to conduct clinical trials and ultimately to market a drug for a particular indication. In this context, the term sponsor generally refers to a biopharmaceutical company that is developing a new molecular entity (NME), but it can also refer to a group of clinical investigators who wish to conduct clinical trials of a drug that is already marketed, in order to investigate its potential benefits for a different indication.

Before a sponsor submits a request to a regulatory agency for a new drug to be registered for human use in the agency’s jurisdiction, a tremendous amount of highly specified in vitro and non-human animal testing (which together comprise a drug’s non-clinical development programme) and clinical research needs to be performed. The later aspects of non-clinical development and all aspects of clinical research fall under regulatory governance, as does the manufacturing process. We cannot over-emphasise the importance of ensuring that development programmes meet regulatory expectations. In all cases, procedures and results must be documented appropriately; from a regulatory perspective, if research is not well documented, for all intents and purposes it has not been done. In many cases, regulatory agencies encourage sponsors to seek their input prior to embarking upon large components of a development programme, so that the sponsor and agency can develop a mutual understanding of the programme’s goals.

This commentary presents an overview of the regulatory landscapes for new drug development in the United States (US), Japan, and the European Union (EU), the three geographic regions that came together to form the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals for Human Use, a title abbreviated simply as ICH. Increasingly, the active participation of non-ICH regions in the development of new guidelines (and revisions of existing ones) is being sought. Initiated in 1990, ICH has various goals, key among which is encouraging the implementation and integration of common standards. Since sponsors frequently wish to market a new drug in multiple countries, a harmonised development programme is of considerable benefit in facilitating a more timely introduction of new therapies, and hence their availability to patients. To this end, ICH Tripartite Harmonised Guidelines were developed to describe requirements for various aspects of drug development programmes: non-clinical; chemistry, manufacturing, and controls (CMC); and clinical. In addition to the Safety, Quality, and Efficacy guideline categories, which cover non-clinical, CMC, and clinical topics, respectively, there are also Multi-disciplinary guidelines such as those describing the timing for non-clinical studies relative to clinical trials and the Common Technical Document submission structure. These guidelines have been adopted by individual regulatory agencies, who may also issue regional guidances on specific topics, both of which guide biopharmaceutical research and development activities in their respective jurisdictions. In addition, sponsors “translate” the guidelines into standard operating procedures (SOPs) tailored to their individual organisation; SOPs provide a greater level of operational detail, and multiple SOPs may be necessary to support an overarching ICH guideline.

Bringing new drugs to global markets increasingly requires collaboration between multiple stakeholders that includes regulatory agencies. As Grignolo observed, “The future of the medicines landscape must evolve toward a more collaborative framework, where regulatory agencies will pursue a greater degree of convergence and where sponsors, regulatory agencies, and payers, as essential stakeholders, will undertake drug development with reimbursement in mind to achieve the common global goal of bringing safe, effective, and affordable medicines to the world’s people.” It is our experience that collaboration between regulatory agencies and sponsors is already occurring, utilising mechanisms such as pre-investigational new drug and end of Phase 2 meetings and special protocol assessment in the US, consultations on clinical trials in Japan, and requests for scientific advice and protocol assistance in the EU. Recent communications from regulatory agencies demonstrate continued support for cooperative and innovative approaches. Despite these valuable collaborations, however, differences between regional regulatory authorities still exist, as evidenced by the following overview of the US, Japanese, and European regulatory landscapes.

The US Food and Drug Administration
The US Food and Drug Administration (FDA), housed within the Department of Health and Human Services, is one of several agencies in the executive branch of the US government charged with implementing statutory laws created by the legislative branch, which it does by creating regulations or administrative law. The FDA is responsible for ensuring that regulated medical products comply with public health laws and regulations, and it is therefore a law enforcement agency with both administrative and judicial means at its disposal. It typically attempts to achieve compliance with its statutes using administrative means, e.g., inspections of products and manufacturing facilities, notices of violation of regulations, and recalls of marketed regulated products. However, if deemed necessary, it can utilise the US court system and the Department of Justice’s assistance to invoke its judicial tools, including seizure, injunction, and prosecution.

Results from a drug’s CMC and non-clinical development programme are reported to the FDA in an investigational new drug application (IND). This document is reviewed to see if clinical trials should be allowed to start. FDA reviewers have 30 days to respond to the sponsor following submission of the IND. If a sponsor has not been contacted in that timeframe they have implied permission to commence their clinical development programme as described in the IND. Prior to submitting an IND,
a sponsor may request a pre-IND meeting with FDA to obtain answers to specific questions they have regarding their CMC, non-clinical and clinical development plans.

The purpose of an IND is to provide detailed documentation in four broad areas:

- Manufacturing information. These data address the composition and stability of the drug, as well as the process and controls used for its manufacture.
- Animal pharmacology and toxicology studies that have been completed. These non-clinical data permit an assessment of whether the product is considered to be reasonably safe for initial testing in humans.
- Clinical study protocol(s). Protocols include precise accounts of the design, methodology, and analysis considerations necessary to conduct the proposed clinical trials and analyse their results.
- Investigator information. Information on the qualifications of clinical investigators is provided to allow assessment of whether they are qualified to fulfill their duties at the investigational sites used during the clinical trials.

The clinical protocol included in an initial IND is usually for a Phase 1 study designed primarily to collect safety data on the drug, and oftentimes it will be the first time the drug will be administered to humans. Later, when the sponsor is ready to progress to Phase 2 and ultimately pivotal Phase 3 studies, the protocols for these trials are submitted to the same IND, along with any additional supporting CMC and non-clinical data that have been generated. Unlike with the original submission of the IND, the sponsor may commence these subsequent studies upon receipt of the protocol by FDA, rather than waiting for a 30-day review period; however, FDA retains the ability to halt the trial or request a protocol amendment upon their review. In reality, there is generally some lag time between the submission and dosing of patients due to the logistics of initiating clinical sites and the desire of some sponsors to allow for a preliminary FDA review of the protocol.

After completion of the clinical trials conducted under an IND (and completion of all non-clinical studies being conducted contemporaneously: some of the more lengthy and costly animal studies are performed in parallel with clinical trials), a new drug application (NDA) is filed for small-molecule drugs and a biologics license application (BLA) for a biologic. FDA recently published a guidance that summarises four programmes available to expedite development of drugs to treat serious conditions. In addition to having these programmes, it is a common practice for sponsors to have an End of Phase 2 meeting with FDA to discuss how best to design and conduct the pivotal Phase 3 trials. Sponsors will then typically meet again with the FDA after the completion of all clinical trials to discuss the content and format of an NDA/BLA prior to its preparation. These meetings can be crucial for the sponsor to understand how to best facilitate the review process for a given submission. The FDA’s review of the NDA/BLA determines whether it finds the evidence concerning safety, efficacy, and manufacturing ability to be compelling, and if it is therefore prepared to approve the drug for marketing. After approval of a drug, FDA reviews post-marketing safety surveillance data that it receives in the form of individual adverse events reports submitted by patients, healthcare providers, and the sponsor, as well as periodic safety update reports from sponsors.

The Japanese Pharmaceuticals and Medical Devices Agency

Like the FDA, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) regulates medical products in a single country or jurisdiction. As noted by the PMDA’s Chief Executive, Dr Tatsuya Kondo, the agency takes a drug lifecycle approach and focuses on three key areas: “relief services for adverse health effects, product reviews, and post-marketing safety measures.” Because the agency is responsible for providing relief compensation for sufferers from adverse drug reactions and infections caused by biopharmaceutical products, this “safety triangle” is unique to Japan.

A second notable aspect of the PMDA’s operations was detailed recently by Asahina et al. While all concerned would agree with the authors’ assertion that “Drug monitoring after regulatory approval, mainly in terms of safety under conditions of actual use, is as essential as evaluating data before marketing [approval],” the PMDA has formalised re-examination and re-evaluation systems that “play important roles in continuously ensuring the positive benefit-risk balance of drugs in Japan.” At a specified timepoint following marketing approval (which is eight years for an NME) a sponsor must submit all available information that has been accumulated since approval, and the PMDA determines whether or not unacceptable risks associated with the product have occurred in clinical practice.

In addition to the emphasis placed on safety, PMDA offers consultations regarding clinical trials, advising sponsors how to improve the trial. In 2009, PMDA also began to offer consultations on clinical trial data prior to submission for marketing approval.

The European Medicines Agency

Unlike the FDA and PMDA, the European Medicines Agency (EMA) brings together the scientific resources of multiple nations, namely the member states of the EU, of which there are 28 as of the writing this commentary in January 2014. Sponsors submit a clinical trial application (CTA) to the individual member states in which they intend to conduct the clinical trial. In March 2014, Parliament will vote on revisions to the EU clinical trial regulations that would enable a single application to be filed through a central portal, and would designate one country to lead the review process and coordinate the input from the other countries. In contrast to an IND, a CTA is protocol-specific; therefore, one must be filed for each study a sponsor wishes to conduct, and hence a collection of CTAs accumulates during a clinical development programme. A separate document, called an investigational medicinal product dossier (IMPD), is submitted with the CTA and contains summaries of CMC, non-clinical, and any previously generated clinical data, as well as an assessment of overall risks and benefits. This document is updated as the development programme progresses, but unlike a US IND, full non-clinical study reports are not included.
Scientific advice on the acceptability of any particular clinical trial can be sought from the regulatory agencies of the individual member states in which the trial is to be conducted, but because of the potential for the drug to be approved for marketing throughout the EU via the centralised procedure (described in due course), sponsors often seek scientific advice/protocol assistance for development programmes from the EMA. Having the prospective input of the EMA on a clinical programme is valuable, because the EMA is the agency that will review the centralised application and recommend to the European Commission whether or not the drug should be approved. When a clinical development programme is completed for a new drug or biologic, a marketing authorisation application (MAA) is submitted.

There are multiple submission routes for MAAs: the centralised authorisation procedure, the decentralised authorisation procedure, the mutual recognition procedure, and the national authorisation procedure. The centralised procedure, initiated in 1995, leads to a single marketing authorisation that is valid in all EU countries. The centralised procedure is compulsory for various drug classes, including, for example, those for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, viral diseases, and rare diseases (‘orphan diseases’). The centralised procedure, in which the European Commission grants marketing authorisations for all countries in the EU, is intended to allow a sponsor to begin making the drug available to patients and healthcare professionals in all EU member states, but it carries with it the risk that if some countries raise objections during the procedure that impact the vote, then approval is not possible in individual countries.

For drugs not falling within the specified classes for which the centralised procedure is mandatory, sponsors can choose which route to follow: national, centralised, decentralised, or mutual recognition. The latter two are closely related in that the sponsor selects the member states from which it seeks approval and, if a choice between the centralised and the decentralised or mutual recognition routes is possible, a sponsor will weigh various strategic factors, including medical practice in the different countries, manufacturing plans, market forces, and its size, resources, and strengths in the EU.

After approval of a drug, the national regulatory agencies review post-marketing safety surveillance data including individual adverse events reports as well as periodic safety update reports (PSURs) submitted by sponsors (for centrally approved drugs, PSURs are reviewed by EMA).

References

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<th>Regulatory Agency</th>
<th>Document to Request Clinical Trial Authorisation</th>
<th>Document to Request Marketing Approval</th>
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TABLE 1: Documents and Websites for the Regulatory Agencies Discussed

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