

# Exploring the Opportunities and Challenges in Repurposing a Master Dossier



It is known that developing an innovative healthcare product from bench to market is a very expensive and complex effort, as the pharmaceutical industry is highly regulated to protect the consumer. Global spend on medicines is forecast to reach nearly \$1.4 trillion by 2020, an increase of about 32% over 2015. This is driven by population growth and improved access to emerging markets.<sup>1</sup> Interestingly, the revenue driver at many leading companies remains the innovative medicines portfolio, despite some companies' diversification into generics, consumer medicines, diagnostics and other related healthcare products. To save time and money in bringing products to market, product development activities should be conducted in accordance with predefined global and region-specific regulatory requirements.

For any biopharmaceutical, submitting a new drug application (NDA) is the ultimate goal and a mandatory step for commercialisation. As biopharmaceutical companies plan to put their product out in multiple markets, they have to consider a global regulatory strategy for registration in the developed countries as well as in several emerging market countries. However, differing registration requirements across markets are a burden. Knowledge of the drug registration processes and submission content is key for effective planning and execution of global regulatory strategy. A step-by-step approach is essential to make any global submission successful.

This article will discuss regulatory requirements for product registration in different geographic regions, key similarities and differences in the regulatory requirements and the opportunities and challenges in repurposing or reformatting an existing market dossier for registration in new markets worldwide.

## Background

The application dossier for marketing authorisation is called an NDA in the US or marketing authorisation application (MAA) in the European Union and other countries, or simply registration dossier. It consists of a dossier with data

proving that the drug has quality, efficacy and safety properties suitable for the intended use, additional administrative documents, samples of finished product or related substances and reagents necessary to perform analyses of finished product as described in that dossier. The content and format of the dossier must follow rules as defined by the competent authorities. For example, since 2003, the authorities in the US, the European Union and Japan ask for the common technical document (CTD) format, and more recently, its electronic version – the electronic common technical document (eCTD). The application is filed with the competent drug regulatory authority in the concerned country, which can be either an independent regulatory body or a specialised department in the ministry of health.

In accordance with local legislation, the resulting document allowing the applicant to market the product may be more detailed (in addition to data identifying the product and its holder, it may contain addresses of all manufacturing sites, appended labelling, artwork of packaging components, etc.) to a one-page document called the certificate of registration (containing

minimal data identifying the product and its source).

## Harmonisation of Technical Requirements for Registration of Pharmaceuticals

Given the major resources needed to assemble registration dossiers in multiple countries, there has always been an incentive to promote as much similarity as possible in the regulatory requirements and content of registration applications. Through the International Conference on Harmonization (ICH) process, considerable harmonisation has been achieved among the US, Europe and Japan in the technical requirements for the registration of pharmaceuticals. However, until now, there has been no harmonisation of the organisation of the registration documents. To avoid the need to generate and compile different registration dossiers, the agreement to assemble all the quality, safety and efficacy information in a CTD (Figure 1) has revolutionised the regulatory review processes. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.

Non-ICH countries have also expressed the need to ensure harmonisation, which

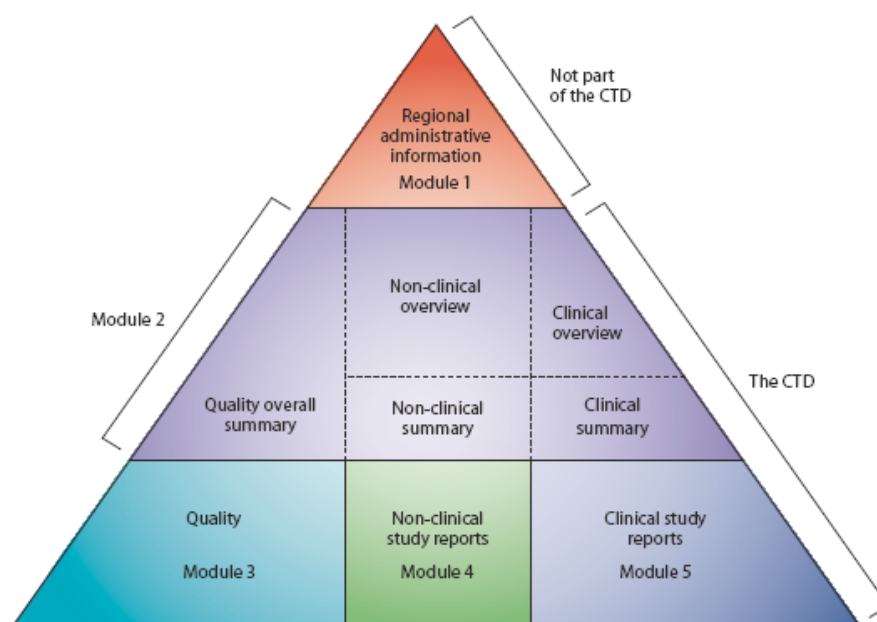


Figure 1: The CTD is organised into five modules. Module 1 is region-specific and modules 2, 3, 4 and 5 are common for all regions.

has resulted in regional initiatives. In Asia and the South Pacific, the Association of South-East Asian Nations (ASEAN) countries has agreed to a common approach to medicines regulation, and established an ASEAN CTD to harmonise pharmaceutical product dossiers, much like has been done with ICH. In Latin America the Pan American Health Organization (PAHO) via the Pan American Network for Drug Regulatory Harmonization (PANDRH) is aiming to establish a regional drug regulatory harmonisation network and now has a working group on drug registration.

account for 52% of the projected increase in total medicines spending of \$305-\$335 billion.<sup>3</sup>

With the slowing growth in developed markets, biopharmaceutical companies have made substantial investments into emerging markets, striving for rapid, simultaneous global launches. Aligning regulatory strategy across countries saves time and cost for drug developers, and results in quicker access by patients. Hence, it is a logical approach to reuse and reformat the core dossier submitted in regulated countries to meet

for the non-ICH countries. Generally, the master dossier is kept up-to-date with all new information requested by health authorities from the time of initial approval and through the product's life cycle. These updated core dossiers are tailored to suit other country-specific submission formats and requirements. From this core dossier, the CMC sections are shortened for confidentiality and intellectual property issues.

For a generic, a company develops a dossier that contains data primarily about the pharmaceutical chemistry of the product and some limited clinical data. In some instances, a product can be registered on the basis of chemical and manufacturing data only, describing the method of synthesis and quality control for the product. The requirements for generic product registration do vary from country to country, and within a country there are variations in the data required, depending on the type of generic product.

Modules	Location	
	ICH CTD	ASEAN CTD
Regional administrative information	Module 1	Part I
CTD overview and summaries	Module 2	Incorporated in parts II, III and IV
Quality documents	Module 3	Part II
Non-clinical documents	Module 4	Part III
Clinical documents	Module 5	Part IV

Table 1. Difference between ASEAN CTD and ICH CTD

Despite the harmonisation initiatives, the structure and content of the product dossier today differs from region to region and country to country. From the industry perspective, harmonisation would increase the registration and marketing chances of a particular molecule in several countries in a short time. Reduced development time, less cumbersome approval processes across countries, and increased speed-to-market are important business drivers. In addition, harmonisation would give patients faster access to new medicines and might lower the costs of drug development, which could lower the price, making new drugs more affordable in many more markets.

**The Demand to Repurpose Dossiers**

New product introductions are on the rise, with 86 new drugs being approved across the US and EU in 2014.<sup>2</sup> In the past years, the rate of new drug approvals by the US Food and Drug Administration (FDA) was greater than 80%. Despite unmet therapeutic need, these players can no longer depend only on their innovation engine and pricing to drive profits. As the focus of global healthcare shifts from value to volume, generics and biosimilars have become an integral part of the strategy. Generics are the largest contributors to growth in both regulated and emerging markets; many companies are monitoring patent expiries and developing generics of small molecules as well as biologics (i.e. biosimilars). On a global basis, generics are forecast to

region- or country-specific registration requirements.

Development of and regulatory approval for 'new uses' of already-approved drugs is an important source of innovation. One study that analysed the number of supplemental-indication approvals by US FDA found over 1000 new-use approvals during 1998-2011.<sup>4</sup> Additionally, the number of new paediatric indications rose substantially over this period due to a legislated market incentive to study already-approved drugs in paediatric populations.<sup>4</sup> This provides an opportunity to reuse the sections or data from the already-submitted dossiers to support the new application with its specific requirements.

**Approach to Repurposing of a Master Dossier**

Preparing one core dossier and adapting it to the regional specificities can optimise resources and may lead to a faster global registration. Similarly, a sequential approach can allow the applicant to obtain feedback from the first agency and make adjustments to the second dossier prior to its submission.

For many biopharmaceuticals, the core or master dossier generally contains the most comprehensive CMC, non-clinical and clinical information available on the product from a regulatory point of view. This master dossier forms the basis of the international master dossier

Issues can arise, for example, if an applicant just deletes some sections of the ICH dossier and submits an "incomplete" dossier, there is a risk of refusal to file. Therefore it is strongly recommended that only the content in some sections should be reduced to fulfil the regulatory requirement. One possibility to make these changes within the dossier is the creation of a master dossier with a high granularity for documents in order to be able to exchange parts quite easily for the emerging countries. This approach helps limit the highly confidential information and reduces the workload in writing and reformatting.

Generally, for any successful submission, creating and managing global submission templates is of paramount importance. Selection of the correct 'submission template' for a specific country and submission type is a critical step for successful submission. The primary purpose to develop and use the standard template is to ensure compliance with the regulatory norms of that particular region. Regulatory agencies have provided granularity guidelines and these guidelines vary based on product, agency and submission type. The template needs to be versatile such that it can be used for submissions in CTD in paper format, non-eCTD electronic submissions (NeeS) and for eCTD. Additionally, the template should be user-friendly, and ensure that

regulatory professionals can perform the reformatting with minimal training.

## Increasing Market Access Through Regulatory Strategy

The number of regulatory requirements has grown exponentially as biopharmaceutical companies enter new and disparate markets, but efforts in global regulatory harmonisation have stalled. To support the global growth imperative, regulatory functions must meet the local needs of a greater number of countries, while supporting an expanding list of products and aggressive project timelines. Altering regulatory strategies to meet new business models will generate faster approvals and help propel growth in emerging markets.

Biopharmaceutical companies have honed their regulatory submission operating models to facilitate the introduction of new products in the US, Europe, and Japan. But those models are not always transferable to emerging markets. To achieve simultaneous global approvals, companies need to focus on the strategy, capabilities, and processes. An effective global regulatory strategy must address both the differences and the similarities across markets. Companies should maximise common elements of the global dossier while ensuring that each submission for market authorisation can be tailored to meet local regulatory requirements. Standards of care, clinical trial requirements, distribution needs, and local regulations vary greatly across countries and regions.

Emerging countries often make product approval contingent upon regulatory approval in a reference country, where the product undergoes a more advanced and rigorous health authority review. To limit approval delays in emerging countries, biopharmaceutical companies can generate the emerging-market filing in parallel with the primary filing and completing pre-reviews with those health authorities so that the filing can be submitted as soon as approval has been granted in the reference country. Companies' global regulatory strategies should outline the type and sequence of such submissions, taking into account the unique requirements of each country involved in a development plan.

Companies must not only evolve their commercial, R&D, and supply chain organisations to meet the needs of the

global marketplace, but they also must adapt their regulatory organisations. It is important for companies to focus on optimising their global footprint with internal resources and strategic partners. The challenge is to develop a sourcing and organisational model that builds global capabilities without increasing cost and infrastructure. Collaboration among global and local resources, both within a company and involving its strategic partners, is essential for delivering products that meet the needs of local markets.

## Summary

In order to protect consumers, the pharmaceutical industry is highly regulated, with rules enforced by the health agencies. These requirements are growing all the time as companies enter new markets. However, regulatory functions must meet the local needs of a greater number of countries, while supporting an expanding list of products and aggressive project timelines. Preparing one core dossier and adapting it to the regional specificities can allow for optimising resources and lead to a faster global registration.

Harmonisation would give patients faster access to new medicines and could lower drug costs, making them more affordable in many more markets. By redefining regulatory operating models, companies will be better positioned to achieve near-simultaneous global market approvals and reach populations in need of their products, wherever those patients may be.

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