Regulators make benefit-risk decisions based on the three pillars of quality, safety, and efficacy. CMC is applied throughout the product development spectrum from the initial synthesis of a molecule to reach a hypothetical target, to commercial scale up and beyond. This article helps the reader navigate the CMC regulatory landscape and understand the multiple considerations needed in order to devise a strategy which is efficient with respect to cost and time to approval.

Keywords—CMC, pharmaceutical quality, strategy

Introduction

There are three key components to a pharmaceutical product investigational or marketing application. These modules, which are the basis of any application, include clinical, nonclinical, and quality. The quality component is where chemistry, manufacturing, and controls (CMC) becomes a significant consideration for an organization. CMC plays an integral role, enabling nonclinical and clinical studies and reducing a product’s time to market. Efficient planning and long-range product and regulatory strategies can have lasting impacts on overall lifecycle management.

This chapter provides an overview of the basic considerations to facilitate and guide product development from inception to commercialization. CMC regulatory strategy does not start or end with a marketing application. An effective CMC regulatory strategy must manage the challenging path of drug development within the global regulatory landscape’s evolving structure. The goal is to provide information to facilitate interactions with technical personnel and negotiate with regulatory authorities to refine and optimize global regulatory CMC strategies. The main emphasis is on product registration and postapproval changes in the US, EU, and Japan, with a separate section for emerging markets.

Increased globalization has significantly expanded the importance and need for strategic product development and CMC regulatory strategy. Increased harmonization among the major regulatory authorities, through the International Council for Harmonisation (ICH), has resulted in more standardized requirements, however, it is unlikely that regional CMC differences will be completely eliminated. According to ICH, its mission is to achieve greater harmonization worldwide to ensure safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. This collaborative regulatory group includes regulatory
and industry members as well as a number of observers working toward the globalization of medicines.

For the most part, pharmaceutical regulations are divided into five geographies:
- North America (US, Canada, Mexico)
- Europe (UK, Switzerland, EU, and Eastern Europe)
- Japan
- China
- Rest of world (RoW; Asia Pacific minus Japan, Australia/New Zealand, Gulf Co-operation Council, Association of Southeast Asian Nations, Latin America, Commonwealth Independent States, and Central East Europe (non-EU countries)

From a regulatory perspective, the world generally is divided between “established” and “emerging” markets. The established markets, with more defined laws requirements, include the US, EU, Japan, Australia, Canada and, increasingly, China, following its full ICH membership in 2017. Emerging markets are those with less defined laws and regulations. Approval to market pharmaceutical products is typically granted by a national authority on a per country basis.

The EU, however, has the centralized procedure, which enables pharmaceutical companies to submit a single marketing authorization application. An approval by the European Commission of a centralized application is valid in all EU member states and the European Economic Area–European Free Trade Association states. The centralized procedure is required in some instances, such as those outlined in Table 1, and is optional for other product types. To determine whether a product should be evaluated under the centralized procedure, companies may submit an “eligibility request” with appropriate justification that the product falls under one of the described categories.

The EU submission procedure is important to commercialization strategies that are impacted by the submission procedure chosen, as well as regional pricing considerations, which vary widely across regulatory regions. While most new medicines use the centralized procedure, a sponsor could choose to follow a national, mutual recognition or decentralized procedure. Since these approaches are less common, they will not be discussed further. Depending on the regulatory region, additional quality requirements that can impact the pharmaceutical product commercialization process may apply. Table 2 provides various countries’ or regions’ regulatory authority names.

**Product development and global regulatory strategy**

Planning a global regulatory strategy can start as soon as the decision is made to transition a discovery candidate into development. To ensure a product’s long-term clinical and commercial success, it is essential to develop an efficient CMC regulatory strategy. The foundation
<table>
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<tr>
<th>Country/region</th>
<th>Regulatory authority</th>
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<tr>
<td>US</td>
<td>FDA, Food and Drug Administration</td>
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<tr>
<td>EU</td>
<td>EMA, European Medicines Agency (each member state has a national competent authority)</td>
</tr>
<tr>
<td>Japan</td>
<td>PMDA, Pharmaceuticals and Medical Devices Agency</td>
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<tr>
<td>Canada</td>
<td>HC, Health Canada</td>
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<tr>
<td>UK</td>
<td>MHRA, Medicines and Healthcare products Regulatory Agency</td>
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<tr>
<td>Australia</td>
<td>TGA, Therapeutic Goods Agency</td>
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<tr>
<td>China</td>
<td>NMPA, National Medical Product Administration (formerly CFDA, China Food and Drug Administration)</td>
</tr>
<tr>
<td>South Africa</td>
<td>MCC, Medicines Control Council</td>
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<tr>
<td>India</td>
<td>CDSCO, Central Drug Standards Control Organization</td>
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<tr>
<td>Brazil (member of LATAM)</td>
<td>ANVISA, Agencia Nacional De Vigilancia Sanitaria</td>
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<td>Switzerland</td>
<td>Swissmedic</td>
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<td>Mexico</td>
<td>COFEPRIS, Mexico Ministry of Health</td>
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<td>Latin America</td>
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of a robust CMC development program and regulatory strategy must include:

- Clear understanding of corporate objectives and priorities,
- Thorough understanding of the drug substance and drug product,
- Strong understanding of country- or region-specific quality requirements,
- Good communication with regulatory authorities,
- Strong internal and external cross-functional teamwork.

To develop a strategic global regulatory plan, the first step is to understand the vision of the idealized product relative to existing therapies. Is the product being positioned as a first-in-class therapy, a product being evaluated for providing benefit beyond the standard of care, a generic of an existing approved product or a biosimilar? The global product strategy is the key foundation for establishing a quality target product profile and development plans to achieve the vision. This vision enables key CMC strategy development considerations and should be captured in various strategy documents. Ultimately, details such as proposed commercial image will dictate container closure systems, pack sizes, expiry, labeling, manufacturing, and supply chain strategies needed to complete the overall CMC strategy. Not having an ultimate product vision is comparable to assembling the most intricate and complicated puzzle without ever seeing the picture on the box.

The foundation of pharmaceutical development is establishing a therapy’s viability, as quantified by measures of safety and efficacy, to address a medical need. The altruistic goal is to improve the lives of patients and potentially develop new and innovative approaches to treating disease. Because human lives could hang in the balance, there is an underlying drive to focus on the fastest route to the commercial markets. However, a delay to market can have an enormous financial impact in lost revenue for a company trying to recoup the vast expense of drug development. In addition, being first to market is key for market exclusivity, and any delays to market impact the sales and revenue achievable during the product’s lifecycle. This may result in business decisions that trade global planning strategies for product approval in a major market, with globalization considered later in the product lifecycle. By having a clear vision of what the ideal product will look like, a rationalized and structured development plan can be created. This results from marrying pharmaceutical development and CMC regulatory strategy to enable a development candidate to become a commercialized product.

**CMC regulatory strategy planning**

1. Identify planned and potential registration areas
   - Applicable laws and regulations
   - Review and approval timelines and procedures

2. Product type (evaluate by region)
   - Small molecule or biologic
   - New chemical entity (NCE)
   - Dosage form and route of administration
   - Generic (abbreviated new drug application, ANDA, 505(j))
   - Combination products (drug/device)
   - Novel excipients
   - Proposed container closure and commercial packaging configuration, sizes
   - Product attributes and challenges

3. Drug substance
   - NCE, modified dosage form or generic (drug substance is a significant factor in determining regulatory pathway (generic or modified dosage form), patents, and exclusivity)
   - Characteristics such as polymorphism, physical form, salts, stereoisomers, solubility, ease of manufacture, and potential genotoxic impurities
   - Ability to reference drug master file (US), active substance master file (ASMF; EU) or master file (Japan)

4. Regulatory pathway and considerations
   - NCE
   - Modified release dosage form
   - US 505(b)(2) applications, EU Article 10a – Well-established use
Expedited procedures (innovative, orphan, and breakthrough products)

Combination products

CMC registration documents: US, EU, and Japan

Although the three major regulatory regions, the US, EU, and Japan, have made significant strides toward harmonization, and information regarding laws, regulations, and guidance is more readily accessible than in countries with emerging markets, there are still differences beyond the requirements for the common technical document’s (CTD’s) regional sections. These differences are important considerations to incorporate into a drug development strategy, depending on the intended registration regions. This long-term focus can enable study and data collection efficiencies throughout product development. The marketing authorization name, applicable regulatory authority, and approval times vary across the regulatory regions. All three regions have legal and regulatory provisions to expedite drugs to treat serious conditions, which can impact CMC content because of compressed development or regulatory authority review timelines (inspection, approval, and launch).

The three regions support the use of the CTD by applicants. Module 2.3 is an overview of the CMC technical information located in Module 3 and is more similar across the major regions than Module 3.

For the Japanese new drug application (JNDA), Module 2 should be written in Japanese, but figures and tables written originally in English and used for a US new drug application (NDA/biologics license application, or BLA) and/or EU marketing authorization application (MAA) are accepted. English is acceptable for Module 3, but the table of contents should be in Japanese. It is important to note Japan’s Pharmaceuticals and Medical Devices Agency uses Module 2 as its main review document.

The CTD sections are outlined in the ICH guideline on the organization of the CTD for registration of pharmaceuticals for human use (Quality (M4Q(R4); Step 4, 2016). In addition, each region has a location for regional information in Module 3. Highlights of differences between regions are:

- Executed batch records for primary stability batches (US only)
- Method validation package (US only)
- Comparability protocols (US only)
- Process validation scheme for the drug product (EU only)
- Certificates of suitability (EU only)
- Materials of animal or human origin (EU only)
- Compliance with the TSE [transmissible spongiform encephalopathy] requirements (EU only, located in Module 3 for US NDA)

The CMC regulatory professional also should be aware of potential Module 1 regional differences. US NDA or BLA CMC information includes the field copy certification (certifying CMC information has been sent directly to the field office for inspection purposes), letters of authorization from drug master file (DMF) holders to access their DMFs and the environmental assessment or claim of categorical exclusion.

In all three regions, the amount of information submitted in the marketing authorization application may be reduced by cross-referencing to a DMF. There are differences among the regions: both EU and Japanese DMFs have an open or applicant part and a closed or restricted portion. In both these regions, the open part, which is accessible to the applicant, is submitted as a component node of the MAA or NDA, respectively. For the US, the regulatory authorities are required to receive only the letter of authorization to access the DMF in the application. In the EU, DMFs apply only to small-molecule drug substances and are known as active substance master files. Certificates of suitability of European Pharmacopoeia monographs may minimize Module 3 active substance or excipient information in European applications.

Each region requires adherence to its respective pharmacopoeia for excipients (US Pharmacopeia, European
Pharmacopoeia, and Japanese Pharmacopoeia). However, the regional regulatory authorities support the development of global quality standards and the submission of harmonized compendial standards and methods, especially for excipients.

A significant difference between the EU and both the US and Japan is use of qualified person documentation and batch release. Additional differences include specifications (EU release specifications, additional EU tests), the level of manufacturing process detail, the detail level for excipients, and the US requirement for submitting a postapproval stability protocol and commitment.

While many areas have been challenging to harmonize, recent efforts have been successful in harmonizing approaches toward:
- Genotoxic impurities – ICH M7(R1)²
- Drug substance heavy metals specifications – ICH Q3D(R2)³
- Drug product dissolution specifications – ICH Q4B Annex 7(R2)⁴
- Starting materials' definition for drug substance synthesis – ICH Q11⁵

In other, less harmonized aspects of development and commercialization, early discussion and negotiation with the regulatory authorities is important not only for approval, but also to maximize efficiencies and cost.

CMC regulatory strategy case studies
Operative and successful CMC regulatory strategies are typically situation-specific and incorporate far too many variables for an effective discussion. However, evaluating any new situation against previous regulatory authority experience, current guidance, and scientific understanding can provide a basis for a sound approach to solve the challenges of product development. The authors have provided case studies for a preapproval and postapproval CMC change in order to provide an understanding of the considerations used to develop effective CMC regulatory strategies.

Preapproval CMC changes
CMC changes are an expected part of the product development path from laboratory to market. The amount of product understanding evolves as clinical development progresses from initial first-in-human studies to marketing application submission. Concomitant with this evolution of understanding is the increasing expectation for escalated control of drug substance and drug product manufacturing and testing and communicating this information to the regulatory authorities.

Preapproval case study. During development, the dosage form used to administer the intended human dose to a clinical subject or patient will evolve. It is not uncommon for first-in-human dosage forms to consist of rudimentary solutions or suspensions, or capsule shells filled with a quantity of drug substance. These preparations tend to be more akin to pharmacy compounding than pharmaceutical manufacturing. Individual dosage units are considered more like “preparations” than “batches” but still present a basis of control. The transition from these rudimentary administrations to more-sophisticated dosage forms necessitates the need to demonstrate there is no impact on quality, safety or efficacy.

It is common practice to refer to the applicable postapproval guidances to glean information about evaluating the extent of a formulation change. While this can be a useful approach, it assumes there is a fixed (approved) starting point as with a commercial product registration. Postapproval guidances are established from this perspective, but many hallmark resources have not been updated to reflect current trends, experience or knowledge. The postapproval landscape is far more rigid because an applicant’s engagement with a regulatory agency dramatically decreases following development.

Company A has produced a solid oral tablet of a defined formulation and is using the product in a clinical investigation. The product’s formulation is subsequently adjusted to decrease the quantity of a minor (<1.0% of total composition) glidant component to less than 0.5% of the total composition. This change includes an increase in the filler component to offset the glidant de-
crease. This composition change would be considered in the US as a SUPAC-IR Level 3 change in composition in a postapproval framework for the glidant (only Talc is specified in SUPAC-IR). The bioequivalence requirement to support this change is to conduct a full in vivo bioequivalence study. This could make sense in a postapproval scenario; however, the scientific approach is to evaluate the pre- and postchange products by a performance-based assay such as in vitro dissolution and gain agreement from the regulatory authority that clinical in vivo bioequivalence studies would not be necessary.

The recommended approach is to evaluate product dissolution across a range of biorelevant pH media. Such items as the excipient’s nature and the assumption it does not significantly impact drug substance absorption must be considered, as well as the drug substance’s solubility and permeability. These latter aspects (solubility and permeability) are used to establish the biopharmaceutics classification system (BCS) class that can be used as a guide to determine the breadth of performance testing. For this case study, the drug substance is high solubility, low permeability, which is consistent with BCS Class 3.

The dissolution of 12 units of pre- and postchange products demonstrate equivalent very rapidly dissolving profiles (85% or more of labeled amount of drug substance dissolved in 15 minutes) using USP Apparatus 1 in 500 mL of (1) 0.1 N HCl; (2) a pH 4.5 USP buffer; and (3) a pH 6.8 USP buffer. Based on the similarity in product performance, these data and the details of the glidant identity should be sufficient to demonstrate there is no impact to the product’s performance by implementing the specific formulation change and gain alignment with a regulatory authority that the formulation change does not necessitate a full in vivo bioequivalence study.

**Postapproval CMC changes**

Familiarity with and the ability to communicate and implement postapproval CMC changes are critical regulatory responsibility components. Although all three regions require notification to the regulatory authorities and, potentially, prior approval, depending on the change’s potential or likelihood to impact quality, safety or efficacy, the framework differs among the US, EU, and Japan.

The regulatory submission data requirements and reporting mechanism must be assessed for each region. The change’s absolute nature could be considered a supplement to the approved application in one region and a line extension in another. These differences can result in very different approval times and thus, will greatly affect the time to market. The CMC regulatory strategy is focused more on long-term submission maintenance to enable continued manufacturing of the approved product.

**Postapproval case study.** A high-impact CMC product lifecycle change can include a drug product reformulation and such associated changes as a manufacturer change. Company A holds global licenses for a well-established brand leader product that also is used in the pediatric population. The product is an oral suspension dosage form, and some of the excipients, such as colorants and flavoring agents, no longer are considered appropriate for use in children. With new guidance documents in some territories on developing formulations for use in pediatrics, there is increasing regulatory scrutiny on Company A’s product. In addition, some generic competitors have launched comparable products with improved formulations that some payers deem to be quality and safety improvements.

Company A decides it is prudent to reformulate to mitigate future regulatory scrutiny on its increasingly dated formulation and to preserve its product’s market share. A change control detailing the quality changes is issued, and Company A’s regulatory team joins other company stakeholders, including supply chain colleagues, in regular weekly meetings.

A strategy is devised: The regulatory team begins assessing the proposed changes’ regulatory impact in each market in which the product is licensed. Affiliates in countries with emerging markets provide up-to-date information on their regulatory requirements and timelines for approval. This includes a major Prior Approval Supplement in the US and a major Type II variation in EU.
The regulatory and documentation requirements for the variation submissions are tabulated, along with timelines. Worst-case requirements such as stability data, process validation data, bioequivalence requirements are noted, as well as longer timeframes for approval. Countries where approval is dependent on prior approval in other countries are also noted. This information is shared with other key stakeholders, including supply chain and quality assurance colleagues, who will ensure sufficient product supply is available while the variations are submitted and approved and will assist in generating the required stability data.

The ultimate goal is to have all variations approved at or around the same time to avoid the complexity of managing different M3 documents, formulations, and stock in multiple countries at the same time. This can be challenging and is not always possible, particularly as some countries have a much longer lead time for variation approval. Based on the information gathered, a strategy is devised, prioritizing some countries due to their commercial importance or the fact that approval in other countries is dependent on approval in them. Variation package preparation and submission for other countries may also be prioritized due to their longer variation approval time.

The regulatory team prepares the variation package documentation and submits according to the schedule agreed with key stakeholders. Gradually, the team responds to questions raised by regulators, and approval notifications start arriving. Through regular meetings with key stakeholders, supply continuity is managed, batches of the previous formulation are used up and the new formulation is successfully introduced to global markets.

**Emerging markets**

Commercialization in emerging markets, either directly or through business partners or collaborators, has become an increasingly important corporate strategy component. Therefore, it is imperative the regulatory CMC professional understands these markets’ regulatory requirements and can share this knowledge with the technical and commercial teams. Even with an understanding of a specific region’s regulatory requirements, unless the organization has a local regulatory presence, using local regulatory consultants is highly advisable due to the lack of transparency, language barriers, limited access to information and the myriad of regulatory complexities involved in obtaining marketing approval in these countries.

From a practical perspective, emerging markets are broken down further into markets requiring independent data submission to support approval and those requiring a certificate of pharmaceutical product (CPP) or medicinal product. In the majority of countries requiring a CPP, the regulatory authorities perform only a limited review. For the latter regions, approval in another country is required to support the CPP. In addition, for those countries requiring submission data, consideration should be given to possibly leveraging the US NDA or BLA or the EU’s MAA. Most often, the MAA is used as the basis for developing the RoW submission.

From a development standpoint, it is critical to communicate to development teams and management the need for stability data to support Zone III, Zone IVa and Zone IVb climatic zones for emerging markets. Due to divergence in defining long-term storage conditions for these hot and humid regions, the ICH steering committee has withdrawn ICH Q1F, leaving the definition to the respective regions and WHO. WHO stability testing conditions are provided in WHO guidance. Additional considerations to incorporate into a RoW strategy are:

- Legal infrastructure requirements
- Translation requirements
- Corporate and manufacturing license requirements
- Good manufacturing practice, and qualified person certificates, certificates of suitability
- Regulatory process and review timeframes, including inspection
- Country-specific requirements

One of the most challenging regulatory aspects of international drug registration and approval is managing postapproval changes, since submission requirements...
and approval timeframes can vary significantly (e.g., up to 6 years for significant changes).

The current growth of RoW expansion is expected to continue; thus, it is paramount for CMC regulatory professionals to remain abreast of these regions' current trends and requirements.

**Conclusion**

The continued globalization and complexity of the pharmaceutical industry, especially the increased role of emerging markets, presents a unique CMC regulatory opportunity. Success in this new model requires enhanced strategic planning and implementation skills, teamwork, and adaptability, in addition to knowledge of regulatory requirements.

Significant harmonization has occurred for the US, Japan, and EU, yet it still is important for the CMC regulatory professional to understand the similarities and differences, especially in the postapproval change area. Supporting successful development, registration and postapproval changes in all markets significantly expands the scope of regulatory CMC and increases the need to think strategically and globally.

**Acronyms and abbreviations**

ASMF, active substance master file; BCS, biopharmaceutics classification system; BLA, biologics license application; CMC, chemistry, manufacturing, and controls; CPP, certificate of pharmaceutical product; DMF, drug master files; JNDA, Japanese new drug application; MAA, marketing authorization application; RoW, rest of world; NCE, new chemical entity.

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