Regulatory Requirements

An Assessment of Global Chemistry, Manufacturing and Controls (CMC) Regulatory Requirements in Low and Middle Income Countries

The new Director General of the World Health Organization has stated that one of his top priorities is “Health for all” saying that “ensuring universal health coverage without impoverishment is the foundation for achieving the health objectives of the Sustainable Development Goals – because when people are healthy, their families, communities, and countries benefit.” He emphasized that “[the WHO’s] top priority must be to support national health authorities’ efforts to strengthen all the building blocks of health systems and to enact policies aimed at ensuring health care is equitable and affordable for all.”

(http://www.who.int/dg/en/)

The issue – It is challenging to locate and interpret the regulatory requirements of many low and middle income (LMIC) countries

Access to quality health care means access to high quality, affordable health care products. This is consistent with Sustainable Development Goal #3.8 of the United Nations (http://www.who.int/sdg/targets/en/), which emphasizes the promotion of health through expanded access to quality assured medicines and other health care products. The manufacturing controls and quality assurance systems, including international good manufacturing practices, are the foundation for assuring that the health care products used by patients and practitioners around the world are quality products which they can depend to improve and often save lives.

Knowing the relevant manufacturing control requirements and the systems by which they are enforced in various countries is fundamental to the production of quality health care products. However, easy access to such up-to-date information for low-income countries has been challenging. Lack of easy access to regulations and their consistent interpretation often increased the time and costs of developing and producing medicines for these markets.

A significant portion of the global burden of disease is borne by LMIC with HIV/AIDS, malaria, and tuberculosis (TB) among the deadliest diseases. In 2013, the WHO reported 35 million people were infected with HIV/AIDS, 97 countries reported ongoing malaria transmission, and 8.6 million new cases of TB occurred.

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Unfortunately it is in the LMICs where navigating the local regulatory requirements governing registration of medicines can be the most challenging. Frequently the chemistry, manufacturing, and controls (CMC) requirements are especially difficult to locate and interpret for many LMICs. In addition, the requirements can often vary significantly between LMICs making it difficult for organizations trying to develop the same drug for different countries. Enforcement is equally challenging as LMICs have varying levels of regulatory maturity and consistency.

Many manufacturers marketing medicines that treat these deadly diseases use programmes such as the WHO’s Prequalification Programme (PQ) or the US Food and Drug Administration’s PEPFAR Tentative Approval pathway to help facilitate national drug registration. Manufacturers still need to obtain approval from each individual LMICs’ National Regulatory Authority (NRA) through a) individual country product registration application; b) a facilitated pathway like the WHO Collaborative Registration Procedure; or c) often times an application through both processes to minimize risk and accelerate approvals.

Each LMIC registration helps assure that products entering these markets are safe, efficacious and meet the requisite manufacturing quality standards. Manufacturers must comply not only with the requirements governing the regulatory pathways that allow a medicine to reach the market in LMIC countries, but must also consider often complex import/export requirements such as import licenses, marketing authorization holder restrictions and quality laboratory control testing at import. Import/export requirements are often more significant for medicines developed for LMICs because they are typically manufactured in low cost manufacturing countries such as China and India, to ensure they can be made economically. Finally, for many of these markets, products are purchased by national or international procurement agencies, which not infrequently have their own requirements that affect the manufacturing and packaging of these products.

The Implication – The lack of visibility of regulatory requirements in LMIC can result in higher costs and patients’ delayed access to drugs.

Manufacturers encounter CMC issues at a high frequency both in developed and emerging markets. Even though manufacturers generally have extensive experience and good visibility into the regulation of more established and well-resourced Regulatory Authorities such as the US FDA and European Medicines Agency (EMA) or WHO PQ, literature is replete with assessments of CMC deficiencies within registration dossiers submitted through these pathways. The extent to which companies encounter CMC issues in these more established pathways is illustrated by studies into Active Pharmaceutical Ingredient Master Files (APIMF) and registration dossiers submitted by generic manufacturers to the WHO PQ programme. In one study it was found that over a six-year period, half of APIMF had CMC deficiencies, with the most critical related to the specific manufacturing process and the key materials used (API starting material), which impact the API impurities content. Similarly, a study of generic product dossiers submitted to the WHO PQ programme over a three-year period identified deficiencies in 147 of 162 dossiers assessed. The most common
issues included incomplete / inaccurate API and finished pharmaceutical products (FPP) specifications, deficiencies in FPP manufacturing process and controls, unacceptable comparator product, insufficient stability data (months and batches), and submission without bioequivalence or biowaiver data³.

CMC issues can be even more challenging in LMICs due to the lack of awareness of all the regulatory requirements. Currently there is no single publicly available repository that comprehensively captures the registration and CMC requirements of LMICs. Therefore, the regulatory teams within manufacturers undertake the time-consuming task of locating and interpreting LMIC’s requirements for each country in which they want to introduce their products. Many times, members of these regulatory teams need to ask the NRAs for clarifications, and must continually monitor the relevant publications and websites, if they exist, for regulatory changes that impact their products. In addition, the way NRAs interpret their regulations can also change over time as they gain more experience with the medicines. These efforts can put considerable pressure on smaller organizations and Product Development Partnerships⁴ with limited resources that are focused on global health drugs.

Issues that manufacturers face in navigating and complying with CMC requirements to obtain regulatory approval in LMICs are highlighted in numerous publications. They include the need for certification of documentation from the country of origin, Good Manufacturing Practices (GMP) certificates from specific or multiple countries, and restrictions on the use of specific raw materials⁴, ⁵, ⁶, ⁷, ⁸, ⁹.

Manufacturer’s efforts to comply with these requirements often create delays and increase the cost of pharmaceutical development. Examples of challenges that were encountered in product introduction of global health medicines among Product Development Partnerships include:

- **Stability studies** – During product registration, the marketing authorization holder needs to provide evidence of the stability of the product in local climatic conditions. Stability studies are essential to ensure adequate shelf life during clinical testing and for assigning appropriate expiration timing for the drug product. Different LMICs may have different requirements for demonstrating stability. Some partners faced challenges when their stability studies during development only accounted for climatic zones of the first wave of countries planned for product registration. Subsequently the manufacturer had to repeat stability studies under new conditions once they realized the original data would not be acceptable in some LMICs. The lack of upfront visibility into the required stability study conditions delayed product introduction in some LMICs by at least 6 months and added additional costs.

- **GMP Inspections** – Delays in the scheduling of GMP inspections by LMIC NRAs, often a requirement for product

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⁴ Product Development Partnerships (PDP) are a type of public private partnership that focuses on developing innovative technologies to address high-burden diseases in low- and middle-income countries. PDPs work across the product development life-cycle partnering with private sector, academic institutions, governments, foundations and multi-lateral organizations to develop and deliver new health solutions.
approval, have led to delayed product introduction from months to years in some countries. This delay occurs despite manufacturers having a valid GMP certificate from WHO and/or a well-resourced NRA for the same product produced on the same manufacturing line as intended for the new market. The issue is compounded by a lack of visibility into the timeline for GMP inspection by LMICs and also unclear country-specific requirements when using a facilitated pathways such as WHO CRP.

- **Labeling** - Varying requirements by country including language and content of the label need to be managed both for initial product approval and for the lifetime of the product as variations to the label are enacted.

- **Packaging** – Initial introduction of a global health product can be delayed and involve additional costs as manufacturers navigated different packs sizes for different countries – some countries allowed full treatment packs while others would only accept monthly packs to facilitate reimbursement. In addition, procurers often have specifications for pack size in order for a product to be eligible for purchase.

- **In-country QC testing** – Provision of samples, reference standards, working standards, columns and other testing materials at registration often delayed product introduction and added costs. Particularly, the requirement for a large number of samples with sufficient product shelf life for testing at registration can be costly if not planned ahead of time.

- **Prior NRA Marketing Authorization** – The requirement for a Certificate of Pharmaceutical Product (CPP) for many LMICs, which generally has to be notarized or apostilled can add significant time and complexity to product introduction and maintenance of marketing authorization throughout the lifetime of the product.

- **Reference Product Selection** – Some countries have specific requirements regarding the use of local comparators for bioequivalence studies, where the study should be conducted or which international comparator would be accepted. Manufacturers have experienced delays and added costs because they did not have visibility into some of these requirements early during product development.

In many of the cases discussed above, an easily accessible, integrated and clear view of requirements across all target countries for product introduction would have facilitated planning and mitigated these challenges. Specifically, manufacturers with access to the information can better sequence CMC activities such as stability studies, bioequivalence studies, GMP inspection, manufacturing of samples for registration, design of labels and packaging, and obtain/authenticate CPP to minimize delays and costly reworks. A solution that provides visibility and clarity into LMIC requirements can therefore potentially accelerate product introduction, reduce costs and saves lives.
Our solution – A publicly available CMC regulatory database that covers 75 LMICS

To address varying regulatory requirements and promote the timely delivery of economical, high-quality, approved medicines for use in LMICs, a global health partnership has created a database of the CMC regulatory requirements for small molecules for 75 LMICs that have a high public health burden. The selection criteria for countries included a) large MICs with a drug substance or drug product manufacturing base, b) select participants of the WHO Collaborative Registration Procedure, c) priority global health countries using Gavi eligible countries as a proxy, or d) additional priority global health countries as determined in a survey completed by key Product Development Partnerships.

The output is an increasingly reliable and comprehensive source of up-to-date information for the CMC and registration regulatory requirements, which are critical for the efficient development of new medicines for underserved markets.

The data gathered for the repository were structured based on the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use's Module 3 of the Common Technical Document. The contents of the database include procedural and administrative requirements, submission pathways and approvals for both clinical and commercial manufacturing of API and FPP in the context of local manufacturing use, and export and import requirements by country as shown in Figure 1.

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**Figure 1: The database is structured based on these three domains**

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<tr>
<th>Prerequisites &amp; administrative requirements</th>
<th>Example requirements</th>
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<tbody>
<tr>
<td></td>
<td>• No objection certificate issued by Central License Authority (India)</td>
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<td></td>
<td>• Form 29 as issued by State Licensing Authority (India)</td>
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<td>• Import &amp; export requirements</td>
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<th>CMC requirements for clinical &amp; commercial manufacturing</th>
<th>Example requirements</th>
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<tr>
<td></td>
<td>• Batch size/quantity for clinical supplies, registration, and validation</td>
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<td></td>
<td>• Stability study requirements / environmental conditions (e.g., ACC, CRT, Zone IV etc.)</td>
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<td></td>
<td>• API and excipient requirement</td>
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<td></td>
<td>• Manufacturing facility requirements for clinical/registration batches</td>
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<td></td>
<td>• Process validation requirements</td>
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<td>• Facility cGMP approval and inspection requirements</td>
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<th>CMC requirements for product registration (Dossier submission)</th>
<th>Example requirements</th>
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<tr>
<td></td>
<td>• Specific regional information</td>
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<td></td>
<td>• Executed batch records</td>
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<td>• Documents (chromatograms, CoAs, etc.)</td>
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<td></td>
<td>• Safety requirements</td>
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<td>• Comparability protocol</td>
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<td>• Validation package</td>
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*b The database is in pilot phase and broader access will be available once the tool is transitioned to the commercial partner, Clarivate Analytics, and web-enabled.
The data was compiled through a combination of desk research of published NRA requirements and interviews with regulatory practitioners from the LMICs, pharmaceutical companies and multilateral organizations. Efforts are currently underway to work with individual countries to validate the data for their country in the database. These interviews enabled the documentation of real-life experiences interpreting and navigating the various LMIC regulations, which can differ from the words used in the published regulation. The functionality of the database includes a schematic of the regulatory pathway by country. The search functionality includes a view of requirements by country and comparisons across countries and requirements.

Figure 2: The database covers 75 LMICs across Africa, Asia, the Commonwealth of Independent States, Latin America and the Caribbean

Conclusion – Potential impact of increased visibility into LMIC CMC regulatory requirements for manufacturers, NRAs, and the global health community

The database provides visibility into the consolidated CMC requirements across target LMIC and provides manufacturers with the information to better plan and sequence CMC activities to minimize the challenges and impact of varied LMIC requirements. Through this effort, for the first time, the drug development community will be able to get information to create a product development strategy by accessing 75 LMIC CMC regulatory requirements for small molecules in one database. The information should enable developers and manufacturers to optimize the delivery of medicines to LMICs through advanced planning for unique local requirements and through the sequencing of regulatory activities to expedite approvals.
The database also provides information that LMIC NRAs can evaluate and compare their requirements with those of similarly situated NRAs so as to potentially leverage these alternative approaches that could maintain the quality and safety of medicines while not jeopardizing timely patient access to essential or innovative medicines. The visibility into the type and prevalence of divergent country-specific requirements provides organizations that develop global health medicines with an opportunity to build on the database to identify potential solutions to facilitate the introduction of new drugs. This database could also help with efforts aimed at harmonizing and streamlining local, regional or global regulatory requirements to accelerate the development and delivery of life-saving quality-assured global health medicines to vulnerable populations. A new web-based CMC Database is being designed and developed by a commercial partner, Clarivate Analytics. The database will provide access to LMICs, WHO and select procurement agencies at no-cost by the end of 2018 and will be commercially available in 2019.

References:

7 Wileman, Harriet, and Arun Mishra. "Drug lag and key regulatory barriers in the emerging markets." Perspectives in clinical research 1.2 (2010): 51