CURRENT REGULATIONS FOR MARKETING AUTHORIZATION OF HUMAN GENERIC PRODUCTS GLOBALLY AS PER WHO


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ABSTRACT

Generic medicines are those where patent protection has expired, and which may be produced by manufacturers other than the innovator company. Use of generic medicines has been increasing in recent years, primarily as a cost saving measure in healthcare provision. Generic medicines are typically 20 to 90% cheaper than originator equivalents. As the Pharmaceutical industry is expanding by leaps and bound no single country is capable of manufacturing all the drugs in required quantities at competing prices. Hence the Marketing Authorizations has become an essential part of Global Healthcare. Till sometime back Marketing Authorization procedures were country specific. However currently it has been harmonized. In spite of this there are regional variations that make the authorizations very complex to comply with. The present study describes a brief review of Marketing Authorizations in various countries and regions around the world (WHO).

Key words: Generic, Medicine, Drug, Pharmaceutical, Biosimilar, Prescribing, Healthcare, Economics, WHO.

INTRODUCTION

The pharmaceutical industry is one of the highly regulated industries, with many rules and regulations enforced by the government to protect the health and well-being of the public. As the health care system depends on drug regulatory affairs for availability of safe and effective medicines to patients it is the responsibility of regulatory affairs to ensure efficacy, safety and quality of medicines in the entire product lifecycle, and is expected to carry out its tasks without bias.

The role of the regulatory authorities not only includes in the process of regulating and monitoring the drugs but also the process of manufacturing, distribution, and promotion of it. One of the primary challenges for regulatory authority is to ensure that the pharmaceutical products are developed as per the regulatory requirement of that country. This process involves the assessment of critical parameters during product development.

Virtually every process in the pharmaceutical industry is regulated in some way. The role of regulatory affairs is twofold. One is to develop and execute a regulatory strategy to ensure that the collective efforts of the drug development team results in a product that is approvable by global regulators but is also differentiated from the competition in some way. The second is to ensure that the company’s activities, from non-clinical research through to advertising and promotion, are conducted in accordance with the regulations and guidelines established by regulatory authorities. This broad remit covers activities beginning in the non-clinical laboratories, and continuing throughout the entire clinical development phase, marketing and lifecycle of a product.

Generic Drugs

The pharmaceutical industry has shown a remarkable growth which in turn has raised the economy of India after the introduction of the generics. The usage, manufacturing and marketing of generics has been enormously increased. A combination of factors has been responsible for the trend of increased generic usage globally. The expiration of patents, emerging markets, an aging population, the increase of chronic diseases, and the efforts of governments and health care service providers have all contributed to the increased use and acceptance of generic drugs.

Generic drug is “a drug product which is comparable to a reference (brand) listed drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use”.

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An important factor for increased generic drug usage is that the decreased cost of the generic is attractive to the consumer. Generic drug companies bring the generic version the innovator/brand drug product to the market at a substantially lower price, which benefits the public and makes healthcare more affordable.

The process of bringing a generic version of an established brand name drug to market is not as simple as just copying the brand-name product. The generic company, too, must conduct certain studies, and pass strict standards set forth by the respective regulatory agencies.

**World Health Organization [1]**

World Health Organization (WHO) is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends. The WHO has launched Prequalification of Medicines Programme (PQP) to ensure that medicines supplied by procurement agencies meet acceptable standards of quality, safety and efficacy.

The World Health Organization (WHO) provides United Nations agencies with advice on the acceptability, in principle, of pharmaceutical products for procurement by such agencies. This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended norms and standards of acceptable quality. WHO undertakes a comprehensive evaluation of the quality of pharmaceutical products, based on information submitted by the manufacturers of such products or other applicants, and on an inspection of the corresponding manufacturing facilities and clinical sites. This is done through a standardized procedure which is based on WHO-recommended quality standards. The quality of pharmaceutical products is obviously crucial for the safety and efficacy of such products. The pharmaceutical products found to meet the WHO-recommended quality standards are included in the list of medicines, as manufactured at the specified manufacturing sites, which are considered to be acceptable, in principle, for procurement by United Nations agencies. The list of prequalified pharmaceutical products is principally intended for use by United Nations agencies - including the Joint United Nations Programme on HIV/AIDS, United Nations Children’s Fund (UNICEF) and United Nations Population Fund (UNFPA) - to guide their procurement decisions. The growing list of pharmaceutical products that have been found to meet WHO-recommended standards may, however, also be of interest to other organizations and countries wishing to engage in the bulk procurement of pharmaceutical products.

Inclusion in the list does not imply any approval by WHO of the pharmaceutical products and manufacturing sites in question (which is the sole prerogative of national authorities). Moreover, inclusion in the list does not constitute an endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety and/or efficacy in the treatment of specific diseases.

In order to meet the WHO-recommended norms and standard of acceptable quality a comprehensive set of guidelines are provided in the area of quality assurance of pharmaceutical products. These guidelines are established and maintained through a consultative procedure and adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The guidance texts include recommendations in the area of good manufacturing practices (GMP) and inspection, product assessment and registration, distribution, quality control, laboratory services, and international trade in pharmaceuticals.

**Common Technical Document**

The common technical document (CTD) is the agreement to assemble all the quality, safety and efficacy information in a common format. CTD has revolutionized the regulatory review processes, led to harmonize electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory agencies.

Through the ICH process, considerable harmonization has been achieved among the three regions in the technical requirements for the registration of pharmaceuticals for human use. However, until now, there has been no harmonization of the organization of the registration documents. Each region has its own requirements for the organization of the technical reports in the submission and for the preparation of the summaries and tables. In Japan, the applicants must prepare the GAIYO, which organizes and presents a summary of the technical information. In Europe, Expert Reports and tabulated summaries are required, and written summaries are recommended.

The U.S. FDA has guidance regarding the format and content of the New Drug Application. To avoid the need to generate and compile different registration dossiers, this guideline describes a format for the Common Technical Document that will be acceptable in all three regions. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, U.S.) and the Ministry of Health, Labour and Welfare (Japan). The CTD is maintained by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

A common format for the technical documentation will significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document.
of common elements. In addition, exchange of regulatory information between Regulatory Authorities will be simplified.

**Organization**

The Common Technical Document is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guideline should ensure that these four modules are provided in a format acceptable to the regulatory authorities.

**Module 1: Administrative Information and Prescribing Information**

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

**Module 2: Common Technical Document Summaries**

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the Introduction should not exceed one page.

**Module 3: Quality**

Information on Quality should be presented in the structured format described in Guideline M4Q.

**Module 4: Nonclinical Study Reports**

The nonclinical study reports should be presented in the order described in Guideline M4S.

**Module 5: Clinical Study Reports**

The human study reports and related information should be presented in the order described in Guideline M4E.

**Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use**

**Module 1: Administrative Information and Prescribing Information**

1.1 Table of Contents of the Submission Including Module 1
1.2 Documents Specific to Each Region (for example, application forms, prescribing information)

**Module 2: Common Technical Document Summaries**

2.1 Common Technical Document Table of Contents (Modules 2-5)
2.2 CTD Introduction
2.3 Quality Overall Summary
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summaries
2.6.1 Pharmacology, Pharmacokinetics Toxicology
2.7 Clinical Summary
2.7.1 Biopharmaceutical Studies and Associated Analytical Methods
2.7.2 Clinical Pharmacology Studies
2.7.3 Clinical Efficacy Clinical Safety Literature References

2.7.4 Synopses of Individual Studies

**Module 3: Quality**

3.1 Table of Contents of Module 3
3.2 Body of Data
3.3 Literature

**Module 4: Nonclinical Study Reports**

4.1 Table of Contents of Module 4
4.2 Study Reports
4.3 Literature References

**Module 5: Clinical Study Reports**

5.1 Table of Contents of Module 5
5.2 Tabular Listing of All Clinical Studies
5.3 Clinical Study Reports
5.4 Literature References

In ICH common technical document is referred as M4 document and the sequence of M4 Common Technical Document for the Registration of Pharmaceuticals for Human Use is:

M4 - Organization of the Common Technical Document

M4 Quality (M4Q (R1)) - Quality overall summary and CTD Quality i.e. Module 2 and Module 3

M4 Safety (M4S (R2)) - Nonclinical Summaries & Organization of Module 4

M4 Efficacy (M4E (R1)) - Clinical overview, clinical summary, sample tables for clinical summary and Module 5

**Submission Format**

Throughout the Common Technical Document, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (E.U. and Japan) and 8.5 x 11” paper (U.S.). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text. Every page should be numbered, according to the granularity document. Acronyms and abbreviations should be defined the first time they are used in each module. References should be cited in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE).

**Benefits of CTD**

A common format for the technical documentation:

- Significantly reduces the time and resources needed to compile applications for registration of human pharmaceuticals.
- Eases the preparation of electronic submissions.
- Facilitates regulatory reviews and communication with
the applicant by a standard document of common elements.

- Simplifies exchange of regulatory information between Regulatory Authorities.
- More “reviewable” applications.
- Complete, well-organized submissions.
- More predictable format.
- Easier analysis across applications.

Presubmission Guidelines for Prequalification of Multisource Pharmaceutical Products (Generics) [2]

Presubmission is one of the most important and major part of prequalification of Multisource pharmaceutical products (Generics). So, utmost care should be taken by the manufacturer/applicant during this step. Presubmission guidelines are nothing but guidelines that are to be followed before submission of dossier and these guidelines assist in the preparation of dossier. While preparation of dossier all the guidelines given by the respective regulatory authority should be strictly followed. This section outlines filing considerations for Product Dossier (PDs) in the CTD format.

As discussed earlier the Common Technical Document (CTD) format is followed for submission of dossiers and is organized into five modules, depending on the regulatory authority we are filing the sections covered under these modules will be varied.

The modules for dossier submission for World Health Organization are as follows:

Module 1: Administrative and Prescribing Information
Module 2: Common Technical Document Summaries
Module 3: Quality
Module 4: Non Clinical Study Reports (Not Applicable For Generic Drugs)
Module 5: Clinical Study Reports

Further all the above modules and the sections covered under these will be discussed in detail.

Generic Drug Development

To make a generic product, formulator must know in detail the exact regulatory requirements of each concerned country where the drug is intended to be filed. Generic drug product development uses a different approach and strategy compared to that used to develop an innovator drug product containing a new chemical entity. Generic drug product manufacturers must formulate a drug product that will have the same therapeutic efficacy, safety, and performance characteristics as of its branded counterpart. The key factor is that the generic drug product must meet all the necessary criteria to be therapeutically equivalent to the innovator drug product. Therapeutically equivalent means that the drug product shows pharmaceutical equivalence as well as bioequivalence. Table 1 shows regulatory requirement for generic drug product development in some selected countries.

The decision to proceed with the development of a generic drug product should therefore be based on well-researched data that primarily indicate market value together with a sound knowledge of patent expiry dates, predicted market share, and growth rate for the product, amongst others. The predicted profitability of the new generic product will require strategic planning for the subsequent launch timing, which must take into account the expected generic price and knowledge of anticipated competitors, such as who they are and when they are expected. According to Hamrell R.Michael “The Drug Price Competition and Patent Term Restoration Act” in 1984 changed the regulatory climate for generic drugs. This law allowed for the approval of generic “me-too” copies of many approved drug after the patent had expired [3]. As per Kathy Redmond the regulatory agencies have a responsibility to ensure that high-quality, safe, and effective medicines are made available to patients in a timely manner. Despite the fact that all regulators worldwide share the same aims, they do not adopt a consistent approach to drug approval requirements, and as a result, medicines are often approved quicker in some countries than others [4]. Therefore, there is need for a harmonized drug regulation globally.

Filing a Generic Drug Application

When a dossier is ready as per the regulatory requirement of the respective country, it is submitted to the regulatory agency of that country. Various regulatory agencies worldwide are tabulated in the Table 2.

- Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceutical and Medical Devices Agency (PMDA), Therapeutic Goods Administration (TGA), Medicines Control Council (MCC), Tanzania Food and Drugs Authority (TFDA), Agência Nacional De Vigilância Sanitária (National Health Surveillance Agency) (ANVISA), Commonwealth Independent States (CIS), Department of Health (DOH), The Gulf Co-Operation Council (GCC).

United States of America

USA is the major market for the pharmaceutical industry. The USA has evolved from no regulations in the 18th century to one of the highly regulated and admired regulatory authority in the world. The Food and Drug Administration (FDA) within the U.S. Department of Health and Human Services regulates the drug approval system in United States with help of six product centers including Center for Drug Evaluation and Research (CDER) [5]. Drug registration in USA is majorly categorized by two types of applications: New Drug Application (NDA) and Abbreviated New Drug Application (ANDA). ANDA is filled for generic drug products; those require marketing authorization and are of exact or close copies of already approved drugs [6]. The ANDA approval process is depicted in Figure 1 [7]. Indeed, the way this country regulates drugs typically has been born out of adversity, out of events that have killed and injured thousands. The
The evolution of the current drug regulatory system in USA is recognized globally as the gold standard for drug safety and efficacy. During 1990, FDA began work to develop standards for the exchange of electronic information critical to the agency’s mission. This recognized both the inefficiency of paper for transferring mass quantities of data and the need to develop a harmonized format that would be usable by FDA as well as its counterparts in the European Union and Japan. Consequently, firms are now able to submit paperless product applications and related material to world regulatory agencies more efficiently, while each review authority maintains its own high standards for product evaluation. Because all drugs have some risk, FDA task force advised the agency to make more systematic use of the principles of risk management in the way FDA oversees drug development and marketing.

### Table 1. Regulatory requirement for generic drug product development in some selected countries

<table>
<thead>
<tr>
<th>Requirement</th>
<th>USA</th>
<th>EU</th>
<th>Brazil (LATAM)</th>
<th>Tanzania (AFRICA)</th>
<th>Russia (CIS)</th>
<th>Hong Kong (AISA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of exhibit batches required for submission</td>
<td>1 exhibit, Mfg Batch size: 100,000 units, or 1/10th of commercial batch size whichever is larger.</td>
<td>2 exhibit, Mfg Batch size: 100,000 units, or 1/10th of commercial batch size whichever is larger.</td>
<td>3 exhibit, Mfg Batch size: 100,000 units, or 1/10th of commercial batch size whichever is larger.</td>
<td>3 exhibit batches, Mfg Batch size: 100,000 units, or 1/10th of commercial batch size whichever is larger.</td>
<td>3 representative exhibit batches</td>
<td></td>
</tr>
<tr>
<td>Stability condition</td>
<td>CRT 25 ± 2°C/60 ± 5%RH Accelerated 40 ± 2°C/75 ± 5%RH Intermediate 30 ± 0°C/60 ± 5%RH</td>
<td>CRT 25 ± 2°C/50 ± 5%RH Accelerated 40 ± 2°C/75 ± 5%RH Intermediate 30 ± 2°C/60 ± 5%RH</td>
<td>CRT 30 ± 2°C/75 ± 5%RH Accelerated 40 ± 2°C/75 ± 5%RH Intermediate 30 ± 2°C/60 ± 5%RH</td>
<td>CRT 30 ± 2°C/75 ± 5%RH Accelerated 40 ± 2°C/75 ± 5%RH Intermediate 30 ± 2°C/60 ± 5%RH</td>
<td>CRT 30 ± 2°C/75 ± 5%RH Accelerated 40 ± 2°C/75 ± 5%RH Intermediate 30 ± 2°C/60 ± 5%RH</td>
<td></td>
</tr>
<tr>
<td>Stability commitment while filing</td>
<td>On 3 commercial batches CRT till shelf life</td>
<td>On 3 commercial batches, Accelerated data till 6 months and CRT till shelf life</td>
<td>On 3 commercial batches, Accelerated data till 6 months and CRT till shelf life</td>
<td>Optional</td>
<td>Optional</td>
<td></td>
</tr>
<tr>
<td>Min stability data required during submission</td>
<td>3 months accelerated and CRT data.</td>
<td>6 months accelerated and CRT data.</td>
<td>12 months accelerated and CRT data.</td>
<td>6 months accelerated and CRT data.</td>
<td>6 months accelerated and CRT data.</td>
<td></td>
</tr>
<tr>
<td>Packaging requirements</td>
<td>Child resistant packing.</td>
<td>Blister.</td>
<td>Multimedia (min 3 media’s from pH range 1-7) 12 units data.</td>
<td>Multimedia (min 3 media’s from pH range 1-7) 12 units data.</td>
<td>Multimedia (min 3 media’s from pH range 1-7) 12 units data.</td>
<td></td>
</tr>
<tr>
<td>Dissolution requirements</td>
<td>Fast/Fed condition, against RDJ/UUS innovator at FDA approved center.</td>
<td>Fast condition, against EU innovator (fed only if required).</td>
<td>Fast condition, against Brazilian innovator and at ANVISA approved center.</td>
<td>Fast/Fed condition, against any innovator EU/EU BE data is acceptable.</td>
<td>Fast and Fed condition, against any innovator Clinical trials are also required</td>
<td>US/EU BE data is acceptable.</td>
</tr>
</tbody>
</table>

### Table 2. Various regulatory agencies worldwide

<table>
<thead>
<tr>
<th>Name of Country/Group</th>
<th>Regulatory authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>FDA</td>
</tr>
<tr>
<td>EU</td>
<td>EMA</td>
</tr>
<tr>
<td>Canada</td>
<td>HPFB</td>
</tr>
<tr>
<td>Japan</td>
<td>PMDA</td>
</tr>
<tr>
<td>Australia</td>
<td>TGA</td>
</tr>
<tr>
<td>South Africa</td>
<td>MCC</td>
</tr>
<tr>
<td>AFRICA (Tanzania)</td>
<td>Independent regulatory agencies/TFDA</td>
</tr>
<tr>
<td>LATAM (Brazil)</td>
<td>Independent regulatory agencies/ANVISA</td>
</tr>
<tr>
<td>CIS (Russia)</td>
<td>Independent regulatory agencies/ROSZDRAVNADZOR</td>
</tr>
<tr>
<td>ASIAN (Hong Kong)</td>
<td>Independent regulatory agencies/DOH</td>
</tr>
<tr>
<td>GCC</td>
<td>Independent regulatory agencies/National filling</td>
</tr>
</tbody>
</table>
Table 3. Submissions for receiving Marketing authorization in Europe (Different types of procedures for marketing authorization applications in Europe)

<table>
<thead>
<tr>
<th>Agencies responsible</th>
<th>Procedure type</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>Centralized procedure</td>
<td>It is for single application, single evaluation and authorization allowing direct access to the single market of the member countries.</td>
</tr>
<tr>
<td>Reference member state (RMS)</td>
<td>Decentralized procedure (DCP)</td>
<td>Application is submitted to all member states where intended and choose one of them as reference member state. The assessment report is prepared by RMS including the concerned member states and based on both comments MA is granted.</td>
</tr>
<tr>
<td>Reference member state (RMS)</td>
<td>Mutual recognition procedure (MRP)</td>
<td>It is followed where an applicant having MA in one member state, wishes to obtain the same in other member states. It is based on mutual recognition of concerned member states, granted by the reference member states.</td>
</tr>
<tr>
<td>Member states</td>
<td>National authorization</td>
<td>MA is granted by Member states and hence an application must be submitted to the particular member state.</td>
</tr>
</tbody>
</table>

Figure 1. ANDA approval process

Applicant → ANDA → Acceptable and Complete

Refuse to file - letter issued

Yes → Review by OGD/CDER

Bioequivalence Review Acceptable → Yes → Chemistry / Micro / Labelling Review Acceptable

Bioequivalence Review Acceptable → Bioequivalent Deficiency Letter

Not Approvable Letter

Preapproval Inspection

Approval deferred pending satisfactory results

ANDA Approved
Figure 2. Types of Application filed in Europe

Figure 3. Scheme of the registration process

After submission and payment of necessary fees, registration dossier is directed to -

STAGE III

Finishing of the expertise and submission of the dossier to Roszdravnadzor for issuing of Registration Certificate.
The EU has one of the most highly regarded regulatory systems in the world. The system comprises of European parliament, the council of ministers, and the European Commission. EU consists of 27 member states: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom and three countries which are member of European Free Trade Agreement (EFTA) Iceland, Norway, and Liechtenstein [8]. These EFTA members are those countries which were unable to join rest of the 27 member states as common market. These three EFTA member countries along with 27 EU member states, comprises of the European Economic Area (EEA). The European Medicines Agency is a decentralized agency of the European Union, located in London [9]. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union and applications for European marketing authorizations for both human and veterinary medicines (centralized procedure). Under the centralized procedure, companies submit a single marketing-authorization application to the Agency. Once granted by the European Commission, a centralized (or “Community”) marketing authorization is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway). The European parliament approves the laws together with the council of ministers. The council of ministers is the voice of Member states and is responsible for enactment of directives.

Legal basis for applications in Europe

The eligibility and the requirements are set in the commission regulation (EC) No 726/2004 and defined in articles 8 and 10 of the Directive 2001/83/EC. The Figure 2 [10] represents the types of application filed in Europe.

Types of submission procedure

To market a generic medicinal product in European Economic Area (EEA) which consists of 27 member states and 3 EFTA countries, a marketing authorization has to be issued. European medicines Agency (EMA formerly known as EMEA) regulates the medicinal products marketing authorization through various committees. Different types of submissions for receiving Marketing authorization in Europe are given below in Table 3. In case of Generic drug products, generally the decentralized procedure is followed whereas in case of the new drug products the application for marketing authorization is always submitted through a centralized procedure.

Brazil (LATAM)

Brazil's pharmaceutical market is the 11th largest in the world and second in Latin America after Mexico since the devaluation of 2001 [11]. Brazil's market is clearly a key market to drive the global development of any pharmaceutical company with international ambitions and may have located regional headquarters in the country. The regulatory framework is considerably improved and makes Brazil a preferred gateway to other Latin American markets.

The federal regulatory agency responsible for pharmaceutical product registration in Brazil is ANVISA (National Sanitary Vigilance agency), which was established in 1999 [12]. The 1999 Law (The Generics Law) and the ANVISA regulate the implementation of generic pharmaceuticals policy in Brazil, establishes the technical standards and defines the concepts of bioavailability, bioequivalent drugs, innovators, reference drugs, and similar. According to the Brazilian legislation, all
the pharmaceutical products must be registered with ANVISA before coming to market in Brazil. Product registration in Brazil is a laborious exercise, and is to be requested by the local Brazilian based office of the foreign company or its distributor in Brazil. The registration is valid for 5 years and can be renewed continuously for the same period. Law must complete the registration process within 90 days after the registration is requested, or denied. For registration purposes, ANVISA classifies the products in various categories. The medications for human use are divided into three distinct areas i.e., New Product, Similar Product, Generic Product.

Tanzania (AFRICA)

African medicines regulatory authorities (MRAs) role is to ensure that the pharmaceutical products those are needed, are registered in their country: This process is called “registration,” “marketing approval,” “marketing authorization” or “product licensing”, and involves assessment of product information submitted by the manufacturer (the product ‘dossier’) to make sure that it is safe and effective for use by local patients. Assessment of generic drugs is relatively simple. This is because the regulator only needs to establish two key points. First, generic drug product is bioequivalent to and thus therapeutically interchangeable with the comparator product. Secondly, product meets comparable sustainable quality standards to that of the innovator product. Every country of the African region has its own regulatory framework. Drug product registration was gradually introduced in Tanzania under the Tanzania Food, Drugs and Cosmetics Act 2003, to have a smooth transition, beginning with 1-year provisional registration taken as a notification from 1998. This gave ample time for the Pharmacy Board to prepare guidelines to assist applicants and evaluators to respectively submit and evaluate correctly the required information. Following the preparation of the guidelines, the first application was received in 1997 and the first product was registered in April 1999 [13]. All documents shall be in Kiswahili or English. Applications that do not comply to requirements prescribed in these guidelines will be rejected and returned to the applicant at his own cost. All ingredients used in the formulation of generic medicinal products must comply with specifications prescribed either in the USP (United States pharmacopoeia), BP (British pharmacopoeia), EP (European pharmacopoeia), and International or Japanese pharmacopoeia. In-house specifications shall only be accepted if the limits are tighter than those prescribed in those pharmacopoeias and other specifications may be accepted if they are validated.

Russia (CIS)

According to some estimates, Russia is poised to be among the top five Global pharmaceutical markets in terms of value in the next five years. Today, Russia stands at the threshold of becoming a major force in the global pharmaceutical market. Russia is a member country of “The Commonwealth of Independent States” (CIS) founded in 1991, which is a regional organization whose participating countries are former Soviet Republics, formed after the dissolution of the Union of Soviet Socialist Republics (USSR). The regulatory processes in CIS countries are led and supervised by Regulatory Agencies closely collaborating with or operating within the respective Ministries of Health. Figure 3 depicts the scheme of registration process. Each of the CIS countries has established individual registration guidelines. Registration in RUSSIA is a national procedure. Estimated duration of procedure is up to 24 months. Documentation is done in Russian language in format compliant with Russian requirements. Recommended submission of a bioequivalence study is carried out in certified research organizations within the Russian Federation’s territory. Original and generic products pass the same stages of registration. Original products must pass through all registration procedures while the generic products are exempted from some of them. For example, original product must undergo clinical trials in Russia. For generic products, bio-equivalence studies can be conducted in any other countries and not only in Russia.

Hong Kong (ASIA)

Hong Kong’s market for pharmaceuticals drugs is about $1.5 billion [14]. As a part of developed economy in Asia, it still lags behind other advanced economies of the OECD in medicines regulation [15]. The pharmaceutical regulatory agency in Hong Kong remains conservative in outlook but is facing similar strain of challenge from pharmaceutical sector despite the issues raised are of plain trade and business. The HA’s adoption of purchasing policy favouring use of bulk contract and generic substitution has undercut the market for multinational pharmaceutical companies represented by the Hong Kong Association of the Pharmaceutical Industry (HKAPI). This alongside the difficulty of listing new drugs in the HA Drug Formulary, the delay in new drug registration application submitted to the Hospital Authority (HA) Drug Formulary, the delay in new drug registration applications submitted to the pharmacy and poisons Board (PPB), and Intellectual property rights issues [16], have provoked outcries about deterioration in business environment for the pharmaceutical trade sector that calls for government policy changes. Hong Kong’s pharmaceutical regulatory body and its pharmaceutical business sector evidently lag behind international developments in number of ways. The PPB has not gained membership of Pharmaceutical Inspection Cooperation Scheme (PICS) that facilitates signing of Mutual Recognition Agreement with regulatory bodies in developed countries. This lack of International harmonization of GMP standard makes it difficult for local pharmaceutical manufacturers to go down the path of becoming exporters of medicines.
CONCLUSION

Although there is a continuous process of harmonization taking place all around the world, still we see a huge challenge, which is yet to be overcome by the Pharmaceutical industry in case of generic drug development and filing. This is due to the heterogeneity in the regulatory landscape of the various countries. Therefore, to meet these challenges, a lot of strategic planning is required before the development of any generic drug product.

REFERENCES