A PATHWAY THROUGH REGULATORY INTELLIGENCE TO GLOBAL, COST-EFFECTIVE MODEL FOR GENERIC PHARMACEUTICAL PRODUCTS

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ABSTRACT

This study aimed to address the challenges with the current landscape for managing generic product registration globally. Highly complex regulatory environment, varied approval timelines, specific data requirement including costly and time taking Chemistry, Manufacturing, Control data and Bioequivalence studies data, between countries have been an issue for industry to ensure uninterrupted supply of high quality, safe and effective medicines around of the world. The approval globally. The author expects that this will bring consistency to managing generic product registrations globally, contribute in global convergence and enhance global public health by ensuring timely access to quality medicines for patients. study aimed to understand the opportunities using Regulatory Intelligence and recommendations to build a global dossier in line with Health authorities' expectations, as it could save significant cost and time, and ensure swift and timely

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INTRODUCTION

A generic pharmaceutical product is much needed for millions of patients to have affordable access to medication that could save their lives and improve their quality of life. Not only emerging countries but developed countries like the United States of America (US), European Union (EU) is seeing growing demand of generic products. Even in countries like Japan, where general tendency is to prefer innovator products over generics, the Government of Japan is highly engaged in encouraging their people to use generic products as well as the pharmaceutical industry to approve more generic products in Japan [1].

In the last decade, $1.67 trillion has been saved by the U.S. healthcare system as generics whose costs are much lesser than innovator medicines. In the US, during 2008 to 2016, there was 208% increase in price in innovator/ branded medicines however, at the same time, more than 50% decrease in the price of generic medicines, as represented in Figure 1. Generic medicine in the US is accounted for 89% of prescriptions written by physicians with just 26% of the cost however only 11% of prescriptions are for innovative drugs and yet 74% of the cost [2, 3].

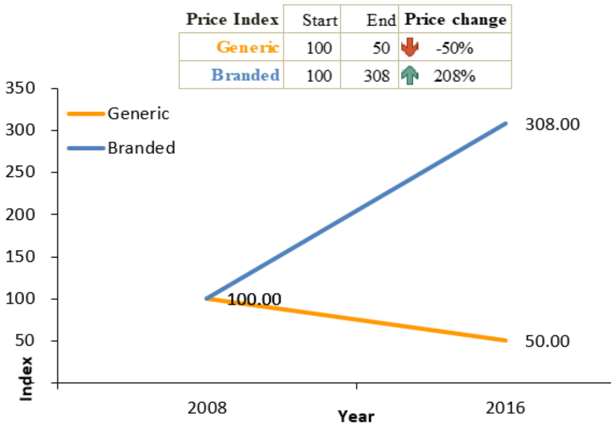

Figure 1:US Price index Generics Vs Branded, year 2008 and year 2016

Not only US, even in EU, in the last 10 years, there is increased demand of generics. In EU, data shows drop in price of medication by more than 50% and an increase of prescription volumes more than 100% [4, 5].

Hatch-Waxman amendments in the US are credited with creating the generic industry and hence called one of the most significant regulations ever passed. This legislation has aided in making generic medications more readily available in the US. This pattern is still present. In the US, the percentage of total prescriptions written for innovator drugs was 39.9% in 2005; this ratio fell to 8% in 2020. As a consequence, as represented in figure 2, the percentage of total prescriptions written for generic medications grew from 50.3% in 2005 to 88.5% in 2020 [2, 6].

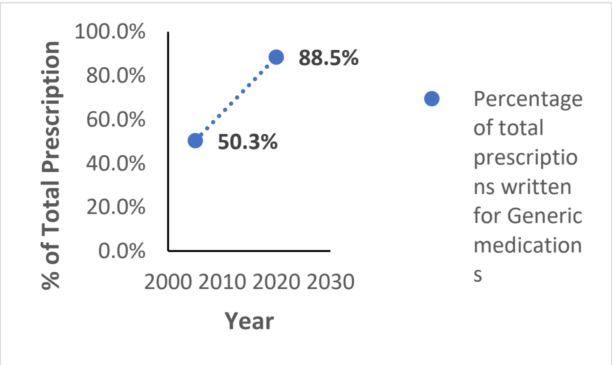

Figure 2: Percentage of total Prescriptions written for Generics in US

Since 2012, most of the generic pharmaceutical industry used to develop their products for US market as there were no fees and very high returns. However, with the application of The Generic Drug User Fee Act (GDUFA) fees for the generic product, growing economy of emerging markets, the significant increase in the need for generic medicines globally, the generic industry has grown tremendously [7]. As a consequence, to that, health regulatory agencies for emerging markets have introduced specific and stringent registration processes and requirements for generic products in their countries. Growing divergence of regulations globally, causing increased complexity across countries [8].

When generic product manufacturers started to apply to a few specific countries like regulated markets of US, EU for their generic product approval, there was no issue [9]. However, with increasing demand of generics in global markets and higher competition, applicant requires to file separate dossiers for each product in hundreds of countries. Companies have to manage multiple variants of the same product or keep multiple processes or test methods running for the same product. Other challenges are increasing risks of stock-outs, mix-ups and non-conformance to market applications and thus need for excess resources to manage.

The Regulatory Affairs department in the pharmaceutical industry is responsible for obtaining drug product approval for marketing in a particular market. Previously, the regulatory affairs job was considered to be a clerical job. However, with growing demand and improvement of the regulatory framework in emerging markets inline regulated markets; regulatory affairs department has become critical, not only for collating data and submission of dossiers but also to get swift approval by supporting the Research and Development (R&D) team right from the start of development of drug products.

For drug product development and dossier preparation, the strategy should be based on regulatory intelligence and experience. It's quite complex to manage multiple applications in a global regulatory environment. The best approach should be to leverage appropriate Regulatory Intelligence (RI) and develop a global dossier for a generic product. A careful assessment is needed considering the cost involved with drug development and requirement to file globally to ensure early approval [10, 11].

MATERIALS AND METHODS

This research work is a mix of Applied, Conceptual and Empirical research types.

Total 145 countries were initially identified to see the feasibility of this research work. After a thorough initial review of the availability of regulatory information for those countries, to avoid duplication where regulations, including like stability data requirements are the same between countries or regions and to cover global coverage, 52 countries and regions were selected for this research study.

Different Regulatory Intelligence (RI) approaches, as outlined below, were used for these 52 countries and regions, including the processing of targeted data and data from a spread of sources, analysis of the information in its pertinent framework, and creation of a meaningful output and regulatory strategy.

- Review, understanding and interpretation was done on established regulatory guidance, draft guidelines, concept papers, queries raised by Health Agencies and trends by Health Agencies,
- Comparative studies were performed to understand the differences and comparison of regulatory requirements of generic drug product development for different markets and regions globally, ways to ensure swift drug approvals and critical factors for global generic product development & global dossier,
- Comparative studies were performed to understand the regulatory submission process of generic drug product development for the global market,
- Comparative studies were performed to understand the differences and Chemistry, Manufacturing and Control (CMC)/ Module 3 requirements for generic products of different markets globally through regulatory intelligence,
- Comparative stuides were performed to understand the different dossier format followed globally and to identify the feasibility of developing the global dossier.

RESULTS AND DISCUSSION

Global generic companies active in many different markets. Most of these markets were found to have different requirements, approval timelines, pre-approval inspections, etc., leading to complexity. The critical differences observed are presented below.

The Difference in Dossier Format:

To assemble and present the dossier for Health Agencies review, different Health Agencies apply country specific or region specific format. For example,

- Most of the regulated countries like EU, US follows The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD) template [12].
- The Association of Southeast Asian Nations (ASEAN) countries like Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Thailand and Vietnam follow ASEAN CTD template [13].
- Singapore accept dossier in ICH CTD as well as in the ASEAN CTD [14].
- Sril Lanka follows template given in the National Medicines Regulatory Authority (NMRA) guideline [15].
- India follows template given in Drugs & Cosmetics act.
- South Africa follows ZA CTD template [16].

The Difference in Approval Timelines:

For planning and buildinga suitable filing strategy, a clear underastanding of approval timelines is require. Approval timelines of drug product vary from few months to years. For example,

- 255 days in Australia [17],
- 10 months in US,
- approximately 15 months in Canada [18],
- 210 days in EU centralised procedure [19],
- Then there are counties where it took more than 2 years in approval, like Venezuela.

The Difference in Renewal Timelines:

Renewal timelines also differ between countries. For example,

- Countries like EU, Sri Lanka require renewal after 5 years [15, 20],
- Venezuela after 7 years,
- Singapore requires renewal every year [21],
- Few countries have indefinite validity for example South Africa [16].

The Differences in Bioequivalence Study requirements:

In Generic product development and approval, bioequivalence study is the most costly and time-consuming task. There are differences in the requirement of bioequivalence study.

- Some countries ask for the bioequivalence study to be conducted on their country innovator product, i.e., EU, USA.
- Few countries accept bioequivalence study against foreign innovator product, i.e., South Africa [22].

The Differences and Challenges in Stability Data requirements:

Stability data is the key component of the dossier. Understanding the minimum amount of data required at the time of filing, country-specific stability requirements and applicable stability conditions for different regions is critical to build filing strategy and submission plans for global markets.

There is a difference in the duration of real time stability data that needs to be submitted during dossier filing. For example,

- 12 months real time stability data should be available at the time of dossier submission for countries like Canada, Philippines, United Arab Emirates (UAE) [23].
- 6 months real time stability data should be available at the time of dossier submission for countries like US, EU.

Generation of stability data to support the shelf-life of the finished products takes significant time. Another challenge is that different regions and countries, due to their specific climate, have their own specific stability conditions. For a generic pharmaceutical company to have their product registered globally, it is essential to understand stability conditions requirments and to generate the data for all required regions from the start. Different stability conditions for countries covering global regions, are presented in Table 1 below [24, 25].

Table 1: Long Term Stability Condition as per WHO

Country	Long Term Stability condition
Algeria	25 °C/60% RH
Angola	30 °C/65% RH
Benin	30 °C/65% RH
Botswana	30 °C/50% RH
Cameroon	30 °C/75% RH
Comoros	30 °C/80% RH
Ethiopia	30 °C/65% RH
Ghana	30 °C/75% RH
Kenya	30 °C/65% RH
Madagascar	30 °C/65% RH
Malawi	25 °C/60% RH
Nigeria	30 °C/75% RH
South Africa	25 °C/60% RH
Zambia	25 °C/60% RH or 30 °C/65% RH
Brazil	30 °C/75% RH
Canada	25 °C/60% RH or 30 °C/65% RH
Guyana	30 °C/70% RH or 30 °C/75% RH
Unites States of America	25 °C/60% RH or 30 °C/65% RH
Venezuela	30 °C/70% RH or 30 °C/75% RH
Iraq	30 °C/35% RH
Kuwait	30 °C/65% RH
Austria	25 °C/60% RH or 30 °C/65% RH
Germany	25 °C/60% RH or 30 °C/65% RH
India	30 °C/70% RH
Nepal	30 °C/75% RH
Australia	25 °C/60% RH or 30 °C/65% RH

DMF procedure requirements:

The Drug Master File (DMF) requirement and registration process also vary globally. For example,

- Countries like the USA, Canada have formal DMF (also called Active Substance Master File (ASMF)) procedures.
- Countries like India and Sri Lanka do not have formal DMF procedure.

Requirement of Legalized Documents

For many emerging markets, Certificate of Pharmaceutical Product (CPP), Good Manufacturing Practice (GMP) Certificates, Price Certificates and Application forms need to be legalized by the Embassy of the particular country or Country of Origin.

The Differences, Challenges and Requirements of Comparative Dissolution Profile

There is difference in comparative dissolution profile requirements among many countries. For example,

- In EU, when more than 85% of the drug is dissolved for both test and reference products within 15 min, dissolution profiles may be accepted as similar without further mathematical evaluation.
- In Brazil, it is necessary to prove the very rapid dissolution products, by the curve graphic, performing collections at time intervals. The variation coefficient, at the 15-min point, may not exceed 10%. If the reference comparator drug presents mean dissolution of 85% in 30 min (rapid dissolution), then the test drug must also present rapid dissolution.

Therefore, considering the time required to conduct dissolution studies, a better understanding of this crucial requirement is needed for accurate strategy creation [26, 27].

Requirement of Drug Product Specifications

There is a difference in requirement of the drug product specifications. For example,

- Assay limits in release specification is 95-105% in EU and 90-110% in US and Canada.
- Assay limits in shelf life specification is 90-105% in EU and 92.5-107.5% in Australia.

Other Ancillary Documentation Requirements (Declarations)

Few countries have a specific need for signed and stamped declarations. For example, Middle East require Alcohol free certification, Pork-free certification, Halal certification, if any component of animal origin used.

Requirement of Primary Registration

Few countries need primary registration around 3-6 months before sending the registration documents. For example, Australia.

Possibility of priority review of marketing authorization application:

Some countries provide an opportunity for priority review of marketing authorization application if the applicant fulfil the eligibility criteria; however many others don't have this provision. For example,

- Australia, Singapore have priority review options [17, 28].
- EU countries' national submissions, i.e., Greece do not have a priority review option.

Sample requirement as part of Dossier Submission:

Many countries require finished product sample submission as part of the marketing authorization application. For example,

- Countries and regions like GCC and South Africa require samples.
- Countries like EU, Australia, Singapore do not require samples.

Extensive CMC data requirement:

Extensive Chemistry, Manufacturing and Control (CMC) data is needed for a generic drug product approval. The amount of CMC data required varies amongst different markets, e.g., Stability, Dissolution, Validation, Pharmacopeial reference and Specification. Hence it is critical to understand these differences from the start of the process and plan the development studies accordingly.

Regulatory Dissonance

Currently, there is extensive regulatory dissonance in the global development and submission requirements for the registration of generic pharmaceutical products. A regulatory professional, by utilizing the Regulatory

Intelligence tool, could create a harmonized pathway and overcome these challenges.

In the current scenario where regulations are ever changing in the healthcare industry, RI helped identify and interpret the changes. RI benefits include but are not limited to reduction in the cost of product development, better chance to get approval and reduced time to get approval

Utilization of Regulatory Intelligence for Global Generic Product Development and Regulatory Submissions

To utilize Regulatory Intelligence for global generic product development and regulatory submissions, an applicant needs to understand from where information can be procured and what information needs to be reviewed.

There are few sources of information available to create the regulatory strategy for global generic product development, and regulatory submissions. The examples of source information to develop the regulatory strategy for the submission of a product is Europe market is presented below.

- ICH and others adopted guidelines in various regions, i.e., the United States Food and Drug Administration (USFDA), European Medical Agency (EMA).
- Draft legislation and guidance
- Committee for Medicinal Products for Human Use (CHMP) monthly meetings reports - EMA publishes the agendas, minutes and highlights of the plenary meetings of its CHMP. EMA also publishes the agendas and minutes of the CHMP's preparatory and organizational matters (PROM) meeting, formerly known as the CHMP's organizational matters (ORGAM) meeting.
- EMA, The Coordination Group for Mutual Recognition and Decentralized Procedures - Human (CMDh) procedural guidance
- EU Commission- implementing guidance for legislation, ad-hoc
- Published literature and PARs (Public assessment reports)
- Reflection papers and Concept papers

Following are some key points to be identified, reviewed and understood while planning for the global dossier and product development:

- Different tools of regulatory intelligence and regulatory pathways. Their usage to generate global generic drug product development and dossier.
- Approval routes.
- Regulations or guidance documents that apply to various regions.
- The generic product submission process of different countries and regions. To check if there is any option for priority review.
- Data required for the Quality part of the dossier.
- Gap and changes in draft guidance as issued by Health Agencies for comments, if any.
- Dissolution requirements for different countries and regions.
- Stability requirements for different countries and regions.
- Latest trends in Health Authority Queries.
- Question & Answer documents issued by different health authorities.
- Format and content of application and dossier for different countries.

Once the regulatory professional has collated the required information, it is essential to assess carefully for sound decision-making with a practical approach and by applying knowledge and experience. Validate the information. To bring an objective approach and watch out for biases. To consider uncertanties and accoridingly develop alternative options for worst-case scenarios. Re-evaluate any new information. To review the impact of the plan and revisit if needed.

CONCLUSION

There is a significant benefit of having a global dossier with the right regulatory intelligence, as it could save high cost and time and ensure global swift and timely approval. Within a pharmaceutical company, the regulatory affairs department plays a significant role in bridging and connecting all dots amongst

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technical teams, i.e., formulation development, analytical development, manufacturing with the company's commercial plan, as well as ever-changing regulatory needs of health agencies. Therefore, well-experienced regulatory personnel are critical who could advise on health agency requirements and suggest filing strategies to develop a global generic product data for global submissions. Obtaining regulatory approval in minimum time is the need for all pharmaceutical companies. It is indeed beneficial for patients for timely access to treatments and also commercially beneficial for the industry.

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