"Regulatory Aspects Concerning Generic Drugs Approval In "Brics" Countries"

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Abstract
Five significant emerging markets—Brazil, Russia, India, China, and South Africa—join forces to form the BRICS. It's important to protect the Businesses regulated by the pharmaceutical industry that are required to adhere to all applicable For the protection and wellbeing of the general populace, regulatory agencies enforce rules and regulations. Regulatory restrictions may change from one centre entry to the next depending on that centre. As a result, it is challenging for pharmaceutical companies to create a single medication and acquire concurrent market approval in several nations. Making sure that products are produced in line with the regulatory requirements of the regulatory body is one of the major problems it faces in the country where they are sold. BE studies must be carried out entirely against Brazilian inventors at centres that have been approved by ANVISA promptly in order to meet ANVISA regulations. It's likely that the process for submitting dossiers will change in the future. For instance, Russia will start using EU procedures in 2020, but South Africa will start adopting eCTD for the submission of dossiers in 2017. The requirements differ from one nation to another and depend on how the dossier is filed. In addition to examining and evaluating the legislative requirements that vary among these five countries. This Review article's purpose is to focus attention on the changes in dossier submission that have made it possible to submit many dossiers simultaneously.

Keywords: BRICS, CDSCO, ANVISA, Regulatory, Registration, Generic Drugs.

INTRODUCTION

BRICS:

Five significant developing markets make up the BRICS (Brazil, Russia, India, China, and South Africa) alliance: Brazil, Russia, India, China, and South Africa. Pharmaceutical-regulated businesses must adhere to severe legal and regulatory regulations in order to safeguard the health and welfare of the general population. Depending on the country, there may be different regulatory constraints from one to the next. Because of this, it is difficult for pharmaceutical companies to develop one treatment and obtain concurrent market clearance in numerous countries. Making sure that products are produced in line with the regulatory requirements of the country in which they are being sold is one of the main challenges encountered by the regulatory authority. BE studies must be conducted entirely against Brazilian innovators at ANVISA-approved institutions quickly to meet ANVISA regulations.[1] Brazil, Russia, India, China (BRICS) was first introduced by Goldman Sachs as BRIC in 2001. South Africa was incorporated in 2010. The idea behind the coinage was that by 2050, the economies of the countries will start to dominate world growth. [2]

Russia's dynamic and hungry conditions, on the other hand, allow for BE tests to be done

against any innovator. It's likely that the process for submitting dossiers will change in the future. Russia, for instance, will start using EU procedures in 2020, while South Africa will start adopting eCTD's approach to filing documents in 2017. The requirements differ from one nation to another and depend on how the dossier is filed. This research intends to examine and evaluate the legal requirements that differ across these five nations. It also wants to highlight the changes in dossier submission that have made it possible to submit many dossiers at once.[3]

AIM OF BRICS

To promote and achieve economic development, Building harmony and relationships among nations, Optimum use of resources, To become a dominant supplier of manufactured goods, services and raw material by 2050, To remove trade barriers, To achieve regional development, [4]

GENERIC DRUG

A generic medication is one that performs, is administered, and is dosed similarly to a branded medication but not bearing the brand name. Although the active ingredient in both the branded drug and the generic drug is the same, the generic drug may also have other inactive ingredients that are distinct (texture, smell, and taste). Contrasts between a generic drug and illegally produced counterfeit medications should not be made. Following the expiration of the brand-name drug's patent, a generic version of the medication may be sold. The FDA must first approve a generic medicine before it may be sold as a brand-name medication.[5] Process flow for registering generic products is depicted in **Figure 1**

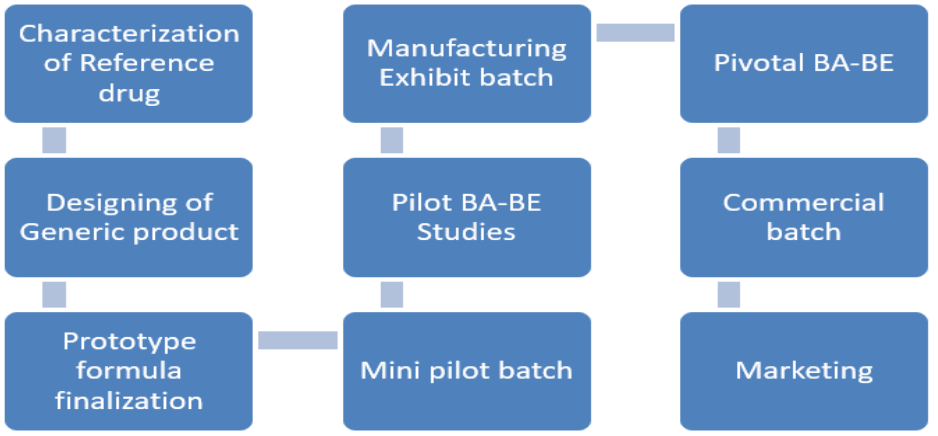

Figure 1: Process flow for registering generic products

DISCUSSION OF VARIOUS REGULATORY REQUIREMENTS

BRAZIL

Brazil, which has a population of more than 200 million, is the biggest nation in South America. Brazil has grown to be the second-largest pharmaceutical market in the developing world, with economic growth of 7 to 10% predicted yearly through 2020. Global biopharmaceutical firms are keen to make investments in this enormous and expanding sector. The interim legislation establishing ANVISA and a new system of user fees for company registration and product registration was approved by the Brazilian President on December 31, 1998. Medical devices and equipment, medicines, and food goods are all impacted by user fees and new certification regulations.[6] Different Registration Steps for Drugs in Brazil.is depicted in **Figure 2.** ANVISA Review Process of Registration Dossier's is given in **Figure 3**. Process and timeline period of review is given in **Figure 4**

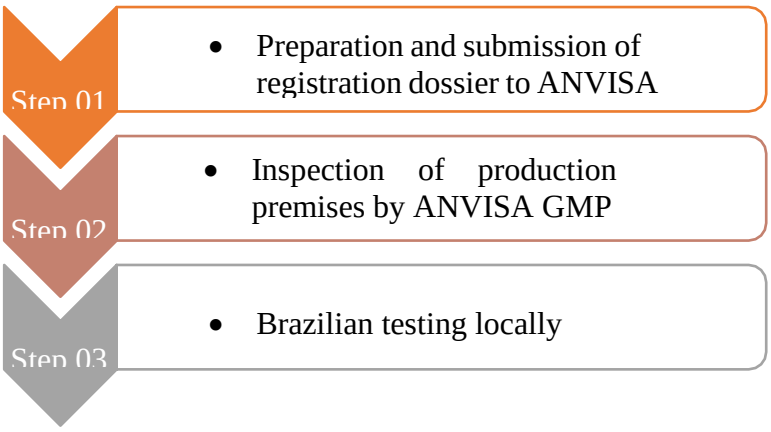

Figure 2: Different Registration Steps for Drugs in Brazil.

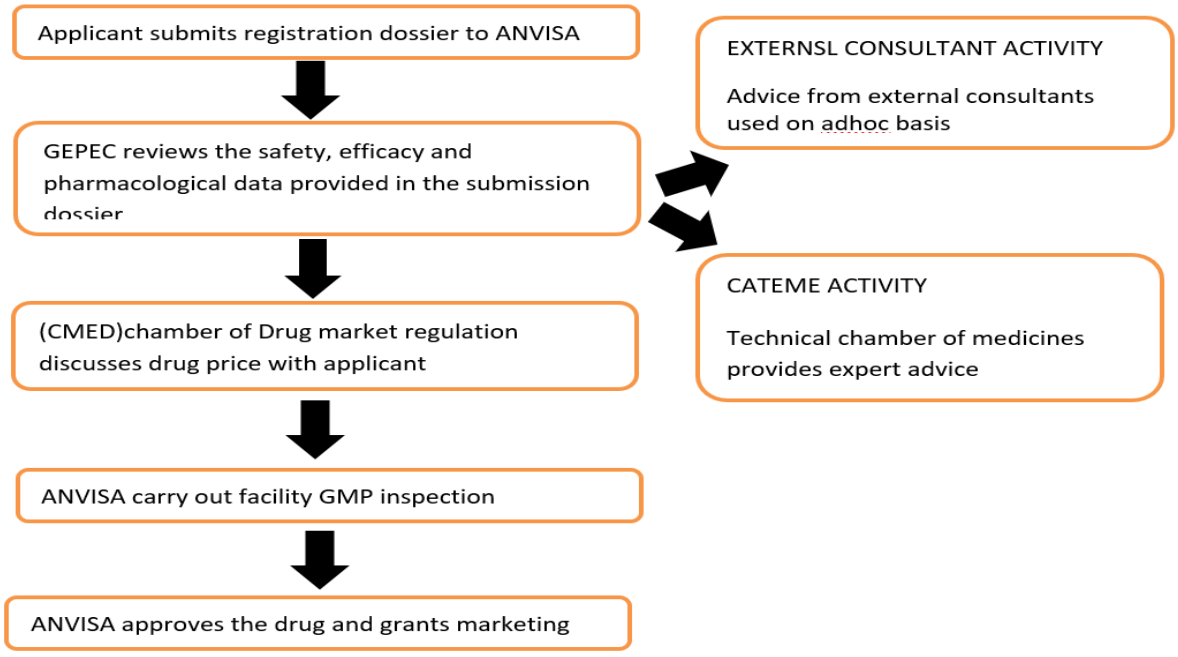

Figure 3 - ANVISA Review Process of Registration Dossier's

Priority review		Standard review	
Registration	Post approval changes	Registration	Post approval
120 days	60 days	365 days	180 days
Registration validity	10 years (may be revalidated for equal and successive periods)		
Revalidation of the registration	180 days before the validity date of the registration		

Figure 4: Process and timeline period of review

(ROSZDRAVNADZOR) RUSSIA (Ministry of Health of the Russian Federation)

Russia's Ministry of Health (Ministry of Healthcare and Social Development) Healthcare-related concerns are handled by an organisation directly under the Federation called the Federal Service on Healthcare and Social Development

Supervision (Federal Health Service or Roszdravnadzor). [7]

ORIGINAL AND GENERIC PHARMACEUTICAL PRODUCT REGISTRATION – STAGES

Three basic steps may be identified in conditional registration:

Step 1: Stage 1 involves the preparation and delivery of a Russian registration dossier to the National Center for Pharmaceutical Products Expertise (FGU).

Stage II: The National Center for Pharmaceutical Products Expertise is knowledgeable about the efficacy, security, and standard of pharmaceutical products (FGU).

Step III: Completing the expertise and submitting Roszdravnadzor with the request for the issuance of the registration certificate.

INDIA

Drug Control Agency According to the 1940 Medicines & Cosmetics Act, it is controlled by both the federal and state governments. The Medicines and Cosmetics Act specifies that the primary responsibility for controlling the manufacture, sale, and distribution of medications rests with state governments. Central agencies are in charge of managing clinical trials for novel medications, creating national drug standards, keeping an eye providing expert guidance to promote uniformity, coordinating the efforts of state drug control authorities, and monitoring the calibre of imported drugs.[8]

DRUG REGISTRATION

1. Drug Enforcement Administration According to the 1940 Medicines & Cosmetics Act, it is controlled by both the federal and state governments. The Medicines and Cosmetics Act specifies that the primary responsibility for controlling the manufacture, sale, and distribution of medications rests with state governments. Central agencies are in charge of managing clinical trials for novel medications establishing national drug standards, monitoring the effectiveness of imported medicines, coordinating the efforts of state drug control organisations, and providing expert guidance to promote uniformity.

2. The applicant must provide proof that the medication for which the application is submitted has already received permission from the licensing authority when submitting an application to the State Licensing Body for a license to manufacture a new medicine or its preparations. It may not be necessary to submit the results of local clinical trials if the treatment is of a kind that allows the licensing body to decide to grant such approval in the public interest based on information from other nations.[9]

- The Ministry of Health and Family Welfare oversees the Central Drug Standards and Control Organization (CDSCO), which conducts drug testing.
- Establishes criteria and steps to guarantee the country's supply of medicines, cosmetics, diagnostics, and gadgets is safe, effective, and of high quality;
- Controls clinical trial requirements and new medication marketing approvals;
- Regulates the import of drugs and grants permits for the production of the mentioned goods;
- The departments of science and technology, commerce and industry, environment and forestry, and finance are also involved in the process of creating regulations Depending on whether the proposal is for a biological therapy or one based on recombinant DNA technology, the medication approval procedure necessitates collaboration from other departments in addition to the DCGI.[10]

REQUIREMENTS FOR REGISTERING GENERIC DRUGS

Copies of the paperwork submitted to the Central Drug Standard Control Organization for registration are included in the registration file (or dossier). In November 2010, India started compiling dossier files in accordance with the ICH M4 Common Technical Document (CTD) standard that is accepted internationally. Modules of registering generic drugs is given in **Figure 5.** And the process involved in Generic Drug Approval in India is depicted in **Figure 6.**[11]

Figure 5: Modules of registering generic drugs

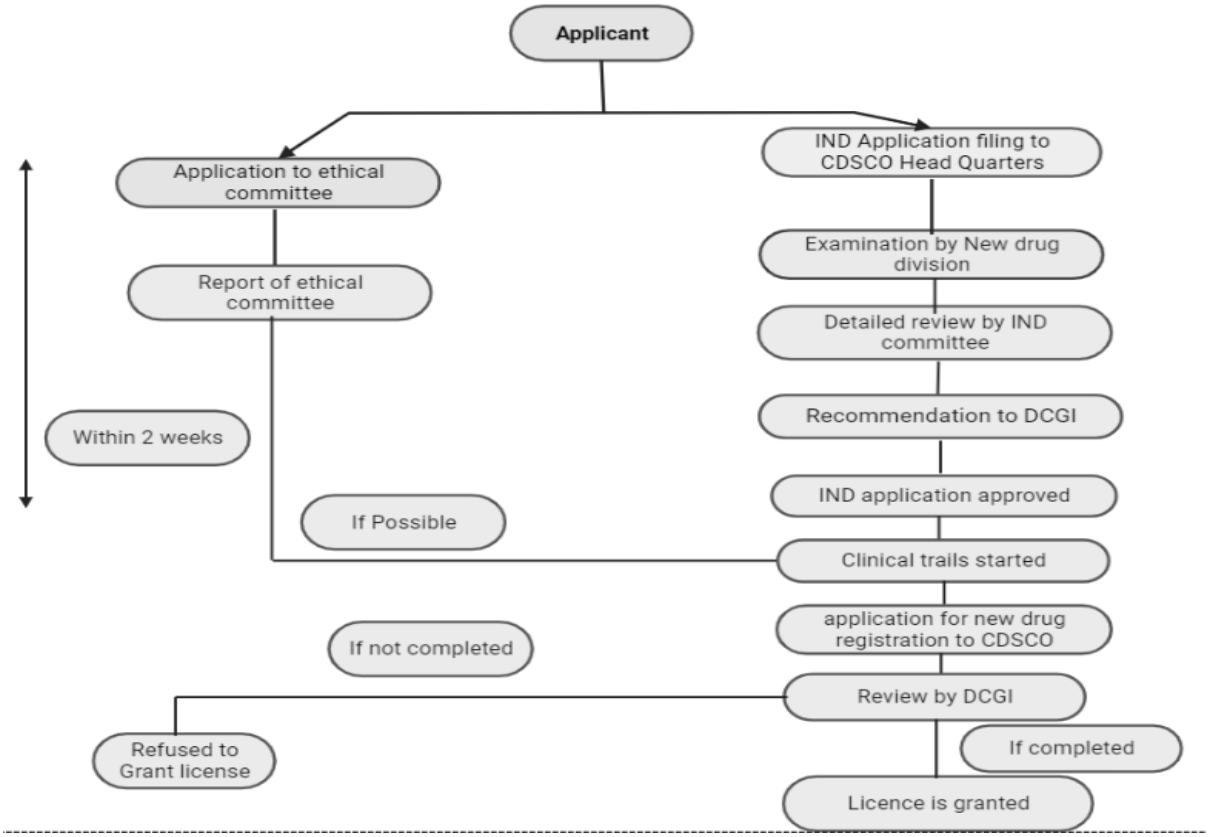

Figure 6: Generic approval process and steps in India

CHINA - National Medical Products Administration (NMPA)

GENERIC DRUG APPROVAL PROCESS IN CHINA

In China, the market for privately operated prescription medications is expanding quickly. In 2011, China is anticipated to overtake the United States as the third-largest market for prescription medications, and by 2013, that market might have doubled. 1 This increase is likely to continue for some time given that China has 20% of the world's population but just 1.5% of the global pharmaceutical market. Additionally, low-cost generic medications will be the main driver of development in China's prescription medicine industry because a sizable section of the country's population does not have access to basic health insurance. Chinese manufacturers are renowned for their capacity to economically adopt Western ideas. Thus, it is not unexpected that China today has over 3,500

pharmaceutical enterprises, the majority of which specialize in the production of generic medications.

Prior to anything else, it's critical to comprehend the fundamental distinctions in the prescription medication regulatory frameworks in China and the United States. This is known as the NMPA generic drug approval procedure. A brand-name medicine with a patent that is marketed in the US under a trademark or proprietary name rather than by its chemical name is sometimes referred to as a "branded drug."

A generic drug is a copy of a branded drug whose usage and sale have been approved by the FDA based on safety and efficacy information acquired by the producer of the branded drug. Pharmaceutical "brand" and "generic" differentiation were not previously covered by China's regulatory system. The Revised Regulation on the Administration of Drug Registration governs the licencing and registration procedures that are pertinent to medicines in China (Amended Regulation), which was published by the SFDA in 2007. In the revised regulation, the phrases "new drug" and "generic drug" are both utilized. A generic drug is one that already has a national drug standard and has obtained approval from the National Medical Products Administration, while a new medicine has never been sold in China. [12] Requirements and Registration process of Generic drugs in China is given in **Table 1.** Modules of registering generic drugs is given in **Figure 7.**

Table 1: Requirements and Registration process of Generic drugs in China

PARAMETERS		CHINA
Regulatory Authority		State Food and Drug Administration (CFDA)
Web Address		http://eng.sfda.gov.cn/
Climatic Zone		Climatic Zone II
Language		All information should be provided in Chinese and original language
Dossier Format		Regional specific, Recently initiated CTD format (still in initial phase)
DMF Type		DMF registration needed
Reference Product		Chinese Reference product
Validity of License		Valid for 5 years
Clinical Trial Permission		2-3 Years
Import Drug Licence approval		10-14 Months
Application Forms		NA
Exhibit Batches		3 Batches Samples
Stability Studies Batches		3 Batches
Testing Frequency	Accelerated	6 months
	Long term	minimum 12 months
Stability Conditions	Accelerated	40°C ± 2°C ;75%RH ± 5%RH
	Long term	25°C ± 2°C ;60%RH±10%RH
Data Exclusivity		6 Years
Type of Submission		Paper
BA / BE Studies		Clinical trials in China is Mandatory

Figure 7: Modules of registering generic drugs

AFRICAN HEALTH PRODUCTS REGULATION AUTHORITY OF SOUTH AFRICA

The South African Health Items Regulatory Authority is the organization in charge of regulating how all medical devices are used in the country (SAHPRA). SAHPRA took over for the National Department of Health's Directorate of Radiation Control (DRC) and Medicines Control Council (MCC), both of which were situated there (NDoH). SAHPRA was created as a distinct entity that reports to the National Minister of Health through its Board. [13] The medicine control council and Export committee is given in **Figure 8.**

Requirements of Generic Drug Registration:

Module 1 – Administrative Information
Module 2 - CTD Summaries
Module 3 - Quality
Module 4- Nonclinical Study Reports
Module 5 - Clinical Study Reports [14

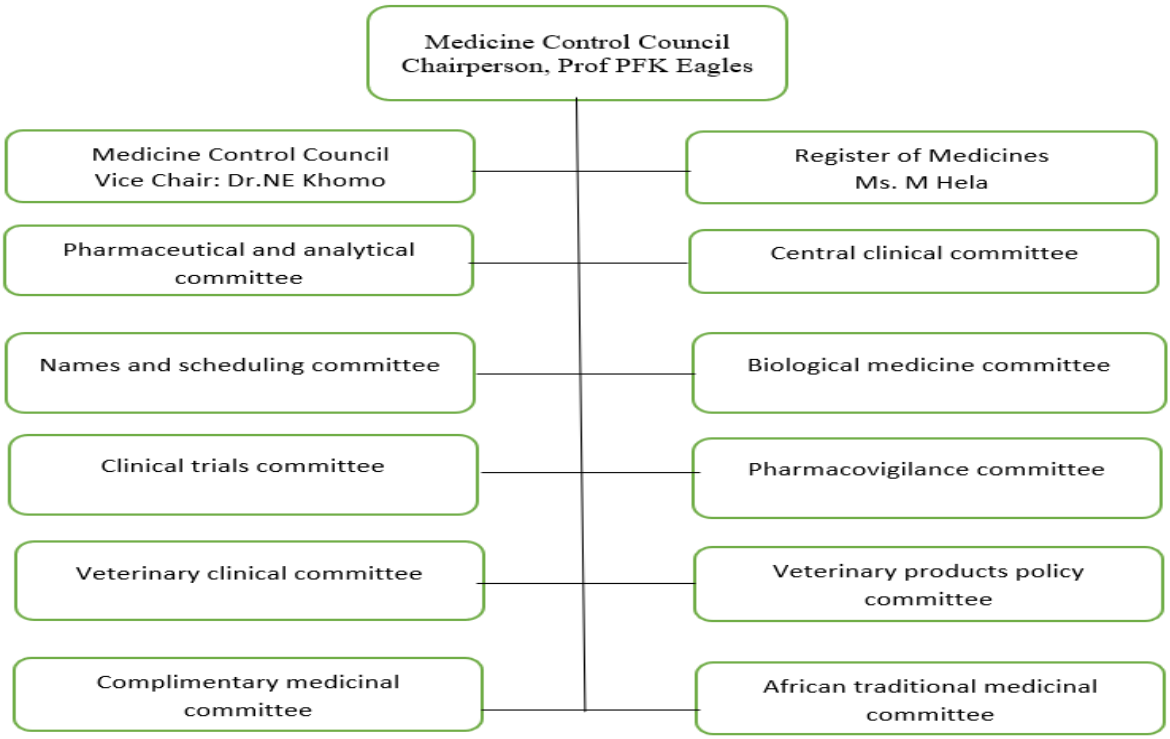

Figure 8: Medicine control council and Export committee

GENERIC DRUGS REGULATIONS IN BRICS COUNTRIES: [15]

In the domains of finance, economics, and international affairs, BRICS is one of the most often used acronyms. Upon South Africa's accession in 2010, the group underwent a change and became the current BRICS. BRICS nations comparative analysis is provided in **Table 2**

One of the major objectives of the BRICS nations is to establish a competitive global power to the mostly Western-dominated (more specifically, US-dominated) international order, even if this objective is not explicitly expressed. It should be remembered that China and Russia are also members of the BRICS group, making them two of the most potent opponents of Western dominance (if not the two most potent). In Yekaterinburg, the then-BRIC countries had their first official summit. proclaimed a new global reserve currency would be more "diversified, predictable, and stable" than the US dollar was required. **Table 3** lists the requirements for stability studies, and **Table 4** compares the stability guidelines.

The development of these nations has, however, run into certain problems. Despite the BRICS' calls for a world system free of Western imperialism, Economic experts claim that the organization's objectives and practises, which involve the exploitation of economic and natural resources, have a sub-imperialist bent. When emerging global powers expand, there will be setbacks. An in-depth knowledge of the BRICS nations' advantages and disadvantages is necessary to explore the potential next world leaders. Many of the BRIC countries are expanding their pharmaceutical industries to a point where they are on par with their more developed Western equivalents. Yet, the capacity for extension of typical corporate structures is constrained.

They are no longer considered to be "developing" countries because of the degree of advancement they have made. Companies are paying particular attention to how these markets developed into world powers after the chrysalis split. According to data from IMS Health, China maintained its position as the third-largest pharmaceutical market in the world in 2011, topping Germany by more than 50% in fourth place and Brazil by more than 50% in sixth place. Both India and Russia experienced substantial advances. According to projections, growth will last for a while.

Table 2: Comparative Study on BRICS Countries

Countries	**Regulatory Authority**	**Language**	**Format**	**Validity**	**Legal Framework & Regulation**
BRAZIL	ANVISA (Health Surveillance agency)	English, Spanish. Label, Package Insert in Portuguese	CountrySpecific	5 Years	Resolution No. 17/2007
RUSSIA	Ministry of Health of the Russian Federation	Russian	CTD	5 Years	on medications Law No. 86
INDIA	CDSCO (Central Drug Standard Control Organization)	English	CTD	5 Years	Drugs and Cosmetic Act 1940
CHINA	NMPA (National Medical Products Administration)	Chinese and English	CTD	5 Years	CFDA Order 28 Special Track System - CFDA Decree No. 21
SOUTH AFRICA	South African Health Products Regulatory Authority (SAHPRA)	English	ZA CTDeCTD	Unlimited	Medicines and Related Substances Control Act No. 101 of 1965

Table 3: Stability Study Requirements

Requirements	Countries				
	Brazil	**Russia**	**India**	**China**	**South Africa**
Photo Stability Studies	R	R	R	R	R
Stability Guideline followed	N	ICH	ICH	N	N
Climatic Zones	IV b	II	IV b	II	IV a

Table 4: Stability Guidelines Comparison

Country	Guideline
RUSSIA	➢ ICH- Q1A(R2)
BRAZIL	➢ Official Gazette of the Union Addition to No. 146, Section 1 of the Brazilian Stability Guidelines. Follow-up research: A stability study report's tests must all be repeated once every 12 months. The report must be made available during the inspection.
INDIA	➢ ICH- Q1A(R2)
CHINA	➢ For stability testing, Chinese Pharmacopoeia 2005 (CP 2005) offers recommendations. The testing circumstances comply with the nations in Climatic Zone II designated by the ICH stability guideline Q1A (R2). Therefore, the long-term storage condition is 25°C, 2°C, 60%RH, and 10°RH. ➢ For applications submitted on or after April 1, 2011, at least three months' worth of real-time stability test data must be made accessible at the time of submission. ➢ Note the distinction from the ICH standard, where the relative humidity (RH) variation is tighter (5%). Reference: Handbook of Stability Testing in Pharmaceutical Development, Editor Kim HuynhBA, July2008, Page no. 65-66
SOUTH AFRICA	MCC country Guidelines ➢ It's also acceptable to store materials for a long time at 25°-2°C/60%-50% RH. ➢ The data is presented in the tabular manner specified in the guideline, and the duration of the long term is 12 months.

CONCLUSION

The study examines the pharmaceutical's registration procedures in order to hunt for inconsistencies and legal violations. The pharmaceutical sector is increasing favorably in the world's largest and fastest-growing emerging markets (BRICS), encouraging direct foreign investment by giving pharmaceutical businesses the enormous potential to expand into these countries' BRICS nations (Brazil, Russia, India, China, and South Africa). The registration processes in Brazil and Russia

are significantly different. Despite the fact that China, India, and South Africa are frequently referred to as BRICS or the BRICS economies Brazil and Russia's registration procedures diverge significantly. They would be the most potent group in existence. In Brazil, Russia, and China, the documentation and registration procedures for drugs must be translated into the native tongue. It takes time to register, as well as learn the rules and legislation. We must work toward harmonization in order to overcome the inequalities in the rules. There is a probability that a global standard may emerge as a result. The ideas won't become reliable for a very long time. Harmonizing the norms will help developing nations like the BRICS, though. The sector anticipates that harmonized legislation will make it simpler for us to submit. A single set of regulations should be established, in my opinion, and all rules should be harmonized as a component of the study for my dissertation.

Conflict of interest:

All the authors have contributed equally to the work done and there is no conflict of interest

Ethics approval and consent to participate:

This review has not involved studies such as human participants, human data, or human tissues

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