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Review Article

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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 rules and regulations, which are enforced by regulatory bodies, for the safety and well-being of the general population. Depending on center entry, regulatory constraints might vary from one to the next. Because of this, it is difficult for pharmaceutical companies to develop a single treatment and obtain simultaneous market approval in several countries. 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 centers 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

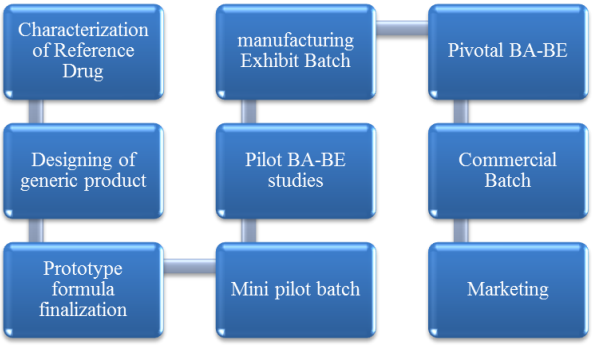
Brazil, Russia, India, China, and South Africa are five significant emerging markets that make up the BRICS (Brazil, Russia, China, and South Africa) alliance. Pharmaceutical-regulated firms are subject to strict legal and regulatory requirements, which must be followed in order to protect the public's health and well-being. 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]

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.[2]

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.[3]

The active ingredient of a prescription drug that is no longer patented is also present in generic medications. (flow chart -1)



Flowchart -1: Process flow for registering generic products.

DISCUSSION OF VARIOUS REGULATORY REQUIREMENTS

BRAZIL

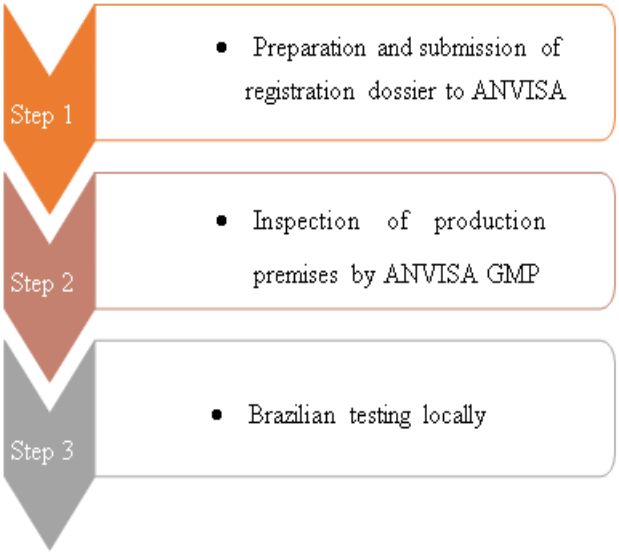
Brazil, which has a population of more than 200 million, is the biggest nation in South America. Brazil has grown to be the second-largest pharmaceutical market in the developing world, with economic growth of 7 to 10% predicted yearly through 2020. Global biopharmaceutical firms are keen to make investments in this enormous and expanding sector.

A temporary statute establishing ANVISA and a new system of user fees for company registration and product registration was authorized 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.[4]

Brazilian agency: ANVISA

Different Registration Steps for Drugs in Brazil.



Flow chart – 2 Different Registration Steps for Drugs in Brazil.

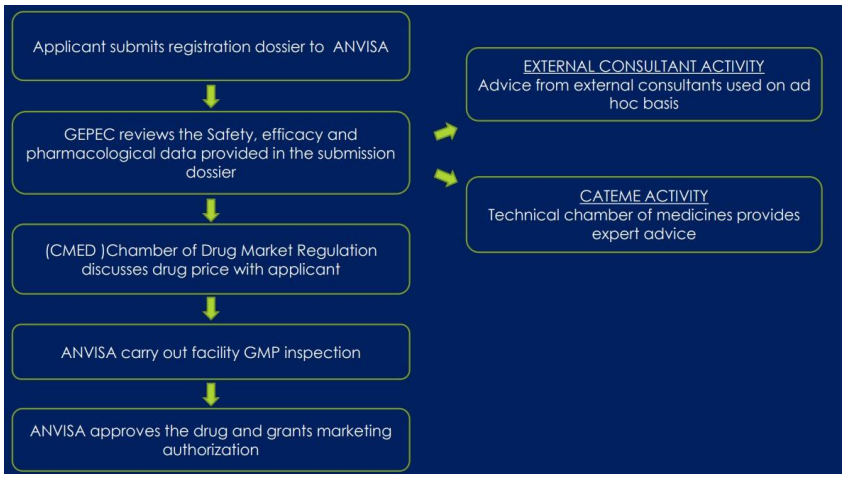


Figure 01: ANVISA Review Process of Registration Dossier.

Figure 02: Process and timeline period of review.

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

The Russian Ministry of Health (Ministry of Healthcare and Social Development) Healthcare-related matters are handled by an agency directly under the Federation called the Federal Service on Healthcare and Social Development Supervision (Federal Health Service or Roszdravnadzor).[5]

ORIGINAL AND GENERIC PHARMACEUTICAL PRODUCT REGISTRATION – STAGES

Three basic steps may be identified in conditional registration

Stage I: preparing a Russian registration dossier and submitting it to the National Center for Pharmaceutical Products Expertise (FGU).

Stage II: The National Center of Pharmaceutical Products Expertise is knowledgeable about the Quality, Efficacy, and Safety of pharmaceutical products (FGU).

- The Institute of Products Quality Control's expertise in quality control
- Institute of Preclinical and Clinical Expertise, Efficacy and Safety Expertise

Stage III: Completing the expertise and submitting the application to Roszdravnadzor for issuance of the registration certificate**.**

INDIA

Drug Regulation Agency Under the 1940 Drugs & Cosmetics Act, it is overseen by both the federal government and state governments. According to the Drugs and Cosmetics Act, state authorities are primarily in charge of regulating the production, sale, and distribution of drugs. Central authorities are responsible for overseeing clinical trials for new drugs, establishing national drug standards, monitoring the quality of imported drugs, coordinating the efforts of state drug control organizations, and providing expert guidance to promote uniformity.[6]

DRUG REGISTRATION

1. In accordance with Schedule Y of the 1940 Drugs and Cosmetics Act, a Form 44 application has been submitted to the Licensing Authority in order to obtain a license to produce the novel medicament and its formulations or to conduct clinical trials.

The maker of a new medicine must submit the information outlined in Appendix 1a of Schedule Y, including the outcomes of clinical trials that were carried out in the nation in compliance with Schedule Y's requirements and the report of those trials in the format outlined in Appendix II of that Schedule.

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.[7]

The Central Drug Standards and Control Organization (CDSCO),

- CDSCO functions under the Ministry of Health and Family Welfare
- 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 request is for a biological treatment or one based on recombinant DNA technology, the medication approval procedure entails collaboration from additional departments in addition to the DCGI.[8]

REQUIREMENTS FOR REGISTERING GENERIC DRUGS

The documents submitted to the Central Drug Standard Control Organization for registration are represented 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.[9] (fig- 3)

Generic Drug Approval Process in India.

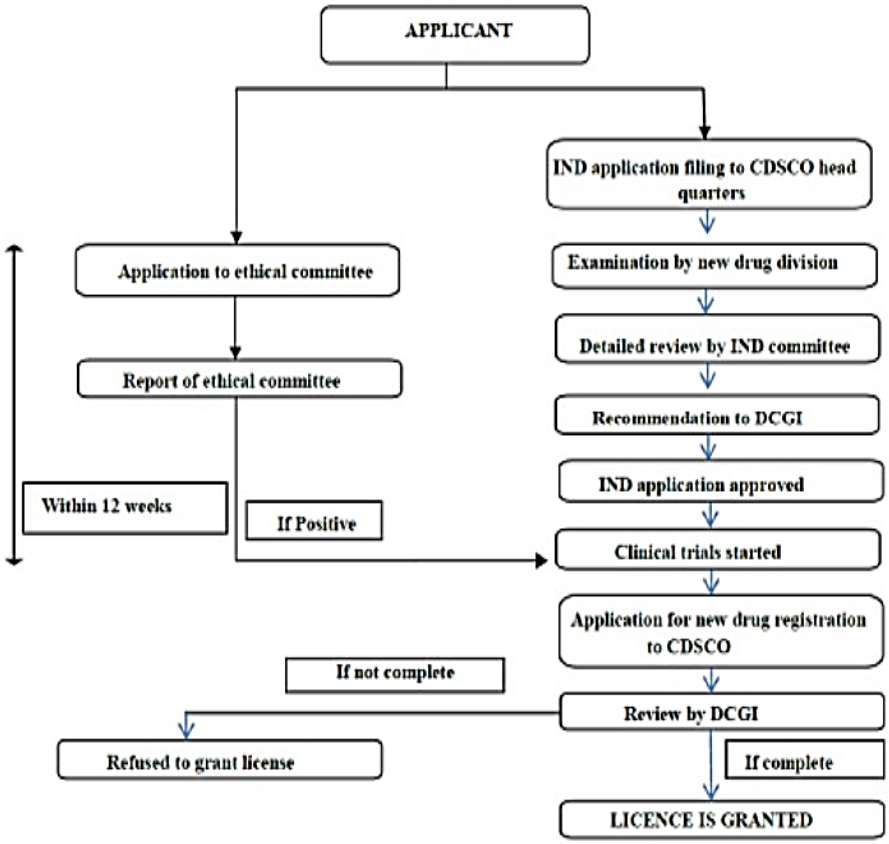


Figure 03- Generic approval process and steps in India.

CHINA - National Medical Products Administration (NMPA)

Table 01: 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

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. People's Republic of China's (PRC) State Food and Drug Administration (SFDA) (PRC)approved 886 domestic drug registration petitions in 2010, 651 of which were for generic drugs (73 percent).[10]

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 licensing and registration processes that are relevant to pharmaceuticals in China are governed by the Amended Regulation on the Administration of Drug Registration (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.[11]

SOUTH AFRICA: South African Health Products Regulatory Authority

The agency in charge of overseeing the usage of all medical items in the nation is the South African Health Items Regulatory Authority (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.[12]

Generic Drug Registration Requirements

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

Generic Drugs Regulations in BRICS Countries

BRICS is one of the most widely used acronyms in the fields of international relations, economics, and finance. Brazil, Russia, India, and China were the four fastest-growing developing economies when BRIC was first coined by former Goldman Sachs economist Jim O'Neill in 2001. The organization then became the present BRICS after South Africa joined in 2010, changing it.[13]

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.

The BRICS countries laid out their objectives and later signed the ratification documents to start the creation of the New Development Bank and a reserve currency pool worth more than $100 billion during the two most recent summits in Durban, South Africa, and Fortaleza, Brazil. Many see this bank as a direct challenge to the historically American and British-dominated World Bank and IMF, even if it isn't stated overtly. If the New Development Bank is successful, it would represent a significant shift from the historically Western-dominated banking and lending industry countries would be able to choose to borrow money from the New Development Bank rather than the World Bank or the IMF, two organizations that have come under fire for acting as platforms for the growth of Western dominance and sustaining the cycle of dictatorship and poverty in the Global South.[14]

However, there have been certain issues with these countries' progress. Economists like Professor Patrick Bond of the South African University of KwaZulu Natal argue that the BRICS' policies and practices tilt toward sub-imperialism through economic and resource exploitation, in spite of its calls for a global system free of Western imperialism. As emerging global powers develop, there will be setbacks. A detailed comprehension of both the good and bad of the BRICS countries is necessary to study the potential new world leaders. The pharmaceutical markets in several of the BRIC countries are growing to be around the same size as those in many of their more developed Western equivalents. However, typical business models have little potential for future expansion.

Due to the level, of progress, they have achieved, their collective classification as "developing" nations is in fact wholly outdated. Businesses are closely observing how these markets evolved into global players once the chrysalis separated. China consolidated its position as the third-largest pharmaceutical market in the world in 2011, surpassing Germany in fourth place by more than 50%, while Brazil eclipsed the UK, Italy, Spain, and Canada to secure the sixth position, according to IMS Health figures. India and Russia both had significant gains. Forecasts indicate that growth will persist for some time.[15]

According to IMS Health, pharmaceutical sales in China would rise from $65.77 billion in 2011 to $143 billion in 2016. Additionally, it projected that overall sales in Brazil would almost double during that time, rising from $27.69 billion in 2011 to $52.94 billion. Russia is forecast to have a compound annual growth of 11.5% in the next three years, with revenues of $25.4 billion by 2016, while India is predicted to overtake it as the third-largest BRIC nation, with revenues doubling from $13 billion in 2011 to $26.3 billion in 2016.[16]

Comparative Study on BRICS Countries

Table 02: Comparative Study on BRICS Countries.

Countries	RegulatoryAuthority	Legal Framework & Regulation	Language	Format	Validity
BRAZIL	ANVISA (Health Surveillance agency)	Resolution No. 17/2007	English,Spanish. Label, PackageInsert in Portuguese	Country Specific	5 Years
RUSSIA	Ministry of Health ofthe Russian Federation	on medications Law No. 86	Russian	CTD	5 Years
INDIA	CDSCO (CentralDrug Standard Control Organization)	Drugs and Cosmetic Act1940	English	CTD	5 Years
CHINA	NMPA (NationalMedical ProductsAdministration)	CFDA Order 28 Special Track System - CFDA Decree No. 21	Chineseand English	CTD	5 Years
SOUTH AFRICA	South African Health Products Regulatory Authority (SAHPRA)	Medicines andRelated Substances Control Act No. 101 of 1965	English	ZA CTD eCTD	Unlimited

Table 03: Requirements among BRICS.

Requirements	Countries				
	Brazil	**Russia**	**India**	**China**	**South Africa**
Administrative Documents					
Application Form	R	R	R	R	R
CoPP- Certificate of Pharmaceutical Product	NR	R	R	R	R
FSC- Free Sale Certificate	R	R	R	R	R
GMP Certificate	R	R	R	R	R
Batch Release Certificate/ Batch Production Notification	R	R	R	NR	R
License of Pharmaceutical Manufacture	NR	R	R	NR	R
Site Master File	NR	NR	R	NR	NR
GMP Manual	R	NR	NR	NR	NR
Information relating to Orphan Market Exclusivity	NR	NR	NR	NR	R
Pharmacovigilance Information	NR	NR	NR	NR	R
Information Related to Pediatrics	NR	NR	NR	NR	R
Certificates of Packaging/Procedure	NR	R	R	NR	NR
Complementary Data- bibliography, narcotic or hypnotic activity/ publications	R	R	NR	NR	R
Product info. Already approved in member state/ other states/state of origin	NR	NR	NR	NR	R
Quality Documents					
Quality Overall Summary	NR	NR	NR	NR	R
Active Substances					
General Information	R	R	R	R	R
Manufacture	R	R	R	R	R
Characterization	R	R	R	R	R
Control of Active Substances	R	R	R	R	R
Reference Standards	R	R	R	R	R
Container and Closure Systems	R	R	R	R	R
Stability	R	R	R	R	R
Finished Pharmaceutical Products					
Description and Composition of medicinal Product	R	R	R	R	R
Pharmaceutical Development	R	NR	R	NR	R
Manufacture	R	R	R	R	R
Control of Excipients	R	R	R	R	R
Control of Medicinal Products	R	R	R	R	R
Reference Standards and Materials	R	NR	R	R	R
Container/ Closure Systems	R	R	R	R	R
Dissolution Profiles	R	NR	R	NR	R
Stability	R	R	R	R	R
Documentary evidence of absence of TSE/Appendices	R	NR	R	R	R
Additional Information	NR	NR	NR	R	R
Literature References	R	R	R	R	R
Non-Clinical and Clinical Study Reports					
Bioequivalence Study Report and Data	R	R	R	R	R
Pharmacological/ Toxicological Information	R	R	R	R	R
Pharmacokinetics and Pharmacodynamic Studies	R	NR	NR	NR	R

Note – NR – Not required, R- Required

Table 04: Stability Study Requirements.

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

Table 05: Stability Guidelines Comparison.

Country	Guideline
BRAZIL	➢ Brazilian Stability Guidelines- Official Gazette of theUnion Supplement to No. 146 - Section 1. ➢ Follow-up study: All of the tests in a stability study report must be carried out once every 12 months. At the inspection, the report must be made available.
RUSSIA	➢ ICH- Q1A(R2)
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 ➢ Long- term storage at 25º ± 2ºC/60% ± 5% RH is alsoacceptable. ➢ Duration Long Term is 12 Months and the data is presentedin the tabulated format given in the guideline

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 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.

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