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REVIEW ARTICLE

Generic Drugs Regulations in BRICS Countries: A Regulatory Assessment

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ABSTRACT

BRICS is an alliance of five major emerging markets: Brazil, Russia, India, China and South Africa. The pharma regulated industries should follow all rules and regulations that are enforced by the regulatory authorities to protect the health and well being of the public. The regulatory requirements of various countries vary from one another. Therefore it is demanding for the companies to develop single drug and get simultaneous market approval in different countries. One of the primary challenges of the regulatory authority is to ensure that the products are developed according to the regulatory requirement of that country. ANVISA requires BE studies should be done only against Brazilian innovator and at ANVISA approved centre in fast conditions. Whereas in Russia it is quite contrast that the BE studies can be done against any innovator in both fast and fed conditions. Further the changes may happen in dossier submission mode. e.g.: From 2020 Russia is going to follow EU procedures and from 2017 South Africa follows eCTD in submission of the dossiers. The requirements vary among different countries and also in dossier submission. The aim of this study is to review and compare the regulatory requirements that vary among these five countries and also to emphasize the changes in dossier submission paving the way for simultaneous submissions.

KEYWORDS

Generic, Regulatory requirements, dossier, compare

INTRODUCTION

In the world of international relations, economics, and finance, one of the most common acronyms used is BRICS. Originally born as BRIC by former Goldman Sachs economics Jim O'Neill in 2001, it stood for the four fastest emerging economies: Brazil, Russia, India, and China. Then in 2010, South Africa gained entry into the group thus transforming it the current BRICS. While not openly stated, one of the major goals of the BRICS countries is to create an alternate dominating power to the primarily Western- dominated (primarily the United States) international landscape. It should be noted that two of the (if not the two most) powerful critics of Western power: China and Russia are part of the BRICS conglomeration. Following the first official summit in Yekaterinburg the then BRIC countries announced the need for a new global reserve currency counter to the US dollar, which would be more "diversified, predictable, and stable. This ambition was furthered in the two most recent summits in Durban, South Africa and Fortlazea, Brazil where the BRICS countries announced the plans and then signed the ratification documents to begin the launch of the New Development Bank as well as a reserve currency pool worth more than $100 billion.

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Again, while not openly stated many see this bank as the creation of a direct competitor to the traditionally American and British dominated World Bank and IMF. If successful, the New Development Bank would mark an important shift away from the traditionally Western dominated banking and loaning system.

Countries would have the option to accept loans from the New Development Bank instead of the World Bank/IMF, which have been heavily criticized for being tools of spreading Western domination and perpetuating the cycle of poverty and oppression of the Global South.[1]

However, the rise of these countries does not come without criticism. Economic experts like Professor Patrick Bond at the South African University of KwaZulu Natal argue that despite their cries for a world order that is not dominated by Western imperialism the BRICS' policies and practices lean towards sub-imperialism through economic and resource exploitation.

The road to the rise of new global powers is not without its bumps. Fully understanding both the good and bad of the BRICS countries will be crucial to understanding the potential new leaders of the international system.

The BRIC nations are developing pharmaceutical markets that are comparable in size to many of their more mature Western counterparts. But in terms of the size of the opportunities for future growth, traditional markets are seemingly being dwarfed by the burgeoning behemoths of Brazil, Russia, India and China. [1]

In fact, such has been the rate of progress that their collective tag as 'emerging' nations is undoubtedly out of date. The chrysalis has fallen away and their metamorphosis into markets of global importance is now drawing widespread corporate attention. IMS Health data shows that in 2011 China cemented its place as the third largest pharmaceutical market in the world – almost 50 per cent bigger than Germany in fourth place – while Brazil overtook the UK, Italy, Spain and Canada to take sixth spot. Russia and India enjoyed similarly impressive uplifts.

Growth is forecast to continue for the foreseeable future. As IMS Health predicted that pharmaceutical sales in China were increased from $65.77bn (2011) to $143bn by 2016.

Likewise, it also anticipated that total sales in Brazil will almost double from $27.69bn (2011) to $52.94bn in the same period. Sales in Russia are expected to enjoy compound annual growth of 11.5 per cent in the next three years, yielding revenues of $25.4bn by 2016 – while India is tipped to overtake Russia as the third biggest BRIC nation, with revenues doubling from $13bn in 2011 to $26.3bn in 2016.[1]

The Journey towards Giants

The grouping of four diverse nations under one general banner – BRIC – has served a useful purpose for analysts, economists and corporate strategists for many years, but it has also masked the idiosyncrasies and challenges faced by each nation as their evolution has played out. Their individual journeys from emerging markets to major players on the global stage have not followed a template, but have been underpinned by local variations on common challenges.

Infrastructure, Reform and Reimbursement

The development of infrastructure and health systems that can help improve access to healthcare for local populations has been a recurrent theme across the BRIC nations. And such development sits at the root of the opportunity for pharmaceutical growth.

But, rather like the rest of the global market, healthcare systems in all of the developing nations have been under sustained pressure to contain cost. Despite the common themes, progress in the BRIC regions has not happened in synchronicity – with the pace and rate of change naturally differing from country to country.[2]

Objective

The objective of this study is to list out the differences in the requirements pertaining to the registration of generic drugs in BRICS countries.

DISCUSSION

Comparative Study on BRICS Countries

i. General Comparison[3,4,5,6,7]

Countries	Regulatory Authority	Legal Framework & Regulation	Language	Format	Validity
BRAZIL	ANVISA (Health Surveillance agency)	Resolution No. 17/2007	English, Spanish. Label, Package Insert in Portuguese	Country Specific	5 Years
RUSSIA	Rozdravanzor	On medicines Law No. 86	Russian	CTD	5 Years
INDIA	CDSCO (Central Drug Standard Control Organization)	Drugs and Cosmetic Act 1940	English	CTD	5 Years
CHINA	CFDA (China Food and Drug Administration)	CFDA Order 28 **Special Track System** - CFDA Decree No. 21	Chinese and English	CTD	5 Years
SOUTH AFRICA	MCC (Medicine Control Council)	Medicines and Related Substances Control Act No. 101 of 1965	English	ZA CTD eCTD	Unlimited

ii. Requirements among BRICS[8,9,10,11,12]

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	NR	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
Chemical, Pharmaceutical and Biological Information-Expert Report	NR	NR	NR	NR	R
Permission to manufacture/ market in the country of origin	R	R	R	R	R
Price Information	NR	NR	NR	NR	NR
Transcript of the Registered Permit	R	NR	R	NR	NR
Notarized/Legalized Documents	NR	R	R	R	R
Letter of Authorization	NR	NR	R	R	R
Labeling Documents	R	R	R	R	R
Petition Forms	R	NR	NR	NR	NR
Sanitary Surveillance Inspection Fee	R	NR	NR	NR	NR
Sanitary Permit	R	NR	NR	NR	R
Functioning Permit	R	NR	NR	NR	NR
Certificate of Analysis	R	R	R	R	R
Certificate of Trademark	R	R	NR	NR	NR
SOPs for test methods	NR	NR	NR	R	R
Patent Information	R	R	R	R	R
Therapeutic Testing Report	R	R	R	NR	NR
Summary of Product Characteristics (SmPC)	NR	NR	NR	NR	R
PIL	R	R	R	R	R
Prototype Sales Pack	R	R	R	R	NR

Mock-up and Specimens	NR	R	R	R	R
Braille	NR	NR	NR	NR	R
Specific Information of Different Types of Applications	NR	NR	NR	NR	R
Environmental Risk Assessment	NR	NR	R	NR	R
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

R- Required

NR - Not required

iii. 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*

Where, N = National/Country Guidelines; ICH- Q1A(R2) ; R= Required.

NOTE: Though few countries have country specific stability guidelines, the requirements as per the ICH are followed and certain requirement as per country specific is included which are mandatory.

ZONES						Duration	Batches	Frequency
Study	I	II	III	IV a	IV b			
Long term	21 °C ± 2°C / 45% RH ± 5% RH	25 °C ± 2°C / 60% RH ± 5% RH	30 °C ± 2°C / 35% RH ± 5% RH	30 °C ± 2°C / 65% RH ± 5% RH(Intermediate)	30 °C ± 2°C / 75% RH ± 5% RH	12 months	3	0,3,6,9,12 months
Intermediate	30 °C ± 2 °C/65% RH ± 5% RH					6 months	3	0,3,6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH					6 months	3	0,3,6 months

iv. Stability Guidelines Comparison

Country	Guideline
BRAZIL	➢ Brazilian Stability Guidelines- Official Gazette of the Union Supplement to No. 146 - Section 1. ➢ Follow-up study: every 12 months, all the tests of a stability study report must be conducted. The report must be made available at the inspection.
RUSSIA	ICH- Q1A(R2)
INDIA	ICH- Q1A(R2)
CHINA	➢ Chinese Pharmacopoeia 2005 (CP 2005) provides guidance for stability testing. The testing conditions are in accordance with the ICH stability guideline Q1A (R2) specified for countries in Climatic Zone II. The long-term storage condition, therefore, is 25◦C ± 2◦C/60%RH ± 10% RH. ➢ At least 3 months real-time stability test data must be made available at the time of submission for applications made on or after 1 April 2011. ➢ Note the difference to the ICH guideline where the fluctuation of the relative humidity (RH) is tighter (± 5%). Reference: Handbook of Stability Testing in Pharmaceutical Development, Editor Kim Huynh-BA, July 2008, Page no. 65-66.
SOUTH AFRICA	➢ MCC country Guidelines ➢ Long- term storage at 25º ± 2ºC/60% ± 5% RH is also acceptable. ➢ Duration Long Term is 12 Months and the data is presented in the tabulated format given in the guideline.

v. Bioequivalence Study Requirements

Generic pharmaceutical products need to confirm to the same standards of quality, efficacy and safety as required of the originator's (innovator) product. Specifically, the Generic product should be therapeutically equivalent and interchangeable with the reference product. Testing the bioequivalence between a test product pharmaceutically equivalent or a pharmaceutical alternative and a suitable reference product in a pharmacokinetic study with a limited number of subjects is one way of demonstrating therapeutic equivalence.

Country	Guidelines Followed	Does it accepts other country's BE studies
Brazil	Country Specific	-----
Russia	World Health Organization guidance "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability"	Accepts Bioequivalence Studies done on its own country population ONLY
China		Accepts other International Guidelines
India	ICH Guideline	-----
South Africa	Country Specific	Accepts other International Guidelines

v(a). Demographic Requirement to Conduct BE Studies

Country	Age	BMI (kg/m^2)	Sex	Population
Brazil	18 to 50 years	± 15% of the ideal BMI	Both Sexes	24
Russia	18 to 40 years of age	Standard weight range	Both Sexes	Varies (Study on Local volunteers only)
India	Drug product for elderly population- 60yrs and above taken	------	Both Sexes	------
China	18 to 40 years of age generally, the same subjects were not different from 10 years of age	Standard weight range	Both Sexes	-----
South Africa	18 to 55 years	Normal range or within 15 % of the ideal weight	Both Sexes	Starts from 12

v(b). Diet and Fluid Requirements to conduct BE Studies

Country	Diet	Fluid intake
Brazil	Follow the study protocol	As per the study protocol
Russia	**Fasting:** A standard meal is usually provided 4 hours after drug administration. **Fed:** Drugs should be administered according to the dosing regimen, within 30 min. after the meal has been completed.	Drug administration with 150 to 250ml water
China		
India	As per the study protocol. If consuming high fat breakfast, it should be taken 15 min before dosing.	As per the study protocol
South Africa	• The time of day for ingestion of doses should be specified. • All meals and fluids taken after dosing should also be standardized in regard to composition and time of administration and in accordance with any specific requirements for each study.	• The volume of fluid administered at the time of dosing should be constant

v(c). Fasting Requirements to conduct BE studies

Country	Fasting
Brazil	As per the Study Protocol
Russia	Medicines are usually given after overnight fasting for at least 10 hours
India	Follows the study protocol
China	Medicines are usually given after overnight fasting for at least 10 hours
South Africa	In fasted studies, the period of fasting prior to dosing should be standardized and supervised

v(d). No. of Subjects and Study Design to conduct BE Studies

<table>
<tr><th rowspan="2">Country</th><th rowspan="2">Minimum no. of subjects</th><th colspan="2">Type of study</th></tr>
<tr><th>Immediate release</th><th>Modified Release</th></tr>
<tr><td>Brazil</td><td>24</td><td colspan="2">Crossover design for two medications (T-test; R-reference) a) 2×2 crossover design b) Replicated crossover design i) Four-sequence and two-period design
ii) Two-sequence and four-period design
iii) Four-sequence and four-period design
iv) Two-sequence and three-period design</td></tr>
<tr><td>Russia</td><td rowspan="2">12</td><td rowspan="2">A two-period, two-sequence, single-dose, cross-over, randomized design is the first choice for pharmacokinetic bioequivalence studies.</td><td rowspan="2">A single dose, non-replicate cross-over, fasting study comparing the highest strength of the multisource and the comparator product should be performed</td></tr>
<tr><td>China</td></tr>
<tr><td>India</td><td>16</td><td colspan="2">Both fasted and non-fasting state. If effect of food on the reference product, not known, two separate two way cross-over studies, one in the fasted state and the other in the fed state, may be carried out. If the effect known, then a three-way crossover study may be appropriate with: a) the reference product in the fasting state b) The test product in the fasted state and c) the test product in the fed state</td></tr>
<tr><td>South Africa</td><td>12</td><td colspan="2">The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a balanced two-period, two-sequence crossover design is considered to be the design of choice.</td></tr>
</table>

v(e). Parameters to be Determined

For single dose study, pharmacokinetic parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ residual area T_{max}, $t_{1/2}$ is determined using plasma time concentration profile of drug For multiple dose studies $AUC_{(0-\infty)}$, C_{max} and t_{max} determined using plasma time concentration profile of drug.

Note: C_{max} is the maximum or peak concentration observed representing peak exposure of API (or metabolite) in plasma, serum or whole blood.

- Area under the plasma/serum/blood concentration–time curve from time zero to time infinity ($AUC_{0-\infty}$) representing total exposure, where $AUC_{0-\infty}$= AUC_{0-t} + C last is the measurable drug concentration and 's' is the terminal or elimination rate constant calculated according to an appropriate method;
- T max is the time after administration of the drug at which C max is observed.
- For additional information the elimination parameters can be calculated:

- $t_{1/2}$ is the plasma (serum, whole blood) half-life.

Statistical Analysis: Statistical analysis will be performed on the data obtained from subjects. Descriptive statistics of all the pharmacokinetic parameters will be computed and reported.

Analysis of Variance (ANOVA): The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of analyte will be subjected to Analysis of Variance (ANOVA). ANOVA model will include Sequence, Formulation and Period as fixed effects and Subject (Sequence) as a random effect. Sequence effect will be tested using Subject (Sequence) as error term. The significance of the sequence effect at will be tested using the subjects nested within the sequence as the error term. An F-test will be performed to determine the statistical significance.

v(f). Reference Product Selection and Acceptance Criteria to conduct BE studies in BRICS Countries

Country	Choice of Comparator Drug	Acceptance Criteria (90 % confidence interval on Log transformed data)		
		C_{max} %	**AUC $_{(0-t)}$ %**	**AUC $_{(0\infty)}$%**
Brazil	Working standard or secondary standard is prepared from the analysis of a lot of an adequate purity material against a standard or SQR (Structured Query Report)-certified one, using official methodology and keeping an analysis record. The term SQR refers to the standards of the study drug and its metabolite(s), when applicable. They may comprise two types: i)Commercially available SQRs ii) Non-commercially available SQR Standards from USP, EU, or British pharmacopoeia, are referred to as "Chemical Reference Substance" or "CRS".	80-125	80-125	---
Russia	• The innovator drug product with Marketing Authorization in Russian Federation should be used as a reference preparation. • If the innovator drug product has no Marketing Authorization in Russian Federation, a most widely used generic drug product (market leader) with Marketing Authorization in Russian Federation should be used as a reference preparation.	80-125 (75-133) justified	80-125	80-125

China	Order of preference: • Nationally authorized innovator. • WHO comparator product. # • ICH et al. innovator. $ • No innovator product. Selection criteria in order of preference • Approval in ICH- and associated countries; • "Prequalified" by W.H.O; • Extensive documented use in clinical trials reported in peer reviewed scientific journals; and • Long and unproblematic period of post market surveillance ("well selected comparator"). # - the primary manufacturing site is indicated in the WHO comparator list and the comparator is to be purchased in that country. $ - Comparator to be purchased from that market;	80-125 (75-133) justified	80-125	80-125
India	Pharmaceutical product which is identified by licensing authority as 'designated reference product' and contains same active ingredient(s) as the new drug. For subsequent new drug applications in India the licensing authority may, however, approve another Indian product as 'designated reference			
South Africa	• Reference Product is preferably innovator product available in South Africa market. • If a foreign reference product used, it will require demonstration of equivalence between the foreign product and the innovator product marketed in South Africa	75-133	80-125	Not Applicable

vg. Biowaiver to conduct BE Studies in BRICS Countries

Country	Biowaiver
Brazil	BCS based Classification- newly implemented from August 3rd 2011. Resolution RDC nº.37 available in Portugese version only.
Russia	Based on solubility and permeability characteristics of the API Classification as per i) HHS-FDA ii) WHO
China	
India	BE studies are not necessary in the case of new drugs which are administered as: a) Parenterals. b) Oral Solutions. c) Gases. d) Powders for reconstitution. e) Otic or Ophthalmic or topical solutions and f) Nasal Sprays. In all the above cases it has to be shown that if there are excipients then they are the same and are present in the same concentration as in the reference product. If it cannot be shown that the excipients are the same, then, especially in the case of otic, ophthalmic and topical solutions and nasal sprays BE studies have to be done.
South Africa	BCS based biowaiver, Classification as per HHS-FDA

SUMMARY

Generic is a "drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use. " It has also been defined as a term referring to any drug marketed under its chemical name without advertising.

BRICS is the acronym for the association of five major emerging national economies: Brazil, Russia, India, China, South Africa. The generics to be registered have to follow the regulations enforced by the regulatory authorities and these regulations vary from country to country.

Following are the few highlights from this study on the filing of generics in BRICS Countries

- Most of these countries accept the filings in the harmonized CTD format except brazil which follow country specific format.
- The language in which the dossier is submitted is mainly country specific wherein English may be accepted only for few sections. Countries like India, South Africa accepts the complete dossier in English.
- Bioequivalence Studies in Russia needs to be carried out on local volunteers and in approved CRO’s.

- Registration of generics in Russia cannot be proceeded easily by mere bioequivalence study reports. Clinical trials have to be conducted for generic drug registration also. The guidelines waives off clinical trials only if the ministry signals the study reports sufficient. Bioequivalence studies are mandatory to be done only on local population. Russia also has tighter limits for impurity levels in pharmaceutical ingredient and finished product.
- Pharmaceutical Equivalence needs to be established for generics in Brazil with the local innovator and local batch release.
- Stability conditions vary in accordance with the zones under which they fall. All the emerging countries come under Zone II, IVa or IV b. In almost all countries three production batches data are required at the time of submission.
- All countries have different timelines for approval of generics and also vary in the term of license. All emerging countries have a term of license of 5 years. In Russia after the first renewal after 5 years, the term becomes unlimited.
- Requirements for registration of generics especially taking bioequivalence studies into concern, showed Russia to have the most stringent regulations followed by, followed by the other emerging countries.

CONCLUSION

As the requirement varies from country to country it is challenging for the companies to get simultaneous market approval in different countries. The above mentioned comparative study among five countries makes easier to know the difference in requirements which helps in simultaneous submissions.

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