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Review Article

REGULATORY REQUIREMENTS FOR REGISTRATION OF GENERIC DRUGS IN BRICS COUNTRIES

P. Mounika *, Brahmaiah Bonthagarala, MV. Nagabhushanam, D. Nagarjuna Reddy, G. Ramakrishna

Department of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh-522002, INDIA.

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ABSTRACT

Brazil, Russia, India, China and South Africa are typically rendered as "the BRICS" or "the BRICS economies". The registration process for Brazil and Russia are completely different. Even though India, China and South Africa follow the CTD format the requirements for Module 1 are different. The purpose of the study was to compare generic drug registration process and to find out the differences, lacunae among the guidelines.

KEYWORDS: *Regulatory requirements, Registration Process, Brics Countries, Regulations, Generic Drug Registration.*

INTRODUCTION

Marketing Authorization:

Marketing authorization (MA) is a process of reviewing and assessing the dossier to support a medicinal product, which is approved by the regulatory authority of a country. A Marketing Authorization, which has been issued by regulatory authority for a product, allows the holder to sale the product in the market [1].

BRICS Countries:

BRICS comprise the developing markets of Brazil, Russia, India, China and South Africa which are all deemed to be at a similar stage of newly advanced economic development. It is typically rendered as "the BRICS" or "the BRICS economies [2]."

Generic Drug:

Generics are defined as "a drug product that is comparable to bran/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use [3]".

BRAZIL: (ANVISA) Agencia Nacional de Vigilancia Sanitaria

On December 31, 1998 the Brazilian President signed a provisional measure that created ANVISA and established a new user fees structure for companies and products registration. The user fees and new certification rules affect medical devices and equipment, pharmaceuticals and food products [4].

*** Corresponding author:**

P. Mounika

Department of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh-522002, INDIA.

** E-Mail: brahmaiahmph@gmail.com*

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Drug Product Registration:

Generic Medicine: a medicine similar to a reference or innovator product which is claimed to be interchangeable with it, generally produced after the expiration or waiver of patent protection or of other exclusiveness rights, its efficacy, safety and quality being proven, and designated by CBD(Common Brazilian Denomination) or, failing this, by the CID (Common International Denomination).

Requirements for Registration:

The process to request the registration of national and imported drug products shall consist of the documentation below [5]:

Legal Aspects:

- Application form obtained from the Brazilian Ministry of Health.

For imported medicines:

- Present the medicine Registration Certificate, issued by the local health authority, stating the place of manufacture or production of the medicine to be registered in Brazil.

Post Registration Measures:

After publication of the registration, the generic medicine manufacturer must supply:

ANVISA with: [5]

1. Proof of distribution of the first three batches manufactured, to allow ANVISA, if it wishes, to collect samples for control analysis;
2. Report on the incidence of adverse reactions and therapeutic inefficacy;

Bioavailability and Bioequivalence requirements:

Standards for BE:

1. Single Dose Studies: [6] *Pharmacokinetic Parameters:* AUC, C_{max} and T_{max}

Analysis of variance (ANOVA) of the pharmacokinetics parameters AUC0-t and C_{max}must be carried out in order to

evaluate the effects of sequence of subjects of period and of treatment

Study Design: The conventional study is of the open, random and crossed type.

2. Sampling Scheme Criteria: The sample collection schedule must observer a length of time equal or greater than 3-5 times the half-life of elimination of the drug or the metabolite.

RUSSIA: (ROSZDRAVNADZOR)
(Federal Service on Healthcare and Social Development Supervision):

Russian federal government, healthcare issues fall within the competence of the Ministry of Healthcare and Social Development (Ministry of Health) and subordinated to it, the Federal Service on Healthcare and Social Development Supervision (Federal Health Service or Roszdravnadzor). The Ministry of Health defines state policy and issues administrative healthcare regulations relating to the production, quality and distribution of pharmaceuticals [7].

Drug Registration-Conception:

To enter into Russian market all pharmaceutical products must be registered.

The Registration Certificate is issued on the basis of quality, efficacy and safety then the product is introduced in the database of registered products in Russian Federation. From 2008 Registration Certificate is unlimited. But before this date Registration Certificates were issued only for 5 years [8].

Registration Process:

Dossier represents the documents submitted to state regulatory authority for registration:

- Administrative documents
- Description of pharmaceutical properties.

Administrative Documents:

1. Application Form
2. Letter of Authorization from MAH (Market Authorization Holder) to Raifarm
3. IP rights (patents, trademarks)

Data on Bioequivalence studies:
Subjects of the studies:

- Bioequivalent estimation is conducted for all dosage forms with immediate or delayed drug substance release [9].
- In the case when pharmaceutical product is not approved in the manufacture country the basement for bioequivalent approval are the positive results of preclinical pharmaceutical products bioavailability investigation [9].

Pharmacokinetic date assay: [10]
Single dosing:

Individual values of AUC (as for AUCt and AUC∞), maximal concentration (C_{max}) and time to maximal concentration (t_{max}) must be evaluated using non-modeling methods based on "concentration-time" determined for each participant for each pharmaceutical product, Values $C_{max}$and t_{max} are evaluated as maximal of determined concentration values and referral times.

AUC – ratio:

The 90% CI for this measure of relative BA should lie within an acceptance interval of 0.80-1.25. In specific cases of a narrow therapeutic range, the acceptance interval may be tightened.

C_{max}-ratio:

The 90% CI of this measure of relative BA should lie within an acceptance interval of 0.80-1.25. In specific cases of a narrow therapeutic range, the acceptance interval may be tightened.

Registration of Original and Generic Pharmaceutical Product – Stages:

Registration process conditionally can be divided into 3 basic stages:

Stage I: Compiling of Registration dossier in Russian and its submission to the National Center of Pharmaceutical Products Expertise (FGU).

Stage II: Expertise of the pharmaceutical product Quality, Efficacy and Safety in the National Center of Pharmaceutical Products Expertise (FGU).

- Institute of Products Quality Control - ***Quality Control Expertise***
- Institute of Preclinical and Clinical Expertise - ***Efficacy and Safety Expertise***

Stage III: Finishing of the expertise and submission of the dossier to Roszdravnadzor for issuing of Registration Certificate.

INDIA: Central Drug Standard Control Organization (CDSCO)

Drug Regulatory Authority:

It is governed by both Centre and State Governments under the Drugs & Cosmetics Act, 1940 [10].

Drugs controller general of India is responsible for approval of licenses of specifies categories of drugs such as blood products, IV fluids, Vaccines and Sera. Central Drug standard Control Organization (CDSCO) is located at the Nirmalbhawan, New Delhi, 110011 and functions under Directorate General of Health Services [11].

Drug Registration:

An application for the grant of approval to manufacture the new drug and its formulations or to undertake clinical trial has be made in Form 44 to the Licensing Authority as per Schedule Y of the Drugs and Cosmetics Act, 1940.

(1) Provided that where the application is for permission to import a new drug (bulk drug substance) and grant of approval to manufacture its formulation/s.
(2) Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with the new claims, is made.

Generic Drug Registration Requirements: [12]

Registration file (or dossier) represents the documents submitted to Central Drug Standard Control Organization for registration. India began to follows the international acceptance format of ICH M4 Common Technical Document (CTD) for compilation of dossier file from November 2010. 10
It contains 5 modules.

- *General Information*
- *Common Technical Document Summaries*

- *Quality Reports*
- *Nonclinical study Reports*
- *Clinical study Reports*

Bioavailability and Bioequivalence Study requirements:

1. Standards for BE:

a. Single Dose Studies: To establish bioequivalence, the calculated 90% confidential interval for AUC and $C_{max,}$ should fall within the bioequivalence range, usually 80- 125%. This is equivalent to the rejection of two one sided t-tests with the Null hypothesis of non-bioequivalence at 5% level of significance [12].

b. Steady State Studies: Describes only about the conditions where steady -state study is appropriate as:

1. When drug has long terminal elimination half-life and blood concentration after a single dose cannot be followed for a sufficient time.
2. Assay sensitivity is inadequate to follow the terminal elimination phase for an adequate period.

CHINA: State Food and Drug Administration (SFDA)

Drug Regulatory Authority: [13]

In March 1998 the government of China was announced the Ministry of Health's Department of Drug Administration merged with the State Pharmaceutical Administration of China (SPAC) to become the State Drug Administration (SDA). As a result, SDA oversees all drug manufacturing, trade, and registration.

SFDA:

In 2003, the SDA was restructured to become the State Food and Drug Administration (SFDA). Other former functions of the ministry have been assigned to different government bodies. The most important of these was the transfer of medical insurance responsibilities to the new Ministry of Labor and Social Security

Drug Product Registration:

- An applicant for drug registration refers to the institution that submits a drug registration application and assumes corresponding legal liability.
- Drug registration applications include applications for new drugs, generic drugs, import drugs, supplementary applications and re-registration applications.

Drug Registration Requirements:

Registration file (or dossier) represents the documents submitted to State Food and Drug Administration for registration. China for preparation files it follows ICH CTD format. It contains 5 modules [14].

1. *Administrative information and prescribing information.*
2. *Common Technical Document Summaries*
3. *Quality Reports*
4. *Non clinical study Reports*
5. *Clinical study Reports*

Bioavailability and Bioequivalence study Requirements: [15]

Standards for BE:

Single Dose Studies:

AUC-RATIO: The 90% CI for this measure of relative BA should lie within an acceptance 80% - 125% range. In specific cases of a narrow therapeutic range, the acceptance interval may be tightened.

C_{max}- ratio: The 90% CI for this measure of relative BA should lie within an acceptance 80% - 125% range.

Steady state studies:

Whenever multiple dose studies are performed, it should be demonstrated that study state has been reached.

P.K.Parameters:

AUC 0→ t, AUC 0→ ∞, C_{max}, $T_{max,}$ t1/2, CL, and V_d,

SOUTH AFRICA (MCC) (Medicines Control Council):

Drug Regulatory Authority:

Since the early 1970's South Africa has developed a medicines regulatory authority that is internationally recognized. The MCC is a statutory body that was established in terms of the Medicines and Related Substances Control Act, 101 of 1965, to oversee the regulation of medicines in South Africa [16].

Drug Registration Process:

- Application for registration of medicines should submitted on MRFI.
- Each page of the application should be numbered and printed should be in a font size with a legibility equivalent to at least Arial 10 point black on white and the copies including tables, photos should be clearly legible.

Generic Drug Registration Requirements: [17]

Module 1 – Administrative Information
Module 2 – CTD Summaries
Module 3 – Quality
Module 4 – non clinical Study Reports
Module 5 – Clinical Study Reports

Bioavailability and Bioequivalence requirements:

1. Single dose studies:

Pharmacokinetic parameters: $AUC_{t,}$ AUC∞, C_{max}

AUC_t – ratio: The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80 – 1.25 (80 - 125%).

C_{max}– ratio: The 90% confidence interval for the test/reference ratio should lie within an acceptance interval of (75 – 133%), calculated using log-transformed data, except for narrow therapeutic range APIs when an acceptance interval of 80 – 125 % will apply[18].

2. Steady – State Studies:

Immediate Release dosage forms:

The acceptance criteria are the same as for single dose studies but using AUC∞ instead of AUC_t.

Controlled/Modified Release dosage forms

The acceptance criteria are as follows:

AUC∞- ratio: The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80 – 1.25 (80 - 125%)

$C_{max(ss)}$ and $C_{min(ss)}$: The 90% confidence interval for the test/reference ratio should lie within an acceptance interval of (75 – 133%), calculated using log-transformed data.

3. Study Design:

The randomized, controlled, balanced two-period, two-sequence cross over design is considered.

CONCLUSION

It can be concluded that the world pharmaceutical economy, the fastest growing and largest emerging markets economies of Brazil, Russia, India, China and South Africa (BRICS) countries are showing positive growth and increasing direct foreign investment by creating significant opportunities for pharmaceutical companies to expand into these markets. They would be the largest entity on the global stage. The drawback in Brazil, Russia and China are the regulations are in their local languages and the documents required for registration of drugs should translate into their local languages. It takes time to understand the rules and regulations and for registration. To rectify the differences of the guidelines; we need to go for harmonization. So that we can expect a common guideline worldwide. It will take time to harmonize the guidelines. But once harmonized the guidelines, emerging countries like BRICS will get benefit. With ICH formation, the industry foresees harmonization of regulations, so that we can do filing easily.

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