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An Overview on Comparative Study of Generic Drug Approval Process in USA, India and Australia

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ABSTRACT

The goal of this study is to examine the registration procedures for generic drugs in United States of America, India, and Australia with regard to regulatory submission. The pertinent publications and the official websites of the corresponding drug regulatory agencies like USFDA, CDSCO & TGA respectively for US, India, and Australia provided the information and data which is compared in the present study.By the current comparative study we have found that not all the countries have the same criteria & process for the generic drug approval. Like for the US, FDA application and ANDA approval (6 month process), For India CDSCO & DCGI type of regulatory bodies which gives the drug approval (90 days process) & for the Australia TGA is governing authority for the generic drug approval (11 months) which is quite slower process then the other two. This review provides detailed comparison of the generic drug approval process in these countries, highlighting variation in regulatory requirements & timelines.

KEYWORDS: FDA, ANDA, CDSCO, DCGI, TGA

INTRODUCTION:

When a medication is created to be precisely the same as a branded medication in terms of dosage form, potency, administration method, and intended use that has already been commercialized, it is referred to as "generic." Every nation has its own regulations and policies regarding the registration of generic drugs [1].

Once a patented drug's patent expires or its marketing rights become available at a reasonable price, generic pharmaceuticals are offered. The country's corresponding regulatory body has approved generic medications as novel medications in terms of their effectiveness, bioavailability, etc [2].

The form, scoring arrangement, release mechanisms, packaging, excipients (colours, tastes, preservatives), and product expiration of generic medications can all vary. In the case where medications with such differences are substituted with one another, patients might get confused. The quantity and nature of the data reinforcing each drug's commercial applicability determines the primary distinction between generic and name-brand medications. It is necessary for a name-brand medication to exhibit strong preclinical and clinical data demonstrating both safety and effectiveness in a patient population. Generic medications are sold once a patented drug's patent or marketing rights expire. Generic medications are still of high quality but are available at reasonable costs [3]. The Hatch Waxman Act of 1984, also referred to as the Drug Price Competition and Patent Term Restoration Act passed during the 98th United States Congress made it possible for ANDA to be implemented by imposing restrictions on pharmaceutical firms. The generic drug's introduction into the market was made possible by the Hatch-Waxman Act of 1984 [4].

Due to the mounting strain of rising healthcare expenses to the extent of 400 billion US$ large innovative enterprises and Indian multinational corporations (MNCs) are expanding their business in the generic market of India. In order to achieve volumes and

gain market share, they are currently attempting to establish a substantial presence in branded generics and over-the-counter (OTC) medications, introduce off-patent items from other innovative firms, and implement local pricing for patented medications [5].

While on the other hand the generic drug scenario in Australia was majorly surrounding to the PBS which is Australia's largest pharmaceutical purchaser, and both domestic and foreign producers compete to provide the proprietary and generic medications it offers. Since they don't have to pay as much for research and development as original brands do, and since they are increasingly being made in nations with relatively cheap labour costs, generic manufacturers may typically enter the market at a low cost once patents expire [6].

In the current study we have done detailed comparison of the generic drug approval process in these countries, with comparing the variation in regulatory requirements & time taken by the respective agencies for generic drug approval.

1. DRUG APPROVAL PROCESS IN USA:

For products made between 1938 and 1962, the Kefauver-Harris Drug Amendments mandated that all producers of similar goods file an Abbreviated New Drug Application (ANDA).

A pioneer drug application's data was comparable to those of ANDAS, with the exception of safety and efficacy. After 1962, the FDA approved the "literature-based" New Drug Application, creating a new method of demonstrating efficacy and safety. This meant that the manufacturer of a generic product might submit published evidence about the safety and effectiveness of a branded product [7].

Over the past three decades, a number of disputes have emerged so The FDA Office of Generic Drugs (OGD) was the subject of an investigation in 1987 in response to a complaint from Mylan Laboratories alleging that some of its ANDAS had been intentionally delayed.

Following an internal evaluation of the OGD, the FDA modified the process for processing ANDAS, tightened the requirements for ANDAs, and controlled other OGD processes [8].

The developer of the pharmaceutically comparable generic medication product now has to demonstrate bioequivalence & pharmaceutical equivalency, since the original active ingredient was already shown to be safe and effective.

Pharmaceutical equivalency denotes that the branded medicine and the generic product have the same active ingredient(s), dose form, method of administration, and strength. When two products are examined under similar settings and their bioavailability is equivalent, this is known as bio equivalency [9].

“Pharmacological equivalency is a very simple concept to understand, while bioequivalency is more complex. The assessment of the AUC and the maximum drug concentration (Cmax) yields the bioequivalency”.

1.1 Types of Reviews in the Generic Drug Approval Process [10]:

a) ANDA Regulatory Review Process: When an applicant files an ANDA to the CDER (Center for Drug Evaluation and Research) or OGD (Office of Generic Drugs), the ANDA procedure gets started. The ANDA is filed by documentation personnel, who also provide the ANDA cover letter with the ANDA number and the date of receipt.

A consumer safety officer receives the ANDA after which they examine the preliminary ANDA verification form. The examination of submitted ANDAs will take into account proprietary bio-equivalency as well as chemical, pharmacological, and microbiological considerations. Within the first 60 days following the filing of the ANDA, finish the data review.

b) Bio-equivalence Review Process: Medication equivalency and bio-equivalence are two crucial characteristics of generic medications that are therapeutically equal to novel medications. Pharmaceutical equivalency requires that the novel medication and the generic medication have the same potency, dosage form, and mode of administration.

When products are tested in the same settings and show comparable bioavailability, they are referred to as bio-equivalent. Analysing the drug's AUC and maximum concentration yields the bio-equivalency. If the relative mean Cmax of a pharmaceutical product

falls between 80% and 125% on the mean AUC and 90% confidence interval (CI), it is considered bio-equivalent to the branded product.

c) Label Review Process: Making sure that prescription medications have the same labels as generics is the goal of the label review process. After the last round of examination, applicants will either obtain a letter of approval or complete approval, depending on any deficiencies found by the administration and specific disciplines.

The applicant is given permission to commercialize the pharmaceutical product upon completion of an approval letter that specifies the criteria of approval. If the medicine being used (RLD) has a patent that is still in effect or has been excluded, then the license is allowed.

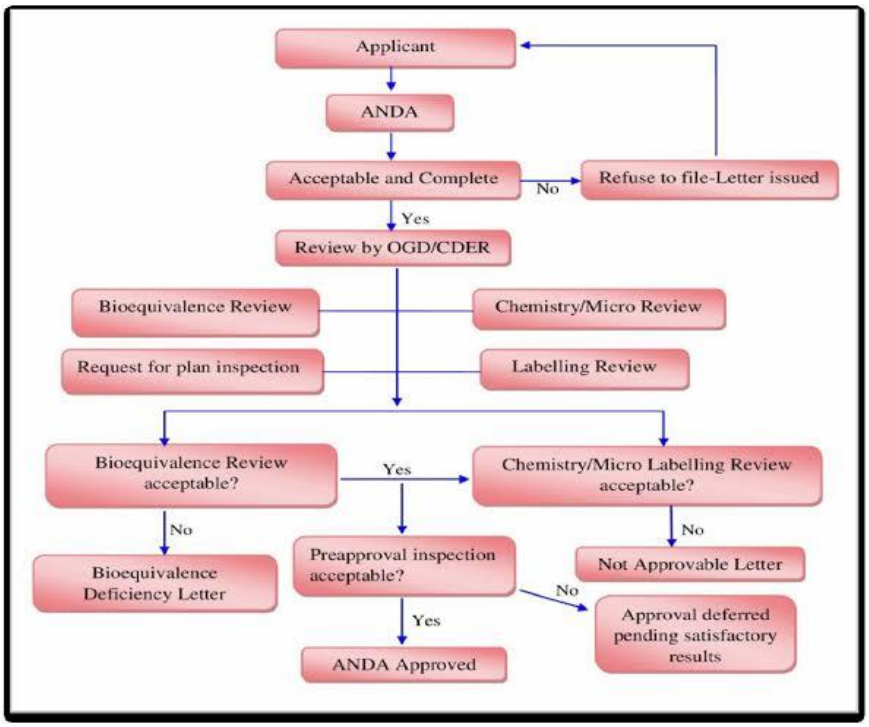

Figure 1:- Drug Approval Process in USA [11]

2. DRUG APPROVAL PROCESS IN INDIA [12]:

The new medication application is not at all like this one. The applicant and regulatory bodies may be permitted to rely on some of the safety and/or the efficacy data for a medicine that has already received approval in this application by CDSCO and DCGI. However, to support new claims for a medicine that has been licensed, further non-clinical and/or clinical evidence are needed.

The new claim determines the additional information required to assess the new generic drug's safety and efficacy. If the medication is currently on the market in significant nations and has received approval from a number of organizations for the suggested new claim.

In the event that the generic medication demonstrates both its pharmacological and bioequivalence to the licensed medication and that there is no metabolic alteration as a result of ethnic differences. If a major, life-threatening illness or a condition of particular significance is the subject of the proposed new claim, the criteria for animal toxicological and clinical data may be lowered or waived.

In order to approve the production or import of such novel medications, CDSCO will assess the applications' rationality. The issue may also be looked at after consulting with specialists or committees of experts, if needed.

2.1 Documents Required in order to submit an abbreviated new medication application:

Ingredients:

- Bio-equivalency and bioavailability
- Examiner/canter's name
- Source and stability of raw materials

Raw material:

- Method of production
- QC characteristics, stability, and requirements
- Animal toxicity

Fixed Dose Combination (FDC) Authorization/License:

- Rationale
- Data related to pharmacokinetics and pharmacodynamics
- any additional data

New dosage forms or further approval, or approval of a new indication:

- The number and date of the prior approval
- The rationale
- Quality, safety, and efficacy data

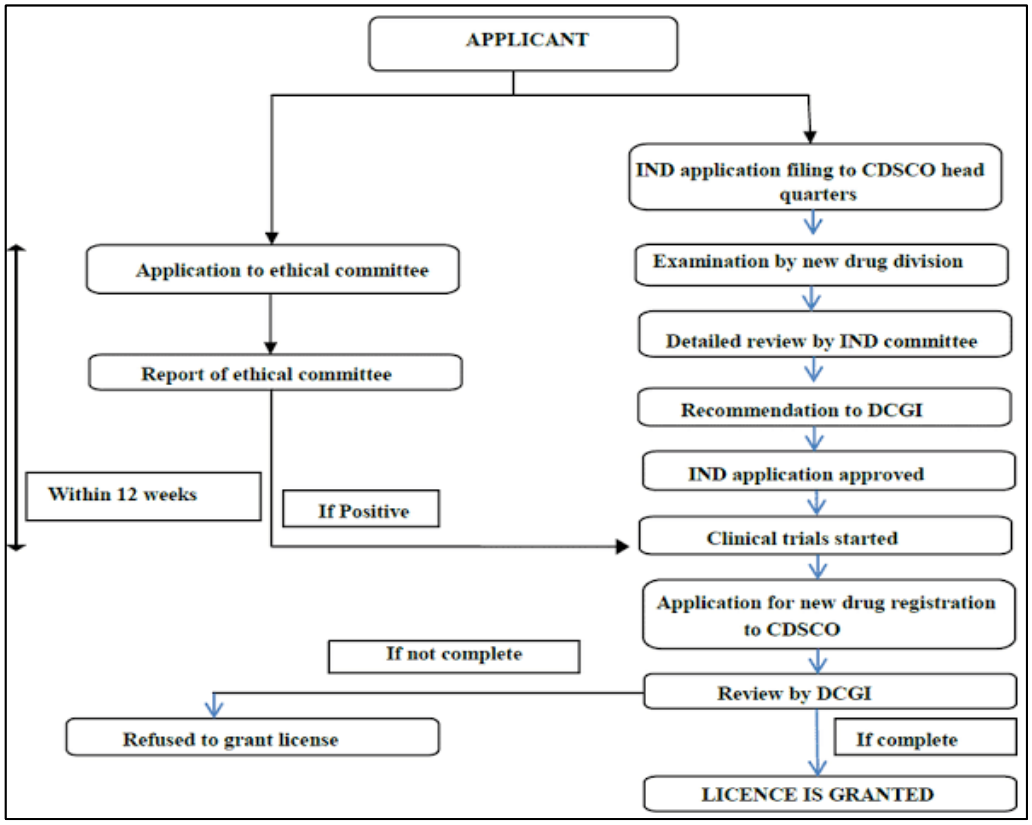

Figure 2:- Drug Approval Process in India [13]

3. DRUG APPROVAL PROCESS IN AUSTRALIA [14]:

The Therapeutic Goods Administration (TGA) is Australia's drug regulatory body responsible for overseeing generic medication goods. A generic medication must be covered by the Pharmaceutical Benefits Scheme (PBS) before it can be registered in Australia. The PBS portal now has a substantial amount of generic medications. In Australia, many generic medications are typically sold under brand names.

TGA is an international standard that meets with US and EU drug laws. Due to the limited size of the market and high registration costs, Australia presents a challenging investment opportunity for multinational generic businesses that are built for high volume markets.

In Australia, TGA requires about 11 months to approve a generic medication.

3.1 List of required documents [15]:

a) Pre-PPF: - (To TGA)

- Notification for each new ingredients
- Application form for new chemical(AAN), biological(ABN), herbal(AHN) name
- Application for orphan drug designation
- Justification of new fixed combination
- Acceptance as submission based on literature

b) PPF:-

(i) Applicant details:

- Applicant name
- eBS client ID
- Postal address
- Address for Correspondence
- Contact numbers
- Position(RA officer/ Agent)
- Email Address
- Facsimile number

(ii) Product details:

3.2 Phases of Generic Drug Approval Process [16, 17]:

Phase 1: Pre-submission: The road for registering generic drugs begins with the pre-submission phase.

It is applicable to both category 1 and category 2 generic medications. It requires submitting the Pre-Planning Form (PPF) and application costs.

Phase 2: Electronic submission of new generic medication application: This stage requires the electronic submission of a new generic drug application via electronic Business Service (eBS).

The applicant will be informed of the application's status—whether it has been placed on hold, is being reviewed, or is being accepted—as soon as TGA receives it. The notice letter explains why the application was placed on hold, if any.

Phase 3: First Round Assessment: During this stage, all the data and information in the dossier will be carefully assessed by the TGA reviewers.

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Phase 4: Response to the consolidated section 31 request: If there are any questions about the dossier during the review, TGA will send a request to the applicant requesting that they respond to the questions presented. The applicant must reply to the questions using a "consolidated section 31 request" form.

A "consolidated section 31 request" is a request for information that TGA sends to the applicant in the event that any queries are raised during the application review process or if the data they give is insufficient.

Phase 5: Second Round Assessment: Following receipt of the applicant's section "31 request form," the TGA evaluation team will confirm the information and go on to the second round assessment of the updated dossier. The final report is compiled by TGA following the completion of the second-round examination.

Phase 6: Expert advisory review: The TGA may ask its Advisory Committee on Medicines (ACM) for independent counsel in addition to further review in order to get their input on the final report.

Phase 7: Decision: Following a thorough examination of the dossier, the TGA expert team will determine whether to approve or deny the proposed application.

Phase 8: Post-decision: The post-decision step starts as soon as the applicant is notified of the TGA decision. During this phase, administrative and regulatory tasks are completed.

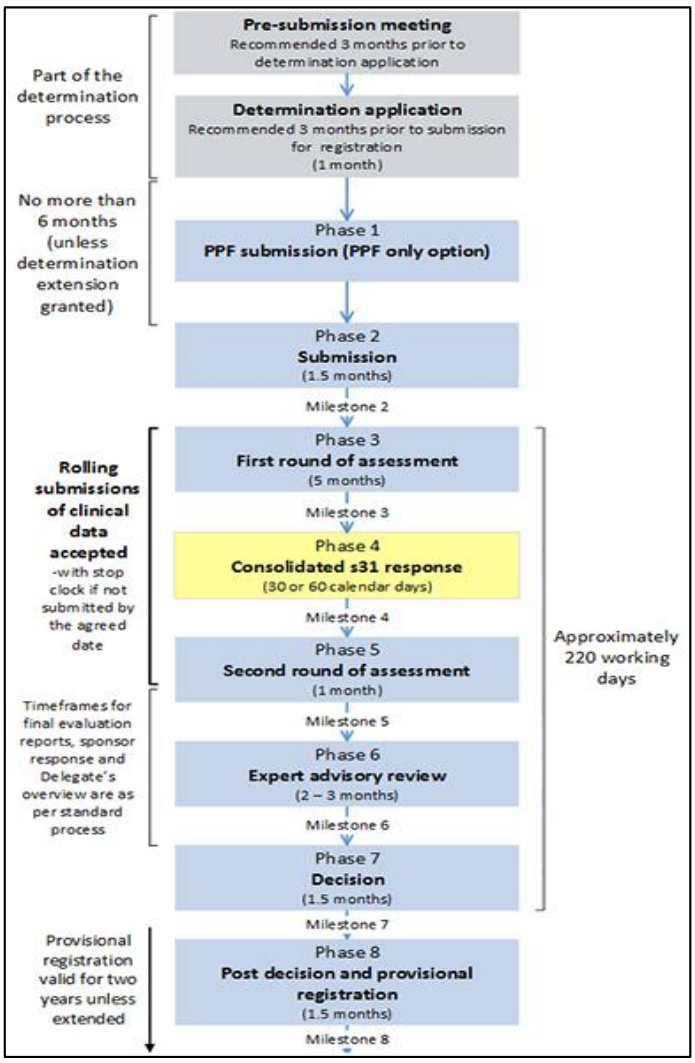

Figure 3:- Drug Approval Process in Australia [18]

4. FAQs [19, 20]**:-**

Q.1 Is renewal of license is possible? How?

Ans. Yes, renewal of license is possible for the drug that are highly beneficial in treatment of certain disease. A Provisional Approval Method is used for the licence renewal process.

Q.2 What should I do if I get rejection in licensing process?

Ans. If your application got rejection by TGA then they will inform you in writing. Then you can withdraw your application at any time & try to find errors in required regulatory requirement & CTD (common technical document) format. Then again apply for approval.

5. COMPREHENSIVE OVERVIEW [21-24]**:-**

Aspects	USA	India	Australia
Regulatory body	Food & Drug Administration (FDA)	Central Drug Standard Control Organization (CDSCO)	Therapeutic Goods Administration (TGA)
Application type	Abbreviated New Drug Application (ANDA)	Abbreviated New Drug Application (ANDA)	New Generic Product
Pre-submission phase	Pre-IND meeting to discuss requirements	Pre-application consultation available	Pre-submission planning form (PPF)
Assessment duration	10 months for standard & 6 months for priority application (avg.)	6 months for NDA approval (avg.)	3 months for new generic drug
Review round	Typically one round; additional information may be requested	Single round review; further queries may extend the process	Two rounds of assessment with potential requests for additional information
Expert Review	Advisory committees may be consulted	Review by Subject Expert Committees (SEC)	Involves expert advisory committees
Decision Notification	Approval letter issued; if rejected, reasons provided	Approval or rejection communicated via official letter	Written notification post-evaluation
Post-approval monitoring	Post-marketing studies may be required	Post-marketing surveillance mandated	Risk Management Plans (RMPs) required
Fees	Fees vary; approx. $2.8 million for standard NDA	Fees vary; typically lower than in Australia & USA	Fees vary; approx. $20,939 for new generics

CONCLUSION:

Drug regulatory bodies have controlled and authorized generic medications, which are exact replicas of branded pharmaceuticals, to lower the cost of branded drugs for the general population. These drugs are then sold to other nations in order to boost market income. Since it is extremely difficult for generic medicine businesses to maintain the quality and safety of their products, regulatory bodies have established strict guidelines for generic drug approval. Regulatory bodies only allow generic medications 20 years after the patent expires. Every one of these three nations have a drug regulatory body that oversees and approves generic medications. The approval process for generic drugs follows distinct formats in each of the three nations. In the United States, India, and Australia, the applications for marketing authorization of generic drugs are referred to as ANDA, MAA, and PPF respectively. The average period for approving a generic medication application is 12 months in India, but it is 16 and 18 in USA and Australia. This indicates that CDSCO assesses generic applications quickly. The US sets the lowest prices for generics, whereas Australia sets high prices. Although generic pharmaceuticals are subject to laws and regulations in every nation, stricter laws must be enacted to ensure their quality and safety on level with branded medications.

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