REGULATORY PROCESS INVOLVED IN GENERIC DRUG APPROVAL PROCESS IN USA, EUROPE AND INDIA

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ABSTRACT
Regulatory involvement in the generic drug development hastens the drug approval process which directly/indirectly accelerated the launching of drug into the market. The regulatory documents whether in-house or documents to be submitted to regulatory authorities should be carefully reviewed by the skilled personnel to minimise the queries raised by the regulatory agencies and speed up the approval process. These are few differences in the dossier submission requirements among the three regions i.e., USA, Europe and India which has been clearly represented through succinct comparisons third part of this work. The literature work, the comparison parameters, difference in generic drug approval requirements has been delineated in this work, which gives clear depict where India lies in its generic drug approval process and the challenges that Indian regulatory authority has to overcome in the near future. Regulatory involvement in the generic drug development hastens the drug approval process which directly/indirectly accelerated the launching of drug into the market. The regulatory documents whether in-house of documents to be submitted to regulatory authorities should be carefully reviewed by the skilled personnel to minimise the queries raised by the regulatory agencies and speed up the approval process.


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INTRODUCTION

A new drug is defined as one that is not generally recognized as safe and effective for the indications proposed. However, this definition has much greater reach than simply a “new” chemical entity [1]. The term “new drug” also refers to a drug product already in existence, though never approved by the FDA for marketing in the United States; new therapeutic indications for an approved drug; a new dosage form; a new route of administration; a new dosing schedule; or, any other significant clinical differences than those approved. A Generic Drug Product is one that is comparable to an Innovator Drug Product in dosage form, strength, and route of administration, quality, performance characteristics and intended use [2].

INDIA

In India drugs are regulated both at central and state level. At the central level CDSCO (Central Drugs Standard Control Organization) under the ministry of Health and Family Welfare are responsible for approving new drugs, clinical trials and licensing of drugs. At the state level state drug regulatory authorities issues licences to manufacture approved drugs to monitor the quality of the drugs along with CDSCO [3]. In India the regulation of drug, medical devices, and biological and r-DNA products is distributed within various ministries.

USFDA

In United States, Food and Drug Administration (FDA) is the drug regulatory authority for approving food, human and veterinary drug products that are to be marketed in USA.

EMA

In Europe, European Medicines Agency is the regulatory agency for approving human and veterinary drug products centrally to market the drugs in European Union (EU). There is also individual National Competent Authorities (NCA) for approving the drug products in individual states.

Methodology

The objective of this study is to figure out the determinants for selecting a generic application and the regulatory aspects involved in generic drug development. Understanding the Generic Drug Approval process in US, EU and India and highlighting the differences between these three Countries. Each and every study has some patterns and follows certain pathways in order to reach the destination. Thus, the method to be followed plays an important role in determining the outputs as well as consequences of the study.

Types of study

The study was conducted with an objective to sketch the regulatory framework for Generic Drug Approval process in USA, EU and India and mainly emphasizing on the application form, approval timelines and sequence of steps in the generic drug approval. The literature was collected using numerous search engines like Pharma knowledge base, Center for Pharmaceutical Information and Engineering Research (CPIER) and official Government websites like FDA, EMEA, HMA and CDSCO. Key words in the search involved generic drug registration requirements along with the name of various parameters associated to pharmaceutical field, name of regulatory bodies and other variations were used. The patent information which is included in this work is obtained for the country specific patent organisations and World Intellectual Property Organisation.

Generic drug approval process in USA

Hatch-Waxman Act

Intended to balance interests of consumers, the brand name pharmaceutical industry (innovator) and the generic drug industry to “make available more low cost generic drugs and to create a new incentive for increased expenditures for research and development of certain products which are subject to pre-market approval. In fewer than 20 years since enactment of the statute, generic drugs increased from 19% to 47% of prescriptions [4].

Title I of Hatch-Waxman Act:

Authorized marketing of generic drugs upon approval of Abbreviated New Drug Application (ANDA). Under this ANDA can be approved upon submission of evidence that the active ingredient of the generic drug is the “bioequivalent” of a drug previously approved by USFDA after submission of a full NDA without having to submit studies establishing the safety and efficacy of drug.

Title II of Hatch-Waxman Act:

This section provided specific extensions of patents covering drugs and other products subject to “regulatory review” by the FDA and government agencies. This provision was intended to balance the benefits of ANDA practice by providing brand name drug companies with the restoration of portions of the terms of their drug patents lost during the testing period required for the approval of the drugs. These patent term adjustments as well as patent extensions implemented 10 years after the enactment of Hatch-Waxman Act.
Abbreviated New Drug Applications (ANDA) [5]:
Under section 505 (j) of Hatch-Waxman Act, an ANDA may be filed for a generic version of any “listed drug”.

Listed Drug: Any drug for which an NDA has previously been approved is deemed to be a listed drug and is listed by FDA in the orange book. Drugs previously approved under ANDA’s and Antibiotics are also regarded as listed drugs. An ANDA must include all information required in an NDA except full reports of investigations demonstrating that the drug is safe and effective in use.

ANDA additionally must show: Labelling of the drug for which ANDA is sought is same as the approved labelling for the listed drug. b) Its route of administration, dosage form and strength are the same as the listed drug or supply such information respecting any differences as FDA may require bioequivalence reports c) Status of orange book listed patents on the approved drug.

Types of Certifications
An applicant for ANDA must certify to FDA that in its opinion and to the best of its knowledge, with respect to each listed patent that claims the drug or use of the drug for which the applicant seeking approvals are: Paragraph I; Paragraph II; Paragraph III; Paragraph IV. The Hatch-Waxman act has undertaken necessary considerations to prevent litigations between generics and NDA applicants [6]. The act is successful in making a pathway for approval of generics without infringing the original patent. The pathway for approval of generics by the Hatch-Waxman begins with the certification procedures. Hatch-Waxman proposed four options for application for generic approval. The first three options avoid litigation.

<table>
<thead>
<tr>
<th>PARAGRAPH I</th>
<th>That the patent information relating to innovator patent has not been filed</th>
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<tr>
<td>PARAGRAPH II</td>
<td>That relevant patent has already expired</td>
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<tr>
<td>PARAGRAPH III</td>
<td>That the generic will not market the drug until after the patent expires</td>
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<tr>
<td>PARAGRAPH IV</td>
<td>The generic manufacturer should certify that an applicable patent is invalid or will not be infringed by the generic product</td>
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ANDA approval process in USA
Initially, an ANDA filer must show that the conditions of use identified in its proposed labelling have been previously approved for the listed drug on which the ANDA is based. According to this statute, ANDA must incorporate the same labelling as that of previously approved for the listed drug except for any changes required because of the differences are approved on the basis of a suitability petition.

Withdrawal of Approval of an ANDA
FDA may withdraw/suspend approval of an ANDA when the approval of the listed drug on which the ANDA relies is either withdrawn or suspended. Further, an approval of an ANDA or 505 (b)(2) application may be withdrawn on the basis of evidence showing that the drug is unsafe for use or ineffective or that the ANDA or 505 (b) (2) application contains any untrue statement of material fact [7]. FDA must withdraw approval of an ANDA if it finds that the approval “was obtained, expedited or otherwise facilitated through bribery, payment of an illegal gratuity, or fraud or material false statement”, or may withdraw approval of an ANDA if it finds that the applicant has “repeatedly demonstrated a lack of ability to produce drug, and has introduced or attempted to introduce, such adulterated or misbranded drug into commerce”.

Generic drug approval process in EU
As for all medicines, generic medicines must obtain marketing authorisation before they can be marketed. Marketing authorisations are granted after a regulatory authority, such as the European Medicines Agency, has conducted a scientific evaluation of the medicine’s efficacy (how well it works as measured in clinical studies), safety and quality. Applicant shall not be required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product. European generic medicines are approved through Centralised procedure, Mutual recognition procedure, Decentralised procedure and National Marketing Authorization [8].

Centralised Procedure
Generic/Hybrid medicinal product applications of the medicinal products authorized via the centralised procedure have automatic access to the centralised procedure under article 3(3) of the regulation (EC) number 726/2004. For generic/hybrid applications of a centrally authorised product, the application should state in their “Letter of intent to submit” that they have automatic access to the centralised procedure under article 3(3).

Letter of intent to submit
Before submission of the dossier, applicants should notify the agency of their intention to submit an application, preferably 6-18 months in advance and indicate that the application is generic/hybrid medicinal product application of a medicinal product authorized via centralised procedure. EMA (European Medicines Agency) will inform the applicant on the outcome of the eligibility request [9].
Generic Medicinal Product
A medicinal product that has; the same qualitative and quantitative composition in active substances as the reference product. The same pharmaceutical form as the reference medicinal product. And whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Hybrid Medicinal Product
Hybrid applications differ from the generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary in the following 3 circumstances: Where strict definition of a “generic medicinal product” is not met, Where the bioavailability studies cannot be used to demonstrate bioequivalence, Where the changes in active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product[10].

Centralised authorisation procedure
The European Medicines Agency is responsible for the centralised procedure for human and veterinary medicines. This procedure results in a single marketing authorisation that is valid in all European Union countries, as well as in Iceland, Liechtenstein and Norway. The centralised procedure is compulsory for, Human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, Veterinary medicines for use as growth or yield enhancers, Medicines derived from biotechnology processes, such as genetic engineering, Advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered, medicines, officially designated ‘orphan medicines’ (medicines used for rare human diseases). For medicines that do not fall within these categories, companies have the option of submitting an application for a centralised marketing authorisation to the Agency, as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorisation would be in the interest of public or animal health. Applications through the centralised procedure are submitted directly to the Agency. Evaluation by the Agency's scientific committees takes up to 210 days, at the end of which the committee adopts an opinion on whether the medicine should be marketed or not. This opinion is then transmitted to the European Commission, which has the ultimate authority for granting marketing authorisations in the EU [11]. Once a marketing authorisation has been granted, the marketing-authorisation holder can begin to make the medicine available to patients and healthcare professionals in all EU countries.

Generic drug approval process in INDIA [12]
1. Form 44
2. Treasury Challan of INR 15,000 if all the active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year.
3. Source of bulk drugs /raw materials: For those ingredients which are approved and considered new drugs - If the applicant has a manufacturing license for bulk drugs, a copy of the same is needs to be submitted. Otherwise, provide the consent letter from the approved source regarding supply of material.

Clarification
In case if the applicant does not have an approval from DCGI to manufacture Active Pharmaceutical Ingredient (API) which is considered as new drug, applicant can, Import the API - Applicant has to file application along with all relevant documents and comply with further requirements for import of API. Manufacture the API - Applicant has to file application along with all relevant documents and comply with further requirements for manufacture of API. Obtain the API from another manufacturer which is not yet approved by DCGI - In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury Challan of requisite amount with all relevant documents. Such application will be processed simultaneously with the application for API. Approval of the formulation will be considered after approval of the API.
4. Chemical and pharmaceutical information including:
Information on active ingredients
a) Brief Chemical & pharmaceutical data
Data on Formulation [13]
 a) Master manufacturing formula
 b) Details of the formulation (including inactive ingredients)
 c) Finished product specification
 d) In process quality control check
 e) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.
 f) Comparative Dissolution data in case oral dosage form as appropriate
 g) Stability study evaluation as per requirements of schedule Y
5. Regulatory status of the drug including names of the company’s marketing the drug in the country
6. Bioavailability/Bioequivalence study reports (for oral dosage forms)

Note: In following circumstances equivalence may be assessed by the use of in vitro dissolution testing:
a. Drugs for which the applicant provides data to substantiate all of the following:
i. Highest dose strength is soluble in 250 ml of an aqueous media over the pH range of 1-7.5 at 37°C
ii. At least 90% of the administered oral dose is absorbed on mass balance determination or in comparison to an intravenous reference dose.

iii. Speed of dissolution as demonstrated by more than 80% dissolution within 15 minutes at 37°C using IP apparatus 1, at 50 rpm or IP apparatus 2, at 100 rpm in a volume of 900 ml or less in each of the following media:
   a. 0.1 N hydrochloric acid or artificial gastric juice (without enzymes)
   b. a pH 4.5 buffer
   c. a pH 6.8 buffer or artificial intestinal juice (without enzymes)

b. Different strengths of the drug manufactured by the same manufacturer, where all of the following criteria are fulfilled:
   i. The qualitative composition between the strengths is essentially the same;
   ii. The ratio of active ingredients and excipients between the strengths is essentially the same, or, in the case of small strengths, the ratio between the excipients is the same;
   iii. The method of manufacture is essentially the same;
   iv. An appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength unless a lower strength is chosen for reasons of safety); and
   v. In case of systemic availability - pharmacokinetics have been shown to be linear over the therapeutic dose range.

c. In vitro dissolution testing may also be suitable to confirm unchanged product quality and performance characteristics with minor formulation or manufacturing changes after approval.

7. In case of injectable formulation, sub-acute toxicity data conducted with the applicants’ product has to be provided.

8. Prescribing information

Proposed full prescribing information containing the following information [14, 15]
   Generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.

9. Draft of labels and carton

10. Copy of License in Form-29

CONCLUSION

The decision to proceed with the development of a generic drug should be made on the basis of well-researched data that primarily indicate the marketing share and annual sales of the innovator drug in the respective country where the generic manufacturer is planning to launch, together with the sound knowledge of patents and marketing exclusivities, availability of API or pharmaceutical materials, Formulation and BE considerations. The predicted profit of the generic product requires a strategic planning for submission of dossier to the regulatory authority shortly prior to the patent expiry such that generic product is ready to enter into market immediately after the innovator drug patent expiry.

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