Detailed analysis of Drug Development and the Non-Proprietary Drug Approval Process

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Abstract

After the original drug's patent period has passed, companies other than the corporation that invented it begin to manufacture and market generic versions of the drug. In the EU and the US, bioequivalence is regarded as the primary requirement for the approval of generic medications. The medications must have the same strength, dose form, and amounts of the same active pharmaceutical component to be considered bioequivalent. Their bioavailability must be comparable at a level where their expected therapeutic effects may be predicted. Two types of rules are present for generic drugs: supply-side and demand-side. Supply-side policies include guidelines for generic drug approval, market access, and pricing. Generic prescribing, substitution, targeting information, academic status, and public awareness campaigns are part of the demand-side policy. The final goal of these two sets of rules is to enhance the accessibility of generic drugs globally, reduce drug prices, and avoid drug scarcity and supply interruption. In particular, the accessibility of cheap generic drugs is essential to boost the financial attitude to drug treatment in relatively poor and middle-income countries. Despite these precautions taken by the government in the aspect of generic drugs, most of the present policies are not executed in the current immature healthcare systems.

Keywords: Cost, Drug, Generic, Medicine, Prescription.

1. Introduction

In terms of dosage, safety, strength, mode of administration, quality, and therapeutic activity, a generic drug is the same as a brand-name drug that is already available on the market [1].

These are like their recognized medicines in dosage form, quality, effect, route of administration, composition, and active ingredients. They appear like the latter but may taste slightly different[2, 3].

The foremost objective of introducing these medicines was to cut down on the prices of the drugs. After the patent expiry of the branded drugs, these drugs are released into the market[4]. These are labelled with drug trade names and non-proprietary name, which is given based on the API in the dosage form[5, 6]. These non-proprietary names are suggested by the WHO panel of experts responsible for publishing pharmacopoeias and are agreed upon by the World Health Organization (WHO). Section 13(b) of the Trade Marks Act, which went into effect in 1999[7, 8].

2. History

In the 1960s, the Indian government started encouraging generic medicines. It was further encouraged when the "Patent Act of 1970" was passed[9]. The act in effect prevented all approved patents on food and drugs. However, companies had the privilege of acquiring patents on the method of manufacturing the product for 5-7 years. This created a well-set, competitive market in not only India but also other countries worldwide, which were filled with Indian companies. Over time, India has become the leading producer of generic medicines. It has now become a common practice among pharmaceutical companies to create contributory generic brands for them to enter the market. The criteria for generic drug approval are defined in the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the "Hatch-Waxman Amendments"[10-12], Under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), sponsors must submit an abbreviated new drug application (ANDA), making the approval process for generics much easierThe statement you provided contains several accurate pieces of information about the pharmaceutical industry and related legislation.

Time Boosted for Patent Security: To compensate for the time lost during the FDA approval process, big-name manufacturers extended the patent security for their unique products to five years. This means that after receiving FDA approval, they were granted an additional five years of exclusive market rights before generic competitors could enter the market.

The Hatch-Waxman Act: The Hatch-Waxman Act, formally known as the Drug Price Competition and Patent Term Restoration Act of 1984, is indeed one of the most significant

pieces of legislation affecting the generic medication industry. It established the modern system of generic drug approval, providing an abbreviated pathway for generic manufacturers to gain FDA approval. This act streamlined the process and reduced the time and cost required for generic drugs to enter the market.

The Uruguay Rounds Agreements Act: The Uruguay Rounds Agreements Act (URAA) was passed in 1994 and increased the patent period for medicines made in the United States from 17 to 20 years. This extension provided additional protection and exclusivity to pharmaceutical companies, allowing them to recover their research and development costs and earn profits for a longer duration.

Code of Ethics, 2002: Although you mentioned the Code of Ethics, 2002, I couldn't find a specific reference to it about encouraging doctors to recommend generic medications. However, it is common for healthcare professionals to consider generic drugs as a cost-effective alternative to brand-name medications when suitable options are available. Encouraging the use of generic drugs can help reduce healthcare costs for patients and healthcare systems.

The pharmaceutical industry has implemented measures such as extending patent security and passing legislation like the Hatch-Waxman Act and the Uruguay Rounds Agreements Act to balance the interests of brand-name and generic drug manufacturers. These actions aim to stimulate competition, improve access to affordable medications, and ensure a balance between innovation and affordability in the healthcare system. In 2016, the Prime Minister of India proposed the "Jan Aushadhi" scheme[13, 14]. These are the pharmacies that provide no other drugs other than generic medicines. It promoted these medicines as well as provided work to Indian PSUs (Public Sector Undertakings) as well. He also persuaded the chemists to sell only generic medicines even if an innovator’s medicine had been prescribed to the patients. This proposal was declined by the Drug Technical Advisory Board (DTAB), which was seen as an offence to their lack of confidence in their PSUs and the quality and safety of the medicines manufactured by them, creating a negative impression on generic medicines[15]. However, the real reason for DTAB's turning down this request was the economy. There are over 1,00,000 branded medicines in the Indian market, but there aren’t enough generic names to cover all medicines. The other reason was the outreach of "Jan Aushadhis". For a population of over 120 crores, there are only around 3000 ‘Jan Aushadhis’

functioning in India. The stores might expand rapidly, but it was not easy to reach the rural areas so quickly. Also, it should be noted that several physicians doubted the effectiveness of these medicines and hence stopped them from prescribing generics to their patients.

3. Process of approval

The approval process for generic drugs differs from that of innovator drugs. While innovator drugs require a New Drug Application (NDA) for approval, generic drugs go through an Abbreviated New Drug Application (ANDA) process. When seeking approval through an ANDA, generic drug manufacturers do not need to provide extensive clinical data on the safety and efficacy of the active pharmaceutical ingredient (API). Instead, they rely on the assumption that the API in the generic drug is already established as safe and effective based on previous studies conducted for the innovator drug. The main requirement for an ANDA is to demonstrate bioequivalence. Bioequivalence means that the generic drug product must have the same rate and extent of absorption as the innovator drug when administered at the same dosage. This is typically assessed through comparative in vivo or in vitro studies, which compare the generic drug to the innovator drug. By proving bioequivalence, the generic drug manufacturer can establish that their product performs similarly to the innovator drug. This approach allows for a streamlined approval process for generic drugs, as it leverages the existing safety and efficacy data of the innovator drug while focusing on demonstrating equivalence in terms of drug absorption. It's important to note that although generic drugs are not required to provide clinical data on safety and efficacy, they still need to meet stringent quality standards regarding manufacturing, labelling, and packaging to ensure that they are equivalent to the innovator drug in terms of quality and performance [16-22].

The criteria for therapeutic equivalence of a generic drug are determined by regulatory agencies, such as the U.S. Food and Drug Administration (FDA). These criteria ensure that the generic drug is therapeutically comparable to the innovator or patented drug. Here are some of the key factors considered for establishing therapeutic equivalence [23]:

Bioequivalence: As mentioned earlier, the generic drug must demonstrate bioequivalence to the innovator drug. This means that it should have similar pharmacokinetic properties, including the rate and extent of drug absorption, as well as similar blood concentration profiles when compared to the innovator drug [24-27].

Active Ingredient: The generic drug must contain the same active pharmaceutical ingredient (API) as the innovator drug. The API is the component responsible for the drug's therapeutic effect [28-30].

Strength: The generic drug should have the same strength or concentration of the active ingredient as the innovator drug. This ensures that patients receive the intended dose and therapeutic effect.

Pharmaceutical Formulation: The generic drug should have the same dosage form (e.g., tablet, capsule, injection) as the innovator drug. It should also be formulated using similar excipients (inactive ingredients) to ensure consistent performance and safety.

Route of Administration: The generic drug should be administered using the same route (e.g., oral, topical, intravenous) as the innovator drug unless otherwise specified.

Labelling: The generic drug's labelling should provide the same essential information as the innovator drug, including indications, contraindications, warnings, precautions, and dosage instructions. This ensures that healthcare professionals and patients have access to accurate and comprehensive information.

Manufacturing Standards: The generic drug must be manufactured in compliance with Good Manufacturing Practice (GMP) regulations set by regulatory authorities. This ensures that the drug is consistently produced with high quality, purity, and safety standards.

Meeting these criteria is essential for a generic drug to be considered therapeutically equivalent to the innovator drug. Regulatory agencies review the data and evidence provided by the generic drug manufacturer to assess if these criteria are met before granting marketing authorization for the generic drug [31-33]. While pharmaceutical equivalence is relatively easy to know, the bioequivalence concept is tricky to understand. AUC is estimated by estimating the AUC and the maximum concentration of the drug (C_{max}). A generic drug is considered bioequivalent to its over-the-counter product only if:

- The confidence interval (CI) of the mean AUC=90%
- The relative mean C_{max} = 80%-125%.

The criteria remain identical for bioequivalence studies of branded drugs with reformulation or manufacturing changes. Bioequivalence is measured by conducting crossover studies on 12 patients, in which 6 are administered the generic drug before the innovator drug, with a brief washout interval. The remaining 6 patients are given the innovator drug first, a brief washout period is taken in between, and then the generic drug. The C_{max}, time is taken to attain C_{max}, and AUC is determined by taking blood samples from the individual patients. If the drug levels vary by more than 10%, they do not meet the bioequivalent criteria of the FDA. The allowable limits of bioequivalence between the drugs are not more than 3.5%. The approval process for a generic drug [34, 35] was illustrated in Fig. 1.

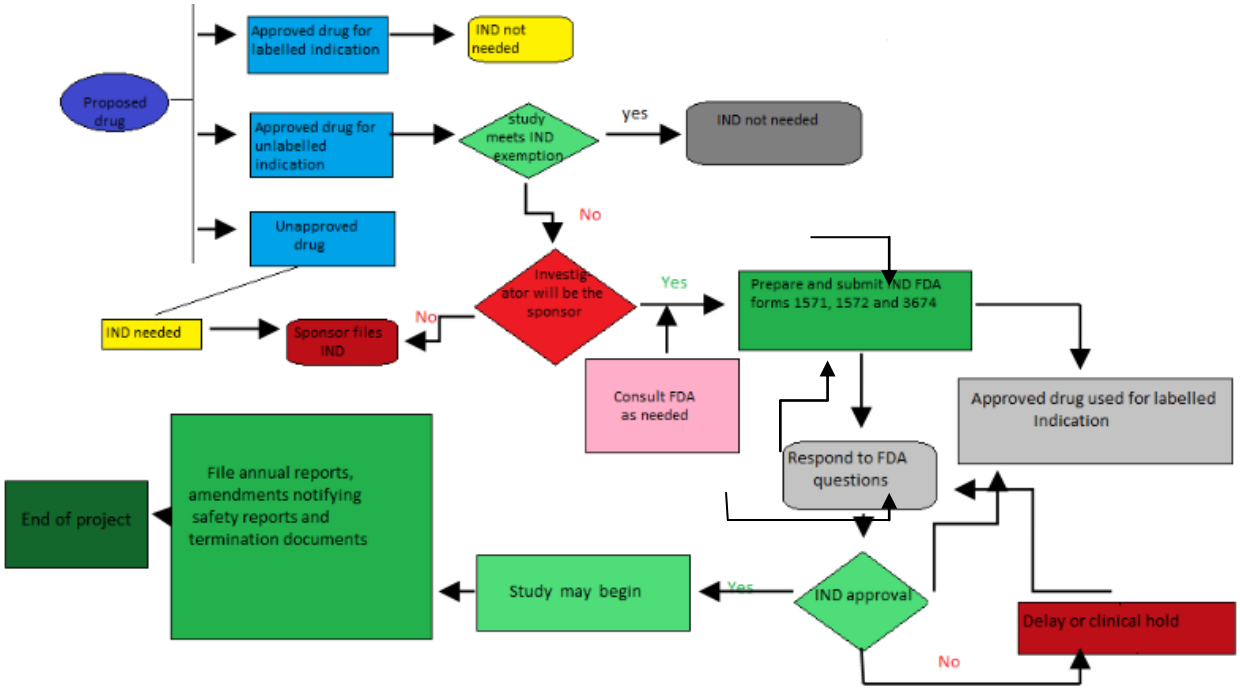

Figure 1. The approval process for a generic drug

4. Process of ANDA approval

4.1. ANDA certification clauses

There are mainly four paragraphs/clauses obligatory for the endorsement of ANDA [36]. They are:

- If the required information in the patent has not been filed, the FDA may approve the ANDA immediately, and more than one applicant can enter.
- The patent has expired, the FDA may approve the ANDA immediately, and more than one applicant can enter.

- If the patent has not expired and will perish on a specific date, the FDA might approve the expiry date of it and more than one applicant can enter.
- The patent is not valid or none infringed upon by the generic applicant. The generic applicant's file is sent to the patent holder.

5. Myths and facts

Many myths and rumors were spread about the generics at the very beginning of their era. Some of them are mentioned below[37, 38]:

- They were thought to be duplicates of the pioneer drugs due to the changes in their brand names, sizes, and shapes.
- They were supposed to be rejected as fake drugs, which were removed by the manufacturing company due to their low prices.
- They were assumed to be ineffective owing to their low cost, as people believed that the cost of drugs determined their effectiveness.
- They were supposed to be manufactured in sub-standard facilities, unlike the branded ones, which are assumed to be produced in modern manufacturing facilities.
- The Orange Book contains a catalogue of drugs and pharmaceutical goods accepted by the U.S. Food and Drug Administration (FDA) that are harmless and efficient. Although commonly called the Orange Book, its official name is "Approved Drug Products with Therapeutic Equivalence Evaluations".
- This book doesn't include information on drugs, which are only accepted as harmless; they must also be effective. Medicines that have been aloof from the market due to safety and efficacy concerns are not in the Orange Book. However, a drug that is at present subjected to regulatory action may still appear in the Orange Book.

The similarities between the innovator and the generic [39] were summarized in Table 1.

Table 1. Resemblances and variations between the innovator drug and the generic drug

Similarities	**Dissimilarities**
Active pharmaceutical ingredient	Size
Strength	Shape

Dosage form	Cost
Route of administration	Inactive excipients
Applications	Process of approval.

6. Advantages

The favourable of generic drugs as summarized [40]:

- These generic medicines provide profit to consumers and pharmaceutical companies.
- These may be supplied by more than one company.
- It consumes less time and little money during approval.

7. Drawbacks

The pitfalls of generic drugs are illustrated below [41]:

- Maybe a few differences through reformulations.
- It is not conceivable in all cases as it takes a long time for the patent to expire.
- Some errors may arise during the bioequivalence studies, which can ultimately affect the results.
- Some patients may be allergic to new flavours, colours, etc.

8. Conclusion

From this review, it is concluded that the aim of bringing generic medicines to the world pharmaceutical market was to lower the prices, which is helpful for the improvement of health all over the globe. These generic medicines are marketed after the patent expiry of the innovator drugs. At present, 50% of all prescriptions are filled with these generic drugs. In the generic market across the globe, India's share is about 35%. Hence, India has a high contribution to the global market for generic medicines.

Conflict of interest

Nil

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Nil

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