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Barriers and Challenges with the regulatory filing of generic medication in the United States.

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Abstract

Generic medications serve as cost-effective alternatives to branded drugs, offering the same quality, effectiveness, and safety. They have a well-established track record for safety and efficacy, making them crucial in expanding global access to affordable healthcare. However, stringent standards set by the US Food and Drug Administration (USFDA) can pose challenges for generic drug approval, causing delays in the registration process. The USFDA has one of the most rigorous regulatory authorities globally, and the application submitted for generic drug registration is called an Abbreviated New Drug Application (ANDA). The USFDA's primary responsibility is to ensure that the drug's development, production, and testing adhere to stringent regulations while maintaining detailed records.
To streamline the registration process, the International Conference on Harmonisation (ICH) has created a consistent framework for submitting applications, helping generic drug manufacturers meet the requirements for market approval in the US.

This study aims to identify the regulatory challenges associated with generic drug approval in the United States. By extensively analyzing data from regulatory websites, government sources, and relevant literature surveys, a comprehensive understanding of the generic medicine approval and registration process in the country has been established. The examination of various criteria for generic drug clearance in the US has revealed that the FDA's regulatory standards are highly effective and well-defined, ensuring the safety and efficacy of these cost-effective alternatives. However, it is crucial for manufacturers to meet these rigorous standards to facilitate the availability of generic medications and enhance global access to affordable healthcare options.

Keywords: USFDA, ICH, Generic Drug, Safety, Efficacy.

Introduction:

The interpretation of a "generic drug" varies between countries due to variations in legal regulations concerning the procedure for approving generic pharmaceuticals and whether the definition encompasses original drugs with expired patents. Some countries have established their own official definitions at the national level, while others rely on definitions provided by government regulatory agencies such as the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), or the World Health Organization (WHO).

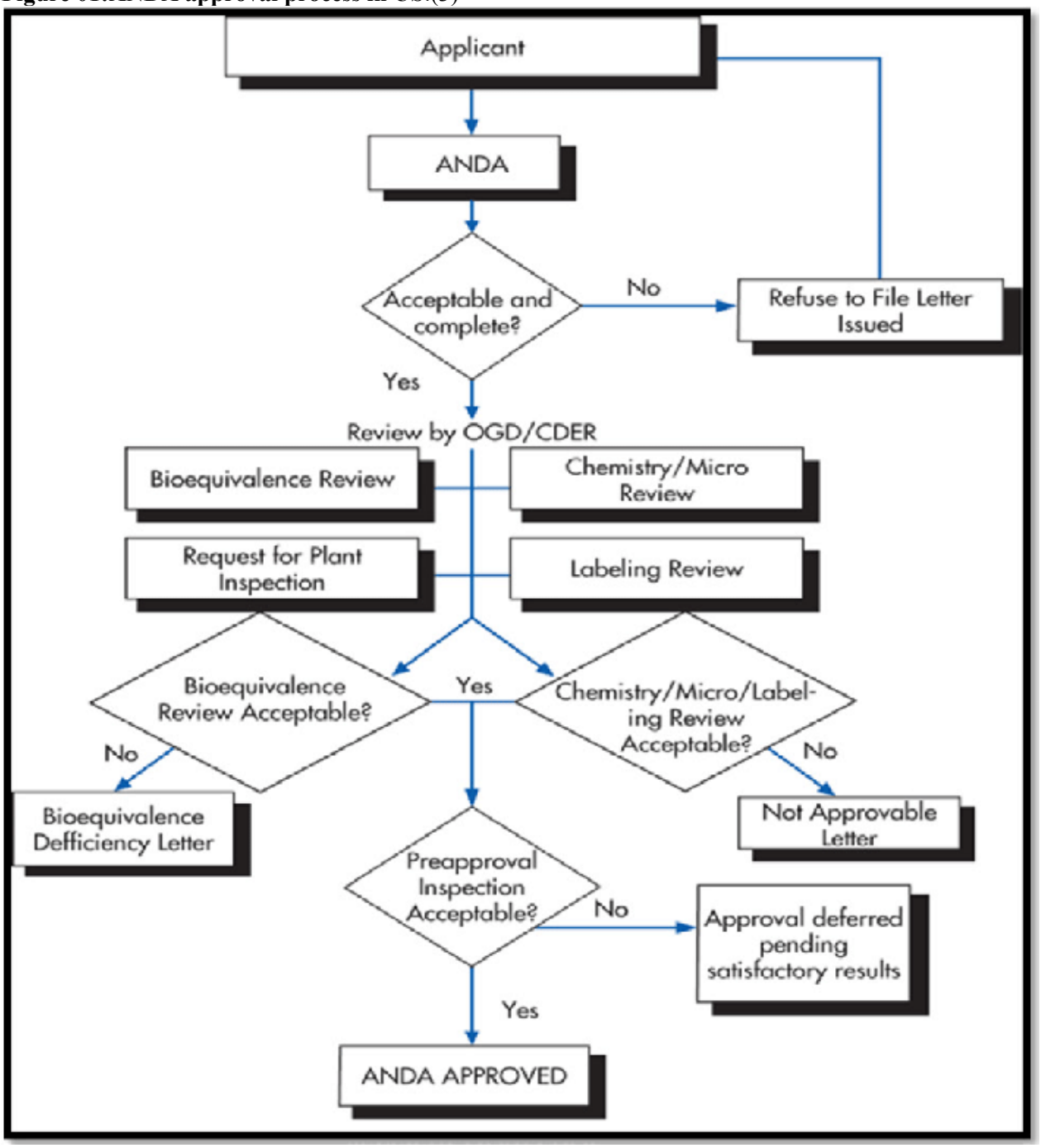
However, most definitions share a common characteristic: a generic drug refers to a medicinal product that can be manufactured and sold by companies other than the one that initially invented it, typically because the original patent has expired. (1) To ensure the well-being and safety of the public, the government implements various laws and regulations within the pharmaceutical industry. As among the most tightly regulated industries, the pharmaceutical sector strives to determine and create generic drug products that can be customized to fulfill a wide range of market needs. In order to safeguard their citizens, governments hold the responsibility of establishing regulatory bodies with strict criteria for medicine and quality control within their corresponding jurisdictions. Recognizing the need for broader uniformity, representatives of Japan, the European Union (EU), and the United States convened the International Conference of Drug Regulatory Authorities (ICDRA) arranged by the World Health Organization (WHO).

Informal talks throughout the forum underlined the importance of unifying standards relevant to new innovative drugs, leading to the creation of of the International Conference on Harmonization of Technical standards for the Registration of Pharmaceuticals for Human Use (ICH). The EU, Japan, and the United States is a cooperating party in the ICH with observers from WHO, the European Free Trade Association (EFTA), and Canada. Over the past decade, various intergovernmental organizations at regional and interregional levels have initiated an attempt to uniform different aspects drugs regulation. These endeavours have been primarily driven by the growth of international trading of pharmaceuticals and the increasing technological regulation's complexity concerning drug efficacy, safety, and quality. With the evolving regulatory landscape in the pharmaceutical industry, the evaluation of drugs for quality control and trade has been developing considerably more. Regulatory framework and standardized tools serve as a foundation for implementing laws, which in turn provide the legal framework for drug control. Across the globe, there are over 100 countries that have established pharmaceutical legislation and regulatory requirements.

When submitting regulatory dossiers on a global scale, it is essential to possess an understanding of country-specific guidelines and norms as a prerequisite requirement.(2) The United States, which had no regulations in the 18th century but today among the most rigorously governed and respected by regulatory organizations in the world, is a significant market for the pharmaceutical sector. The Food and Drug Administration (FDA), operating under the U.S. Department of Health and Human Services (DHHS), plays a crucial role in regulating the drug approval system in the US. The FDA consists of six product centres, which also includes the Centre for Drug Evaluation and Research (CDER).

In United States, the process drug product registration is primarily divided two categories of submissions: the New Drug Application (NDA) and the Abbreviated New Drug Application (ANDA). The ANDA is a filing for generic medicines that seek marketing clearance and are genuine or near imitations of approved pharmaceuticals. The procedure of permission for ANDA is demonstrated in the image that comes with this article. (**Fig.01**)

Figure 01:ANDA approval process in US.(3)



The U.S. drug regulatory system has been shaped by past adversities that resulted in the loss of thousands of lives and injuries. The currently operational American drug regulation system is looked to as a global norm that assures the safety and effectiveness of pharmaceuticals. The FDA started working on guidelines for the interchange of electronic information in the 1990s, recognizing the ineffectiveness of paper-based approach for transferring enormous amounts of information together with the necessity to produce a standard format that is useable by the FDA, the European Union, and Japan. As a result, pharmaceutical companies' applications for products and associated materials can now be submitted electronically to regulatory agencies worldwide, improving efficiency, while each regulatory agency maintains its own rigorous standards for evaluating products.

The FDA task force acknowledged that every medication entails a certain degree of risk and, therefore, proposed the implementation of risk management principles in a more methodical manner to supervise the process of drug development and marketing.(4)

Generic Drug Approval Process in USA:
Within the American medical system, generic drugs are of utmost importance. To promote the availability of generic drugs, Presently, the FDA gives a window for commercial exclusivity to the original firm that gets clearance for a generic version of a branded medication. This exclusivity period spans 180 days during which only two entities could market the medicine: the original manufacturer of the branded drug and the first generic manufacture. After the exclusivity period concludes, other generic companies are allowed to enter the market. There are two routes by which a medication might gain FDA approval and become available in the market. Firstly, if the drug is a new and unique product, the inventor is needed to provide the information for review by the FDA through a new drug application (NDA). Secondly, if the drug is a generic counterpart of a preexisting drug, the producer of the generic drug product might submit an abbreviated new drug Application (ANDA).
A generic medicine must meet several criteria to gain FDA approval, including (5) :

- Containing the identical active component as the original medication. (Although inactive ingredients may vary)
- Possessing the same in dose form, potency, and method of delivery.
- Having identical instructions for usage as the original medicine.
- Demonstrating bioequivalence, meaning it performs in a similar manner to the original medicine in terms of absorption and distribution in the body.
- Meeting the innovative drug's identification, strength, purity, and quality criteria.
- Products being manufactured in accordance with the stringent standards outlined by the FDA's GMP regulations, which are also obligatory for original drug products.

The Hatch Waxman Act: The US Drug Price Competition and Patent Term Act, generally regarded as "Hatch-Waxman Act," which was established in the year 1984 to streamline the process of recognizing generic drugs in the United States. Under this act, generic companies were granted the ability to present Abbreviated New Drug Applications (ANDAs) for drugs that had already been approved. The term "abbreviated" indicates that the generic drug manufacturer is not required to repeat the tests proving the medication's effectiveness and safety, as it is already done by the innovator.(6)
A generic drug producer can submit their application in accordance with the provided regulations:
(I) Manufacturers of generic drugs are accountable to verify that they have not submitted any patent information related to the brand name drug to the FDA.

(II) The generic drugs maker requires verify that the patent stated for the drug is no longer active or expired.
(III) The generic drug manufacturer must confirm that the listed patent will expire on that specific date, and until that date arrives, the generic drug will not be introduced into the market for sale.; or
(IV) It is the generic drug manufacturer's responsibility to demonstrate that either the patent is invalid or there will be no infringement by the manufacturer, use, or sale of the new drug for which the ANDA was filed.(7)

CHALLENGES IN REGULATORY FILLING OF GENERIC DRUG IN US:

This chapter explores several legal, legislative, and regulatory aspects along with miscellaneous considerations related to generic drug development and approval. It is crucial to understand that there is no strict demarcation between the "scientific," "regulatory," and "legal" domains in the present circumstance. While some of the discussed disputes may have scientific foundations, they have often arisen within the framework of litigation. In recent years, several significant amendments have been made to the Federal Food, Drug, and Cosmetic Act (FDC Act) that have had an impact on generic drugs. Some of these amendments include:(8)

- Food and Drug Administration Modernization Act (FDAMA), gained approval in 1997
- Best Pharmaceuticals for Children Act (BPCA), implemented in 2002
- Paediatric Research Equity Act (PREA), enacted in December 2003
- Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA)
- Food and Drug Administration Amendments Act of 2007 (FDAAA)
- QI Program Supplemental Funding Act of 2008 (QI Act)
- Biologics Price Competition and Innovation Act of 2009 (BPCIA)

PUBLIC PETITIONS AND LEGAL OBSTACLES TO FEDERAL APPROVAL FOR GENERIC DRUG:

A citizen petition serves as the official procedural means for any person or organization to formally request the FDA to either initiate or abstain from certain specific actions. The guidelines for citizen petitions are established within the regulatory framework of the FDA.(9)
Unsurprisingly, manufacturers of innovative drugs have frequently contested the FDA's approving choices, or even expected approvals, for generic equivalents of their goods. In many instances, these manufacturers have submitted citizen petitions to the FDA, presenting arguments against granting anticipated approvals for generic form of their drugs. Additionally, generic drug companies can also file citizen petitions for various reasons, such as ANDA suitability petitions and petitions related to disputes over 180-day exclusivity.
When a generic drug manufacturer submits a citizen request to the FDA with the aim of influencing the approval of generic products, it has multiple applications. Firstly, there is a possibility that the FDA might accord the desired guidance, although this has been uncommon in most cases. Secondly, even if the FDA refuses to provide the relief, the review of a citizen appeal may lead to a drawn-out procedure that might postpone the generic product's approval. And particularly, a citizen petition may help to contradict the commonly held belief by the FDA and other corresponding agencies that the individuals who appeal agency decisions in court have not exhausted all administrative options available. Courts may require this "exhaustion" as a means to conserve judicial resources, ensuring that they aren't burdened with cases that could have been resolved through seeking relief from the administrative agency initially. In several instances, innovator drug sponsors, who have been adversely affected, have pursued legal recourse to challenge the FDA's decisions regarding ANDA approvals. In certain cases, the FDA has rejected a genuine citizen's appeal while nevertheless consenting to an ANDA. In similar prior circumstances, the FDA has not taken any action on the appeal regardless of issuing the disputed ANDA approval, leading the innovator company to interpret the FDA's approval as effectively denying their petition. Generally, the innovator company has started a lawsuit against the FDA in an effort to block the agency's authorization of the generic product. Most often, the concerned generic companies were previously authorised to join the action as a party to preserve their money-related interest linked with their separate ANDA approvals.(10) The FDA is barred from prolonging the authorization process of an active ANDA or 505(b)(2) NDA unless and until a request is submitted as a citizen petition and the FDA concludes that a hold up is essential for safeguarding the public health. In the event that the FDA determines a hold up to be necessary, within 30 days of reaching this decision, it must notify the sponsoring organization of the pending application. The notification must provide a concise overview of the particular substantive concerns that have been raised.(8)

EXCLUSIVITY CONCERNS

Five-Year New Chemical Entity Exclusivity

According to the Hatch-Waxman Amendments, an NDA is submitted by an organization for a drug substance that consists a "new chemical entity" (NCE), defined as an active component not previously used in a recognised drug substance, they are granted a 5-year exclusivity period. This exclusivity period commences upon NDA approval and prevents the FDA from considering any ANDAs (Abbreviated New Drug Applications) or 505(b)(2) NDAs (New Drug Applications) referring to the original product for evaluation.(11) However, if the sponsor of an ANDA or 505(b)(2) NDA chooses to challenge a FDA's list of patents -"Orange Book" by filing a Paragraph IV certification and arguing that the patent is either invalid or not infringed, the original product may be protected, they can file the ANDA or 505(b)(2) NDA four years after first NDA approval date. This provision likely to reduces the approval process by one year for the ANDA or 505(b)(2) NDA patron.

Three-Year Exclusivity for Product "Improvements"

Furthermore, The Hatch-Waxman Amendments guarantee a period of three years of protection to NDA sponsors, during the period when generic competition is prohibited, for the issuance of an NDA or additional NDA containing an active component that has already been authorised. This exclusivity period is applicable when new clinical studies have been used to support the approval (excluding bioavailability studies) that are considered crucial for the approval process.(11) Unlike the 5-year exclusivity period granted to new chemical entities (NCEs), Limitations do not apply to the submission of ANDAs or 505(b)(2) NDAs for the Food and Drug Administration (FDA) under the 3-year exclusivity clause. Rather, during this period it merely prohibits making a final decision on an ANDA or 505(b)(2) NDA.

Seven-Year Orphan Drug Exclusivity

The orphan drug exclusivity provision prohibits the FDA from granting ultimate permission of an ANDA during a 7-year period with respect to an orphan product.(12) Moreover, It curbs the FDA's ability to accept a 505(b)(2) NDA for the medicines that are similar or somewhat equivalent to another drug, As long as another medication can establish clinical superiority over the drug entitled to exclusivity.(13)

The existence of orphan drug exclusivity does not hinder the FDA from providing authorization to an ANDA for an indication that is no more safeguarded by orphan exclusivity, provided that a different indication still retains orphan exclusivity and is omitted from the labeling of the generic drug product.(8)

180-Day Generic Drug Exclusivity

The Hatch-Waxman Amendments establish a 180-day exclusivity time interval, wherein the initial sponsor of a Paragraph IV ANDA (which challenges a patent mentioned in the Orange Book for the innovator product being replicated) is granted exclusive rights to be the sole generic product for sale in this time span.(11) In the previous years, there has been a lot of dispute over this rule., with several unresolved issues remaining.

In the year 2003, the MMA i.e., Medicare Prescription Drug, Improvement, and Modernization Act was introduced as a significant alteration to the FDC Act (Federal Food, Drug, and Cosmetic Act) pertaining to 180-day exclusive rights. The amendments mainly pertain circumstances where the initial Paragraph IV ANDA, the FDA received the application after the 8th of December 2003, and was based on an earlier reference product, with few minor exceptions. As a result, there is a declining number of ANDAs that are subject to the "old" 180-day exclusivity regulations at the time of writing. The discussion following this will address the "old" ANDAs and the "new" and are clearly coordinated by the MMA regulations.

Six-Month Pediatric Labeling Exclusivity

When a revolutionary medicine sponsor undertakes a clinical research trial that investigates the safety or effectiveness of the medicines they give to a pediatric population, they qualify for an additional 6-month exclusivity period. This extension is appended to the remaining period of an unexpired patent stated in the Orange Book or an existing nonpatent exclusivity of 3, 5, or 7 years.

The area of concern is how pediatric exclusivity impacts the ability of an ANDA or 505(b)(2) NDA sponsor for securing the ultimate stamp of approval within the 6-month exclusivity period. It is forbidden to grant final approval to an applicant during the 6-month paediatric exclusivity period if they haven't already done so before the end of the underlying patent or exclusivity period, according to the FDA's interpretation of the somewhat ambiguous Legal terms. For example, if an ANDA sponsor faced hindrances in obtaining final approval due to a Paragraph III patent certification or ongoing litigation stay of 30 months, they would be unable to secure its final authorization until after the 6-month pediatric exclusivity period ended. Furthermore, if an ANDA sponsor originally received clearance but later had it modified to preliminary approval due to a setback in patent litigation, they would also be strictly forbidden from achieving official authorization across the pediatric exclusivity time period. Despite the fact not all conceivable cases are currently formally addressed by the FDA or the courts, it is likely that they employ exactly the same logic to postpone final approval until after the 6-month pediatric exclusivity time limit has ended.(8)

Antibiotics

When the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic (FDC) Act were passed in 1984, Comparatively to other medications, antibiotics were subject to distinct provisions of the FDC Act's regulation, and these existing provisions already allowed for abbreviated approvals similar to ANDAs. As a result of it, according to the Hatch-Waxman Amendments of 1984 the initial legislation did not extend the ANDA process, orange Book patent listing, patent certification, 30-month deferral of ANDA final approval, and the 3- and 5-years of exclusivity restrictions to antibiotic medications. However, it should be noted that the term of the patent restoration measures stated in Title II of the Hatch-Waxman Amendments did embrace antibiotics.

In the year1997, the FDA Modernization Act (FDAMA) revoked the previous Section 507 of the Federal Food, Drug, and Cosmetic (FDC) Act, which pertained to the approval process for antibiotics.(14) Applications for antibiotics that had been approved prior were categorized as approved New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs) based on their form and content. The FDA, through guidance, offered an interpretation of the newly established statutory provision. According to this interpretation, drug products that includes an "old" antibiotic API, which had been the subject of a petition submitted to the FDA before November 21st 1997, whether as a standalone ingredient or in combination with another API, would be classified as an "old" antibiotic.(15)

In the year 2008, Federal Food, Drug, and Cosmetic (FDC) Act received significant revisions within the QI Act, notably addressing the restrictions around "old" antibiotics.(11)

PATENT-RELATED ISSUES

Hatch-Waxman Patent Listing Rules' Applicability

The Hatch-Waxman Amendments mandate that every New Drug Application (NDA) sponsor must submit the necessary information to the FDA for the purpose of listing in the Orange Book "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." If a patent is issued after the approval of the New Drug Application (NDA), it is required that the patent related information be submitted to the FDA within 30 days of the patent's issuance.(11) The regulations implemented in 1994, the FDA provided its interpretation of the Hatch-Waxman Amendments, specifically regarding the listing of patents in the Orange Book. According to this interpretation, drug substance patents that make reference to a part of the registered drug product are eligible for listing. Drug product patents may be mentioned if they suggest the authorised drug product itself, whereas method-of-use patents can be listed if they claim approved indications or additional circumstances of use.

It should be emphasised that process patents cannot be mentioned in the Orange Book. Nevertheless, for every formulation, composition, or method-of-use patent filed for Orange Book listing (excluding drug substance patents), the NDA sponsor must include a statement confirming that the patent incorporates the formulation, content, and/or mode of use of the drug product for which approval is being sought or has been previously granted.(16)

In 2001, the Federal Circuit issued a ruling that prohibited an Abbreviated New Drug Application (ANDA) sponsor from suing a New Drug Application (NDA) sponsor to request the removal of a patent listed in the Orange Book. As a response to this ruling, the Federal Food, Drug, and Cosmetic (FDC) Act was amended in 2003 by the Medicare Prescription Drug, Improvement, and Modernization Act (MMA). This amendment granted the right for an ANDA or 505(b)(2) NDA sponsor, who faces a patent infringement lawsuit based on a Paragraph IV certification, to file a counterclaim seeking the removal of the patent. Such a counterclaim can be based on the argument that the patent does not cover the approved drug or a method of using the approved drug.

It's vital for remembering that no damages may be awarded on the counterclaim, and there is no provision for an independent basis of action for patent delisting.

In 2003, the FDA enacted major amendments to its policy on patent listing in anticipation of these changes.(16) The existing requirements, applicable to patents submitted for listing in the Orange Book on or after 18th August 2003, include certain prohibitions. These prohibitions state that patents claiming packaging, such as bottles or containers, intermediates, and metabolites of the active ingredient, cannot be submitted for orange Book listing. However, it is emphasized by the FDA that product-by-process patents are eligible for inclusion in the Orange Book.(17)

The FDA's amendment of its patent listing policy in 2003 has successfully handled many earlier concerns surrounding the scope of patents filed for the addition in the Orange Book. Moreover, there are still significant numbers of patent that were submitted to FDA under prior regulation, and it seems that some of these patents may not meet the current criteria for listing. In recent years, NDA sponsors have requested the FDA to remove certain patents from the Orange Book, possibly driven by concerns over potential antitrust liability arising from inaccurately listed patents.

Hatch–Waxman Patent Infringement Litigation

According to present conception of 180-day generic medication exclusivity, it comes into effect by complying with the filing of a Paragraph IV Abbreviated New Drug Application (ANDA). Although a thorough discussion of patent infringement litigation is beyond the objective of the following write-up, it is worth stressing two essential factors:

Firstly, it should be acknowledged that the sponsor of a Paragraph IV ANDA necessarily confronts a significant chance of getting sued for patent infringement within the 45-day deadline specified by the Hatch-Waxman Act. While it might be a strategic choice for ANDA sponsors to proactively file Paragraph IV ANDAs and pursue patent challenges, the substance of each challenge should be considered objectively. It is crucial to emphasise that in some situations, Paragraph IV ANDA applicants have been ordered to pay hefty lawyers'

costs of the NDA sponsor and patent owners when their patent challenges were ruled to lack substance. These legal expenses may easily amount to millions of dollars.

Secondly, it is crucial to realise that in some situations, Paragraph IV ANDA applicants have faced patent infringement actions within the 45-day timeframe permitted by the Hatch-Waxman Act, even for inventions not mentioned in the Orange Book. The Federal Circuit has recognised that a patent holder may bring a declaratory judgment action, arguing that its method patent (ineligible for orange Book inclusion) will be infringed by the ANDA sponsor. Additionally, there have been cases when Paragraph IV ANDA applicants were sued, again within the 45-day deadline, for claimed infringement or encouragement to infringe orange Book method-of-use patents that claim unapproved uses. However, the Federal Circuit has supported district court rulings awarding summary findings of non-infringement in such circumstances.(8)

Copyrighted Labeling:
In an effort to hinder generic competition, an innovative medicine manufacturer tried to obtain copyrights for key portions of its FDA-approved labeling and later requested a prohibition against the ANDA sponsor, claiming copyright infringement. However, the court finally dismissed this argument, holding that the necessity under the Hatch-Waxman Act for similar labeling takes precedence over copyright law. Nonetheless, the court acknowledged the potential of copyright infringement in other situations, such as advertising, where the use of copyrighted content may be linked.(18)

Conclusion:

In conclusion, the regulatory filling process for generic drugs in the USA is a complex and challenging process that involves numerous hurdles. These challenges include issues with the FDA's approval process, patent litigation, citizen petition, and exclusivity issues, etc. Additionally, the high cost of research and development and increasing competition from overseas manufacturers present further challenges for regulatory filling of generic drug bring the products to market.

Despite these obstacles, the generic drug industry in the USA tends to grow and play an important role in increasing access to affordable medicines for patients. Ongoing efforts to improve the regulatory process and address issues related to drug shortages and bioequivalence testing will be critical in ensuring continued growth and success for this vital sector of the pharmaceutical industry.

Overall, the regulatory filling process for generic drugs in the USA remains a complex and challenging endeavor, but the potential benefits of increased access to affordable medicines make it a worthy pursuit for pharmaceutical manufacturers and regulators alike.

Conflict of Interest Statement:

The author declares that there are no conflicts of interest related to this review manuscript. We have no financial, personal, or professional affiliations that could potentially bias our work or the interpretation of the content within the manuscript. This includes, but is not limited to, any financial relationships with organizations that may have an interest in the subject matter discussed in this review.

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