

EVALUATING THE HATCH-WAXMAN AMENDMENT'S INFLUENCE ON FDA'S GENERIC MEDICATION APPROVAL PROCESS

Subhadarshini Bhagyashree¹, R Kamaraj²

¹Department of Pharmaceutical Regulatory Affairs, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur-603203, Chengalpattu, Tamil Nadu, India

²Head of Department, Department of Pharmaceutical Regulatory Affairs, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur-603203, Chengalpattu, Tamil Nadu, India.

Email: kamarajr@srmist.edu.in

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Abstract

Generics are drugs marketed by their chemical names, not brand names or chemical compositions. Generic drugs are less expensive. The United States Food and Drug Administration (USFDA) allows generic drugs when patents expire or owners renounce their rights. Competition lowers drug prices once generics are accessible. The Food and Drug Administration monitors the drug business. The Senate confirms the Food and Drug Administration Commissioner's nomination. Food and medications are controlled less than lasers, cell phones, and condoms. The Food & Drug Administration designated 1938–1962 medications as "pioneer goods." Kefauver-Harris requires all drug firms to submit accelerated applications (Abbreviated New Drug Application). Medicaid and Medicare modifications to the Social Security Act popularised generic medications. The 1984 law accelerated the launch of generic pharmaceuticals law and boosted generic drug introduction. The 1992 Generic Medication Enforcement Act combats fraud and misuse. The 1984 law accelerated the launch of generic pharmaceuticals.

Keywords: Generic, Hatch-Waxman Act, United States Food and Drug Administration, Orange Book, Amendments, Medicare Modernization Act.

INTRODUCTION

A generic drug is described as "a drug product that is equivalent to a brand/reference-listed drug product in dosage form, strength, quality and performance attributes, and intended use". Generic drugs are those that are sold under their chemical names as opposed to their brand names or chemical composition. [1] Drugs that are "identical, or bioequivalent," to their brand-name counterparts in terms of "dosage form, safety, strength, mode of administration, quality, performance characteristics, and intended use" are considered to be generic by the US Food and Drug Administration (FDA). [1,2]. If the patent expired or the proprietor renounced his rights, the FDA authorised generic drugs. Once a generic drug is available, competition grows, lowering generic and brand-name prices. Generic drugs are less expensive. Generics have safety and effectiveness data. The first active ingredient's benefits are known; thus, the maker should analyse the generic medicine's pharmacokinetic profile. [3].

United States Food and Drug Administration (USFDA)

The FDA, or U.S. Food and Drug Administration, is a government organisation in the United States that oversees the safety of food and drugs. Tobacco products, dietary supplements, pharmaceuticals (both prescription and over-the-counter), vaccines, biopharmaceuticals, blood transfusions, medical devices and electromagnetic radiation emitting devices (ERED), cosmetics, animal diets and feed, and veterinary goods are all under the FDA's watchful eye. [4].

FDA implements the Food, Drug, and Cosmetic Act and Public Health Service Act Section 361. Lasers, mobile phones, and condoms are regulated, as well as pet illness treatment and donated sperm for assisted reproduction. The President nominates and the Senate confirms the FDA's Food and Drugs Commissioner. The Commissioner reports to the Secretary of HHS. [5].

Legislative History of Generic Drugs

Bioequivalence means that the generic medicine is "substantially comparable to the pioneer drug product" (usually a branded drug) in terms of dosing, administering, potency, reliability, tolerability, and functionality. Clinically similar generic versions of drugs must be available.[6].

Before Hatch -Waxman Act

- Generic medication has been controversial since the beginning of American pharmacy and medicine. The American Pharmacists Association (APhA) created the National Formulary in 1888 to combat the spread of fake pharmaceuticals. [7].
- The Federal Food and Drug Act was passed in 1906 by Congress. Labeling was necessary to prevent malpractice, and the government might take action if a product caused death or serious damage. Roosevelt signed labelling legislation. This began the FDA's oversight of pharmaceuticals.[8].
- In 1928, generic medications were used instead of branded ones. A well-known pharmaceutical publication questioned this strategy and warned about generic replacement. Several popular drugs have reached the market.[7].
- After the 1937 Elixir Sulphanilamide disaster, Congress created the FD&C Act (FDCA). In 1938, pharmaceutical businesses were required to submit their products to the FDA for testing. FDCA increased pharmaceutical control, however patent requirements weren't always satisfied.[8].
- Durham-Humphrey split prescription and OTC drugs in 1951. In turn, inventory and counterfeiting issues occurred. APhA enforced brand or generic pharmaceuticals from a recognised producer using anti-substitution regulations and regional legislation. Regulations hampered generics and substitute products.[9].
- The Kefauver-Harris Drug Amendments were enacted into law in 1962. These programmes help pharmaceutical companies show the FDA a product's health and efficacy. All 1938-1962 pharmaceuticals were new. When a product fails, comparable items are also removed from shops.[10].
- Kefauver-Harris All producers of medications developed between 1938 and 1962 are required to file an Abbreviated New Drug Application (ANDA). FDA accepted "literature-based" NDAs after 1962. This showed a generic product's safety and efficacy. Many opposed Kefauver-Harris. *Upjohn v. Finch* (1970) found that financial success doesn't reflect a drug's safety and efficacy.[11].
- The 1965 Medicaid and Medicare reforms and 1967 statutes made brand-name drugs cheaper. Congress mandated that government health and welfare programmes prioritise generic alternatives to minimise price gouging due to market competition.[12].

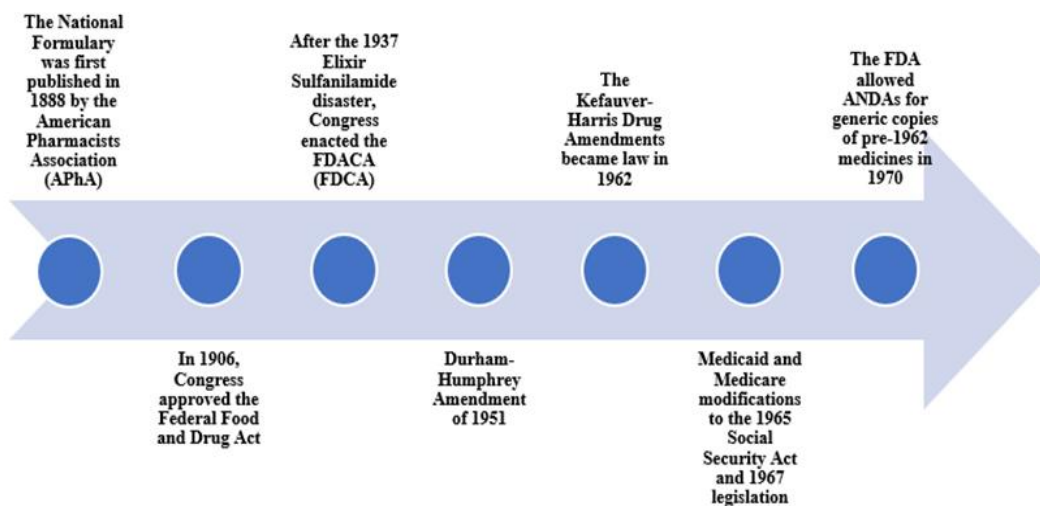


Figure 1. Before Hatch - Waxman Act

Impact and Implication

A law was enacted to speed up the distribution of generic medications in 1984. After 1962, the FDA approved generic copies of branded drugs without effectiveness and safety investigations. Companies can patent new things for five years. This prevented FDA delays. Hatch-Waxman remains important despite greater patent protection.[13].

Two primary sponsors comprise,

- Representative Henry Waxman of California
- Senator Orrin Hatch of Utah,

are responsible for the eponymous nickname given to the legislation.

The Act was a response to a patent law problem considered in 1984 by the Federal Circuit Congress that should address FDA and PA issues, not courts. Section 271-e-1 allowed copyrighted medications in FDA studies, establishing the current FDA approval procedure for generic therapies.[14].

Key Features of Hatch Waxman Act

The law promoted brand-name and generic enterprises. Support generic medicine development and allow generics. Pharmaceutical businesses can't get 20-year patents without clinical trials and FDA approval. Regulation holdups. It extended medication patents. The Act allowed generic businesses to file ANDAs showing "bioequivalence" to branded NDAs.[15]. The Act empowers generic businesses to contest innovators' patent validity. Innovative pharmaceutical companies must disclose NDA patents. Information from the "Orange Book" A corporation wanting to sell a similar drug must validate one of four NDA patents:

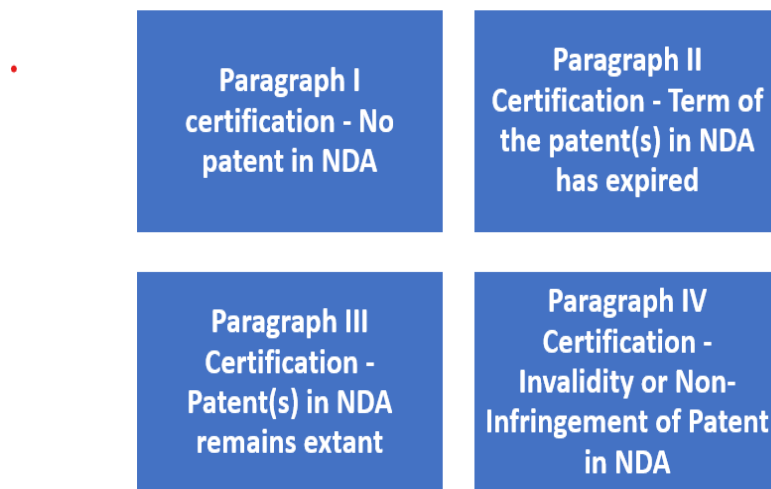


Figure 2. Types of Paragraphs for patents [16]

The certification required by Paragraph IV is the most challenging of the four certifications needed to complete the programme. The generic firm must also notify the patent's inventor and explain why the patent is invalid.

- The infringer has 45 days to sue after receiving notice.
- A lawsuit delays ANDA approval for 30 months.
- When the FDA approves an ANDA, the generic manufacturer receives 180 days of exclusivity.

Generic companies that submitted an ANDA for the same medicine were prohibited from creating a second generic brand of the same innovative drug. Generic firms with exclusivity never sell the drug.[17]. The following are some of the important key features of the act:

1. Safe Harbor Provision: To produce, use, or sell an invention "solely for uses reasonably linked to the creation and submission of information" to the FDA is not an infringement.[18].
2. Patent Term Extension (PTE): If the FDA takes too long to approve the medicine, the developer may claim reimbursement. After 20 years, a formula can prolong the patent. The PTE is the overall time from IND filing through NDA submission to approval.[19].

$$PTE = 0.5(a) + (b)$$

Where,

a= timing of submitting an IND versus an NDA

b= delay in receiving NDA clearance

For PTE purposes, a maximum of five years is allowed.

3. ANDA Filing: The company does bioequivalence studies to verify its generic drugs are "equivalent." An ANDA can quote a brand-name NDA. ANDA only applies to NCEs in general (New Chemical Entity). After 5 years, the FDA will accept an ANDA for a generic drug.[20].

4. 180-days Exclusivity for ANDA Application: To contest copyright, the first ANDA registrant to submit a Paragraph IV certification has the upper hand. The first company to submit an ANDA will have marketing exclusivity for the first 180 days. For the next 180 days, the FDA will not approve a new generic drug.[21].

5. 30-Month Stay: First ANDA applicant with Paragraph IV certification will trigger a 30-month wait until a favourable court ruling. NDA holders have 45 days to litigate after getting an ANDA with Para IV certification.[22].

This act gave brands five years to patent new products. Manufacturers may compensate for FDA review time. Despite expanding patent protection, the Hatch-Waxman Act is vital for generic pharmaceuticals.[23].

- The 1962 Drug Amendments' requirement for "sufficient and well-controlled research" improved the efficacy and safety of new therapies but increased pharmaceutical company costs.
- In 1970, the FDA authorised generic versions of drugs approved before 1962 to be filed as ANDAs (ANDAs).
- Manufacturers may file "paper NDAs" based on scientific literature to seek approval for generic versions of post-1962 drugs.
- In the 1980s, 150 post-1962 medications went off-patent without generic equivalents.[24].
- In 1984, Congress extended the ANDA procedure to encompass medications approved after 1962 whose patents expired.

Generic medications were allowed to differ from brand-name drugs in inactive ingredients and appearance.[24].

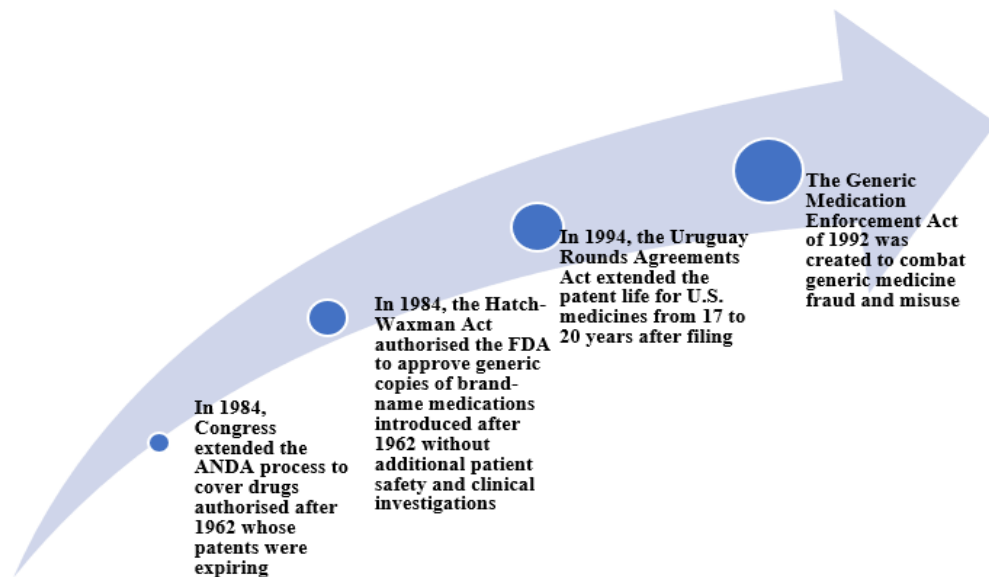


Figure 3. Impact and Implication of the Hatch-Waxman Act

Progress and Inability Due to the Hatch-Waxman Act's provisions

This Act increased drug competitiveness and lowered prescription rates. Section A briefly discusses these developments. Section B discusses Hatch-Waxman's discussions.

A. Effectiveness in Increasing Competing Generics

- Hatch-Waxman accelerated ANDA medication approval. Formulaic pharmaceuticals take 3–5 years and up to \$500,000 to develop and receive FDA approval, whereas NCE-NDA pioneer drugs take a decade and cost millions.
- ANDA approval increased generic medication usage. Since 1984, generic business expansion boosted prescriptions 2004 by 53%.
- Generics cut drug costs. FDA studies show generics have lower prices. The initial generic version decreases costs by 5%. New generic rivals cut the pioneer drug's price more than the second and sixth.
- Savings on drugs benefit consumers, states, and the feds. Over 10,000 generic medications are FDA-approved, saving millions. By encouraging generic competition, the Act decreased drug costs.

B. Hatch-Waxman Act Disagreements and Differences

- Complexity, length, and ambiguity hampered Hatch-Waxman.
- Several Hatch-Waxman clauses were explored since innovators and generics worked together.
- Senator Hatch, who wrote the Hatch-Waxman Act, stated its wording allowed anti-competitive activities. He suggested several generic and research-based medication businesses cheated.
 - The Generic Medication Enforcement Act of 1992 fined anybody caught fabricating medication applications and forced generic drug companies to reveal the quality and bioequivalence data. As health care expenses skyrocketed, the generic drug industry was reformed.[25].
 - In 1994, the Uruguay Rounds Agreements Act extended pharmaceutical patent protection from 17 to 20 years after the first filing.[26].

FDA final rule and Medicare Modernization Act of 2003 Amendments

The Hatch-Waxman Act's patent listing requirement, 30-month stay clause, and 180-day exclusivity provision were fiercely disputed. "The changes" closed loopholes in the Hatch-Waxman plan that enabled generic companies and inventors to "game" the Act.

A. 2003 Regulation of FDA

- On June 18, 2003, the FDA established a definitive policy on patent ranking and 30-month stays.
- The regulation changed Hatch-Waxman in two ways:
 - First, the rule "clarified patent filing and listing criteria, reducing misunderstanding and preventing abuse."
 - Second, the regulation limits ANDA and 505(b)(2) applications to one 30-month stay.
- The FDA thinks eliminating 30-month stays will accelerate generic drug clearance and market access.
- They reasoned that eliminating 30-month stays would hasten generic medication approval and market launch.

Law requires a trailblazer to present patent paperwork with its NDA (FDA Form 3542a) and after FDA clearance (FDA Form 3542). FDA requires NDA applicants to include thorough patent disclosures. A 240-character use description is required. The FDA wanted a claim-by-claim listing of method-of-use patents to assess if an ANDA applicant could "carve out" or swear to the patent. 18 August 2003 brings new patent requirements. As per a 2003 guideline, NDA applicants must disclose any relevant

patent information (related to medication supply, medicinal components, and use procedures) (such as metabolites and intermediates).[27].

B. Legislative Background

The 107th Congress amended Hatch-Waxman in 2001. The House rejected S. 812 in July 2002. Based on a 2002 FTC study, the 108th Congress introduced 1225 in June 2003.

The FTC Study showed the anti-competitive implications of these provisions and recommended two significant recommendations:

- a 30-month pause per ANDA to address Orange Book patent issues before filing;

- Every relevant patent accord must still be submitted to the FTC and DOJ.

Accordingly, FTC made three proposals recommending minor changes to the 180-day confidentiality stipulation, including elucidating that:

- The "commercial marketing" trigger includes the generic company's marketing of the pioneer drug product;

- The "court decision" trigger includes a trial court's decision on patent disqualification or non-infringement; and

- The "court decision" trigger includes a court dismissing a precedential judgement intervention for the scarcity of content area discretion.

On June 27, 2003, both the House and Senate voted to approve a bill including:

- a maximum stay of 30 months per ANDA;

- a peremptory judgement execution for a paragraph IV ANDA registrant, whereas if the visionary corporation doesn't review an intrusion civil case in less than 45 days of receipt of intimation;

- a utility model redemption counterclaim in a patent infringement case for a Paragraph IV ANDA filer;

- assorted revocation incidents for a first-paragraph IV ANDA filer's 180-day exclusivity; and

- a mandate that the law be different.

On August 13, 2003, the Senate Judiciary Committee reviewed HR 1 and S1. Two reforms were discussed. The 180-day exclusivity and forfeiture restrictions were questioned. The FTC has proposed a fail-to-market clause to prevent this from happening:

- instead of citing an appellate court ruling, you should cite a district court ruling;

- A court decision "dismissing a declaratory judgement action for lack of subject matter jurisdiction would trigger the first applicant's 180-day period."

The judgement provision in Section 1 was challenged. Under Article III, federal district courts have subject matter jurisdiction to consider a generic applicant's declaratory judgement action if the patent owner fails to prosecute a patent infringement lawsuit within 45 days after receiving notice.[27].

C. Medicare Modernization Act of 2003

Title XI of the Medicare Modernization Act, "Access to Affordable Pharmaceuticals," revised 1984 Hatch-Waxman Act.

- Subtitle-A modifies the 180-day exclusivity as well as the 30-month stay and terms;
- Subtitle-B assesses patent judgments for monopolistic offences.

Eight Hatch-Waxman innovations include:

Generic applicants have 30 months before filing an ANDA. If NDA holder sues within 45 days,

generic applicant's ANDA is delayed 30 months. An appeals court upholding a district court's patent judgement ends the 30-month stay. According to the MMA, an ANDA applicant cannot add a substitute prescription but can change therapeutic potency.

The MMA mandates generic applicants to notify NDA and patent holders 20 days after the FDA files an ANDA.

MMA changed to 180-day exclusivity. Initial retail supply of a generic drug or a summary judgement motion dismissing or not exceeding patent commencement 180-day exclusivity.

The 180-day exclusivity is per medicament, not patent. The first Subsection IV-certified generic petition will have 180 days of exclusivity.

- The MMA abolished the applicant's 180-day exclusivity period. Failed market entry has two deadlines. If an ANDA licensee doesn't start selling the drug within 75 days of acceptance or 30 months after filing, the licensee loses 180 days of exclusivity.
- Once the court rules that the pioneer's patent is invalid or not infringed, when a settlement is reached, or when the patent holder removes the patent from the Orange Book, 5-MMA events are rescheduled.
- The first ANDA applicant:
 - retracts their candidacy;
 - revokes or revises all Para IV certifications, authorising them for 180days of exclusivity;
 - within 30 months of filing, is unsuccessful in obtaining conditional approval for its ANDA;
 - enters into a regulatory capture memorandum of understanding with the registered proprietor or perhaps another generic company; or
 - All patents in which the preliminary applicant stated exclusivity are set to expire.

If a patent owner or an NDA holder brings patent infringement charges against a generic medicine supplier, the generic firm may counterclaim, delist the patent, or update the Orange Book.

MMA adds declaratory judgement. Unless the NDA holder or patent inventor sues the Paragraph IV ANDA filer for patent infringement within 45 days of being notified, the filer might argue the patent's validity or non-infringement.

The FTC and DOJ must approve patent settlements-

1. An ANDA signed with Paragraph IV certificates by generic industries and a pioneering company on discovery, production, marketing, and consuming of the precursor medication, generic medication, or any generic agency's 180 days of exclusivity upon the founder substance.

2. A contract between two generic firms shows ANDAs with Paragraph IV certificates on the same list and which bills the MMA denied.

Senator Hatch's "successful challenger" plan backfired. The MMA didn't amend other portions of Hatch-Waxman, and Congress dismissed the compelling manner.

Congress did not present an NDA patent bureaucratic evaluation.

Congress didn't rule reverse-payment settlements unlawful.

Congress didn't amend Hatch-patent Waxman's extension or market exclusivity criteria.

Hatch-Waxman did not strengthen patent or market exclusivity for innovative pharmaenterprises.[27].

D. Issues Addressed by 2003MMA and Final Rule of FDA

The final Rule of FDA and MMA outlined the two concerns of the Hatch-Waxman Act. Many drug companies battled Orange Book patents before 2003. New FDA regulations clarify patent listing requirements. The 2003 regulation mandates Orange Book medicine patent reporting and forbids by-products, metabolites, processes, and storage. MMA's 30-month stay provision offers two advantages.

The MMA gives Orange Book patent actions a 30-month stay per ANDA, which includes:

- The FDA rule and 30-month stay modification clarifying patent listing standards have eased patent listing disputes.
- A 30-month stay clause provision prohibited "evergreening," which delayed generic competition.

MMA explained 180-day exclusivity and states that it is per medication, not per patent. With the Paragraph IV certification, the very first generic company to apply for a patent on a pioneer drug gets 180 days of exclusivity. No future paragraph IV ANDA applicant may acquire exclusivity if the first lose it.[27].

The recent controversies of Hatch-Waxman following the implementation of MMA's

The Medicare Improvements for Patients and Providers Act of 2003 updated Hatch-Waxman to add a delisting counterclaim, a failure-to-market forfeiture, a declaratory judgement process, and a patent settlement notification. These new regulations have been debated in light of Hatch-Waxman. This section discusses Hatch-2003 Waxman modifications.

- The effect of patent delisting on a first generic applicant's 180-day exclusivity;
- The effect of patent expiration on a first generic applicant's 180-day exclusivity;
- The interpretation of the patent delisting counterclaim provision;
- The application of the declaratory judgement action provision;
- The legality of patent settlement agreements; and

- Complications with Approved Generics

(1) Impact of patent delisting on a first generic applicant's 180-day exclusivity

Due to MMA, inaugural generic petitioners cannot "park" their 180-day exclusivity. An applicant's 180-day exclusivity terminates upon forfeiture. Failed promotions cost. Paragraph IV ANDA applicant loses 180-day exclusivity if medication isn't launched within 75 days after ANDA approval or 30 months after ANDA filing. The court says the pioneer's patent is faulty or not infringed until a settlement is authorised or the patentee removes the information from Orange Book.

(2) Changes to the first generic applicant's 180-day exclusivity period when a patent expires

Patent expiry (apart from inevitable obsolescence) affects whether NDA delisting constitutes a forfeited event (VI). When "any patents for which the applicant confirmed 180-day exclusivity have expired," an ANDA applicant no longer has the right to the market for that product. (First Paragraph IV).[27].

(3) The basis of the counterclaim for patent revocation

In situations of Paragraph IV patent infringement, the MMA authorised generic producers to request Orange Book patent material. The ANDA "applicant may file a counterclaim seeking an order ordering the holder to alter or remove the patent information supplied by the holder under paragraph (b) or (c) of this section because the patent does not claim (aa) the authorised medicine or (bb) an approved method of utilising the drug."

(4) Utilization of Declaratory Judgment Clause

Declaratory judgement lawsuit challenging Hatch-constitutionality Waxman's is disputed. If the NDA holder or patent creator doesn't file a class action case within 45 days, the generic applicant can seek a patent invalidity or noninfringement ruling. Federal courts have "constitutionally" enlarged their ability to issue Article III declaratory judgements in recent decades. [27].

(5) Patent licencing agreements and their legitimacy

Following the passing of the MMA and the FDA's 2003 final rule clarifying patent compliance standards, many antitrust lawsuits against pharmaceutical corporations no longer contain patent deceit or fraud. Patent agreements hurt competitiveness before MMA. FTC found 14 "parked" IP agreements with 180-day exclusivity. Generic competitors won't be permitted to reach the market until the original drug's price stabilises (180 days).

(6) Complications with Approved Generics

Both the MMA and FDA underestimated generic drugs' anti-competitive impacts. When a pioneer NDA drug loses exclusivity and patent protections, generics may compete. The innovator drug company may provide a generic version under its own NDA or licence a generic medication business. Approved generics. Brand-drug NDA holders approve generics.[27].

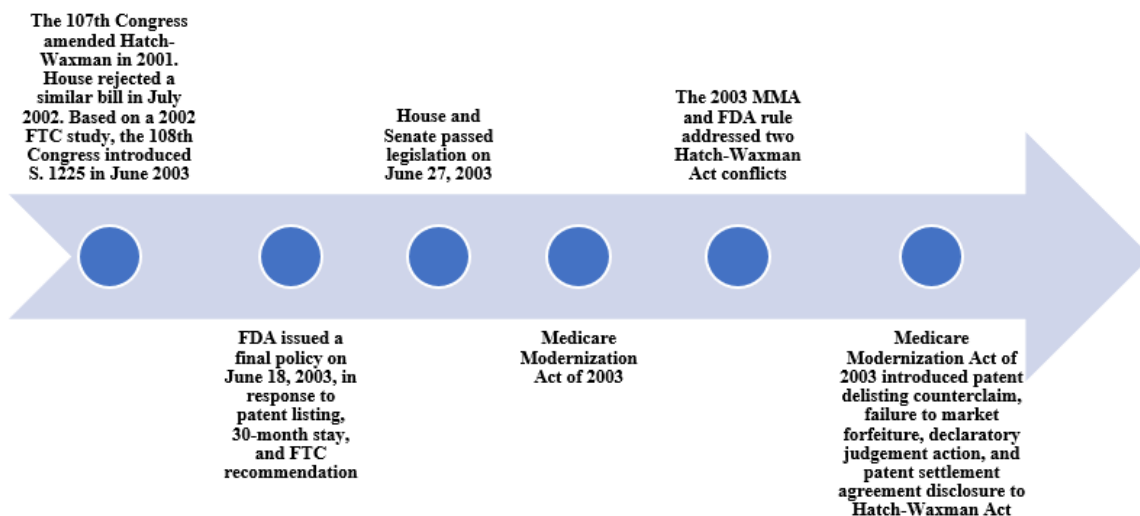


Figure 4. Final rule of FDA and Medicare Modernization Act of 2003

Approval Procedure for Generic Drugs

In order for the US FDA to approve the commercialization of a generic drug, the applicant must submit an ANDA. The generic applicant must show that their drug is significantly comparable to the RLD. The USFDA accepts traditional or CTD ANDAs (CTD). USFDA designed the generic ANDA framework. CTD reduces registration time and resources in all ICH nations. ICH's eCTD submissions have expedited regulatory filing and assessment. FDA reviews an ANDA in 15–24 months. ANDA reviews labelling and CMC of active pharmaceutical ingredient(s), excipients, and drug products. In vitro dissolution and in vivo bioequivalence are studied. FDA's staff inspects all manufacturing, testing, packaging, and control facilities to ensure they meet regulations.[28].

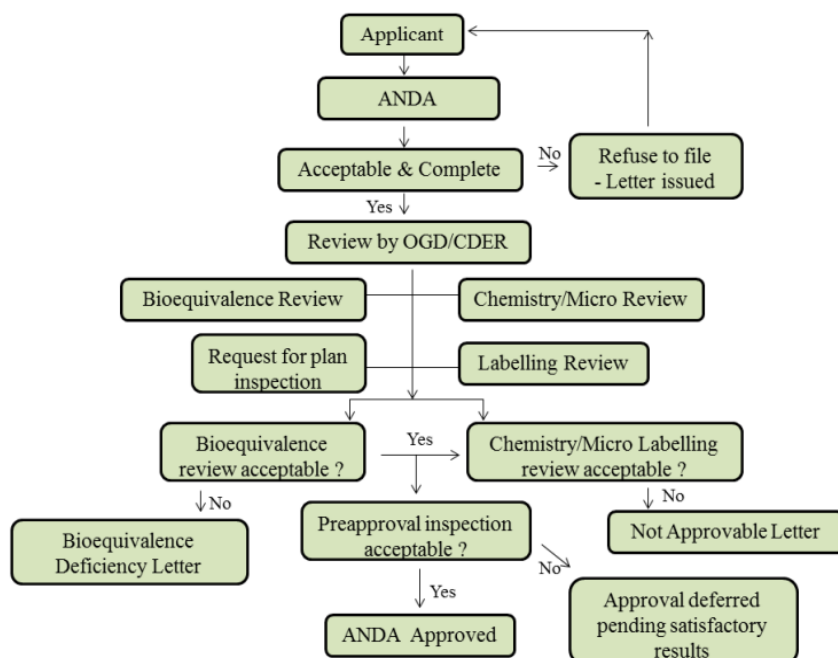


Figure 5.Process for Approval of Generic Drugs

CONCLUSION

The generic medication market of today is driven by a wide variety of stakeholders. Buyers who want more affordable options to pricey big brands are in the spotlight. The federal government and individual states were early proponents of generic pharmaceutical products, and they are currently the ones that lead the charge in encouraging healthy competition and ensuring the safety and effectiveness of generic prescription goods. Pharmacists and physicians have had a rocky history, but they've discovered common ground in areas like pharmacotherapeutic decision-making and medication replacement and are working together to find cost-effective solutions to fulfil patients' needs. Regardless of who is involved or the disputes involving economics, professional interests, and pharmaceutical research, the generic medicine industry has been and will continue to be an essential component of the healthcare sector. This is the case even though there are now ongoing discussions.

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CONFLICT OF INTERESTS

Authors declare no conflict of interest among themselves.

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