Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 1187-1196 | ISSN:2251-6727

Regulatory Frameworks Adopted by the US and EU for Bringing Complex Generics in the Market

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(Received: 16 September 2024 Revised: 11 October 2024 Accepted: 04 November 2024)

KEYWORDS

Generics, Complex drugs, Complex generics, USFDA, EMA, GDUFA, Regulatory frameworks.

ABSTRACT:

The regulatory requirements of complex generics in the USA and EU have similarities and differences in some ways which impacts the introduction of these products into the market. Thus, this article focuses on a comparative study of the approval procedures, requirements for bioequivalence, regulatory guidelines, preclinical and clinical data, post-approval data, quality and safety standards, flexibility and the user fees for drug applications between both the USA and the EU. Due to the current situation, there has been a need to come up with harmonized regulations, and guidance documents for the authorization of complex generics. The regulatory approval of complex generics in the USA is through filing an Abbreviated New Drug Application (ANDA), which is a fast and flexible method. EMA uses a Centralized Procedure which has high quality and safety requirements and is more costly and time-consuming as compared with the FDA. Thorough pre-clinical and clinical studies of complex generics are requested by the FDA and EMA to ensure the safety and efficacy of these products. This helps in promoting the global market, affordable costs, and availability of complex generics to the patients. This study is useful for manufacturers, regulators, and others who are involved in developing and regulating complex generics.

1. Introduction

Pharmaceutical regulatory agencies in the world set up and establish standards that the generic manufacturers must follow in the development, manufacture, packaging, and labeling of their products to meet the standard of the innovator drug product. According to the US FDA complexity is defined by five main categories of complexity; active pharmaceutical ingredients formulations dosage forms routes of delivery and a drug–device combination. The process of developing and receiving approval for complex generics must entail studies that are not captured in the guidelines formulated for simple generics[1].

The U.S. FDA provides the PSGs (Product Specific Guidance), for the extent of the extra studies needed to gain approval and lead the manufacturers through the difficulties in the development of complex generics[2]. The European Medicines Agency also acknowledges the fact that more in-vivo investigations are needed for further research and approval of generic variants of some of the products referred to as hybrid medicines[3].

Complex generics are large, difficult-to-manufacture, biologically active substances in the form of large, highly complex synthetic blocks, and are divided into groups depending on the active substances and the technological process of their production. At the same time, overwhelming competition has put pressure on and limited the opportunity for generics. They are therefore turning their attention to complex generic products. This shift is being driven by the possibilities of a higher price and less competition in the highly saturated generic drug industry packaged with near-expiration exclusivities and patents on many of the current complex drug products[4].

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Definition of generics:

FDA:

A generic drug, according to the FDA, is a medication designed to be identical to a brand-name drug that is currently on the market in terms of dosage form, safety, strength, mode of administration, quality, performance characteristics, and intended use. The bioequivalence revealed by the similarities shows that generic medications function similarly to branded ones and have comparable clinical advantages. Generic drugs are carefully reviewed and approved by the FDA to ensure that they meet the same standards of quality and efficacy as their branded versions. They offer more affordable options to patients without compromising on treatment quality, thereby playing an important role in the healthcare system by improving accessibility to essential medications[5].

European Union (EMA):

The European Medicines Agency (EMA) evaluates businesses' applications to sell generic medications in the EU. The goal of developing a generic medication is to make it identical to an approved reference medication. A generic medication is used to treat the same condition at the same dosage and has the same active ingredient as the reference medication. However, the name, look, packaging, and inactive components of a generic medication may differ.

The same quality criteria that apply to the reference pharmaceuticals also apply in the manufacture of generic medications. The marketing authorization application for a generic medication can only be submitted by an applicant once the reference medicine's data exclusivity period has ended. Only after the marketing protection has ended—typically 10 or 11 years after the reference product's first permission date—can generics be sold[3].

Complex drugs:

A complex product typically has one or more of the following five characteristics, per the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 letter (GDUFA II Commitment Letter):

1. A complex active ingredient: Complex mixtures of APIs, polymeric compounds, peptides'
2. A complex route of delivery: Locally acting such as ophthalmic, otic, dermatological, and inhalational drugs.
3. A complex dosage form or formulation: Liposomes, suspensions, emulsions, gels, long acting injectables and implantable, transdermal, MDIs
4. A complex drug-device combination product: Metered dose inhalers (MDI), auto-injectors
5. Complexity or ambiguity around the approval process or a potential substitute strategy that would profit from early scientific involvement: Abuse- deterrent opioids[6].

The European Medicines Agency refers to complex generics as "**hybrid medicines**," whose "authorization depends partly on the results of tests on the reference medicine and partly on new data from clinical trials[3]."

Drugs that are comparable to an approved medication and have the same active ingredient but differ in other ways, such as in potency, indication, or pharmaceutical form, are known as hybrid medicines. Developing complex generics is very challenging, time-consuming, and expensive, and it also requires demonstrating the equivalency, safety, and efficacy of the therapy[7].

Drug Application Approval Procedures:

The applications for approval process of drugs in the USA and Europe is as follows:

US-FDA:

Fig.1

European Union:

Fig. 2

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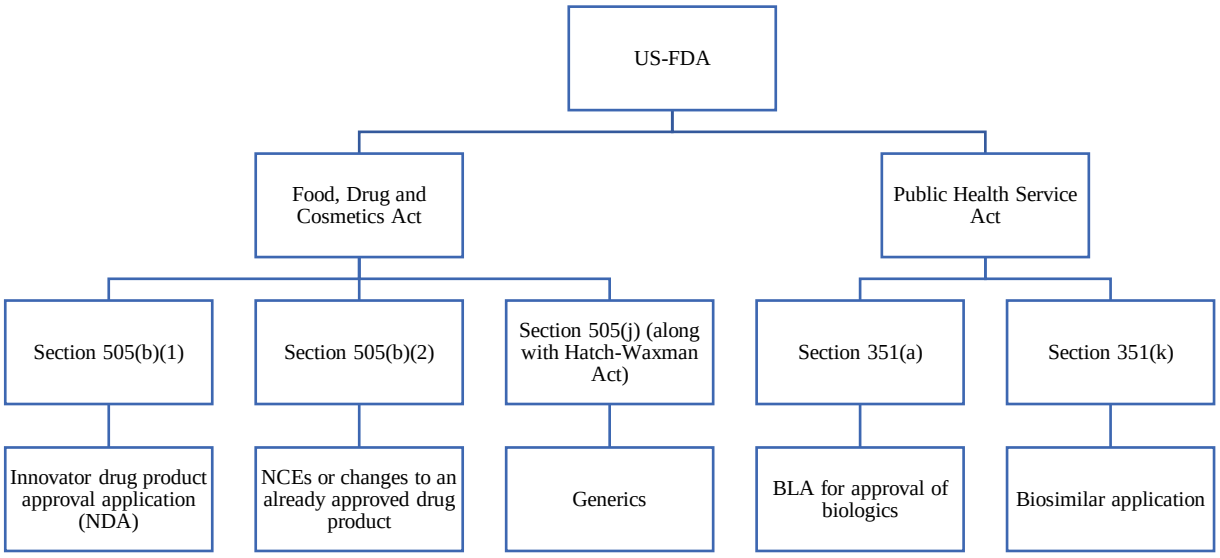

Figure 1 Types for Drug Application in the US

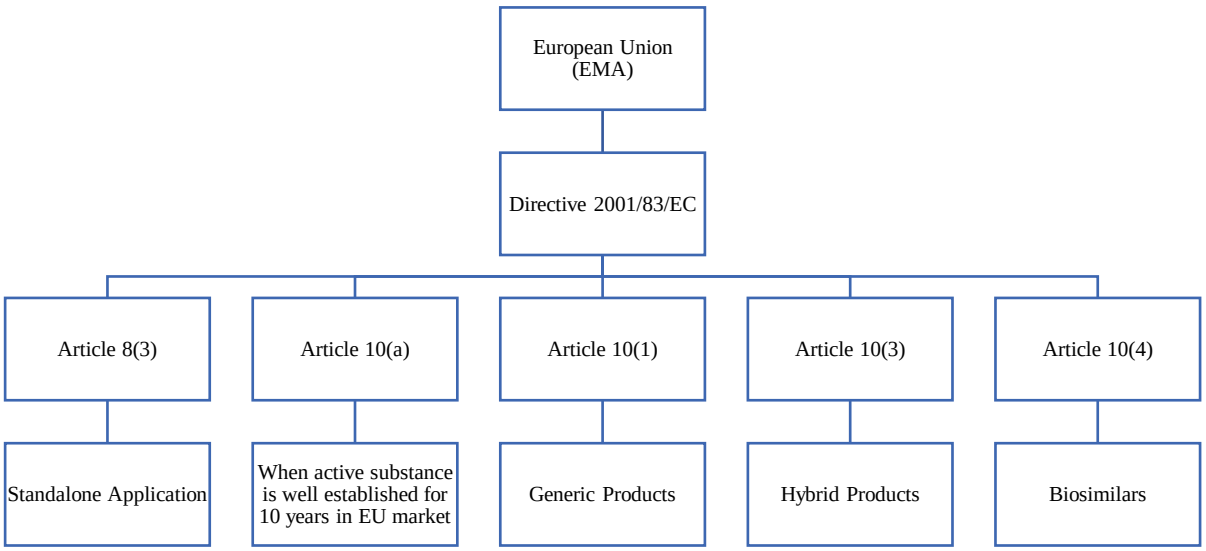

Figure 2 Types of Drug Application in EU

2. Regulatory Frameworks:

Generic forms of small molecule products and biologicals have very different pathways for its approval in the USA, and European Union, and both pathways are well-defined with clearly documented requirements.

US Regulatory Framework:

The US FDA acknowledges the follow-on version of complex- drug products as complex generic products. Therefore, the FDA reviews and approves these drug products via the ANDA approval process[4]. The Generic Drug User Fee Amendments III plays a vital role in the regulation of generic drug products. GDUFA was reauthorized on September 30, 2022 (GDUFA III), with

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provisions that are in effect from October 1, 2022, through September 30, 2027[8].

Research Center:

The Office of Generics Drugs and the Center of Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration collaborate to carry out in-depth research for the appropriate evaluation of complicated drug products[2]. The FDA has awarded the University of Michigan and the University of Maryland a five-year funding to establish a Center of Research on Complex Generics (CRCG). In order to support the FDA's objective of expanding access to safe and efficient generic pharmaceuticals, CRCG's primary purpose is to expand research partnerships with the generic industry. The FDA, the generics industry, and stakeholders will exchange resources, conduct webinars, arrange workshops, and conduct cooperative research and training in order to accomplish the aim[9].

Approval Pathways:

1. 505(b)(1) pathway: This is an approval pathway for the approval of new drug with previously unapproved active ingredients. The submission of data for this pathway requires thorough research, clinical and non-clinical study data for ensuring the products safety.
2. 505(b)(2) pathway: This is an approval pathway for the approval of a new drug containing previously approved active ingredients. The submission of data for this process requires full reports on safety and efficacy data. This pathway provides an alternative for the approval of complex generic products that need clinical studies to show the TE.
3. 505(j) pathway: The 505(j) or ANDA process, the applicant needs enough data to show that the generic drug product is similar to the reference drug product[10,11].

Guidelines:

1. Abbreviated New Drug Application (ANDA): Under the Hatch-Waxman Act, 505(j) pathway and FDAs ANDA pathway approves the complex generic products. However, because of the complexity of the drug product, the manufacturers are required to submit preclinical and clinical study data[12].
2. Product-Specific Guidances (PSGs): The PSGs provide guidance for developing generic drug products and prepare the data required to support the ANDA approval process[2].
3. Pre-ANDA Program: The FDA has come up with a pre-ANDA program whereby they assist the manufacturers in understanding the regulatory forum for the above complex generics, offers the manufacturers scientific advice regarding the development of the product which encompasses recommendations of the study of bioequivalence and the general approach to clinical trials[13].
4. Comparative Clinical Studies: In the case of some complex generics the FDA may insist on comparative clinical trials to show that the complex generics are therapeutically equivalent to the reference products for the respective complex generics. This is of much relevance with drug-device combination products as well as with long-acting injectable products[4].

EU Regulatory Framework:

The EU's regulatory framework for hybrid medicines is regulated by the European Medicines Agency (EMA), emphasizing the Centralized and Decentralized Procedure for approving these drug products. The EMA reviews the applications if the reference medicine was centrally authorized or if the generics provide a significant innovation or advantage for the patients[3].

Authorization of hybrid medications is based in part on new information from clinical trials and in part on the outcomes of testing on the reference medication. This occurs when a producer creates a generic medication with a somewhat different indication, a different strength, or a different method of administration than the reference medicine[14].

In EU, the generic drug product, hybrid medicines and biosimilars can be approved by centralised, decentralised, mutual recognition or national procedures. The Article 10(1) for and Article 10(3) of Directive 2001/83/EC states the procedures for the approval of Generic Medicinal Product Application and Hybrid Medicinal Product Application respectively[15,16]. The

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Article 3 and Article 8 of the Regulation (EC) No. 726/2004 states the procedure for the Marketing Authorization of the drug products[15,17].

Hybrid Marketing Authorization: Complex generics can be approved by the hybrid application process, unlike simple generics. This allows the applicant to submit additional information required to demonstrate the complexity of these products, including preclinical and clinical studies. Bioequivalence cannot be demonstrated through pharmacokinetic studies alone, for the complex formulations or complex drug-delivery systems[14].

Scientific Advice and Protocol Assistance: The EMA offers scientific advice to manufacturers in the development of complex generics and products similar to the FDA Pre-ANDA. The manufacturing companies can certainly clear particular bothersome points or guidance about bioequivalence, formulation, or drug delivery systems at one go much before the completion of all these processes[18].

Comparative Efficacy Trials: The EMA may require comparative efficacy studies where pharmacokinetics studies are insufficient to support a bioequivalence claim on the products. EMA may require comparative efficacy studies for products with such delivery to the target site as a critical factor for therapeutic effect, such as inhalers or transdermal patches[4,19].

ANDA Approvals:

The U.S. Food and Drug Administration have approved hundreds of generic applications between 2020 to 2024.

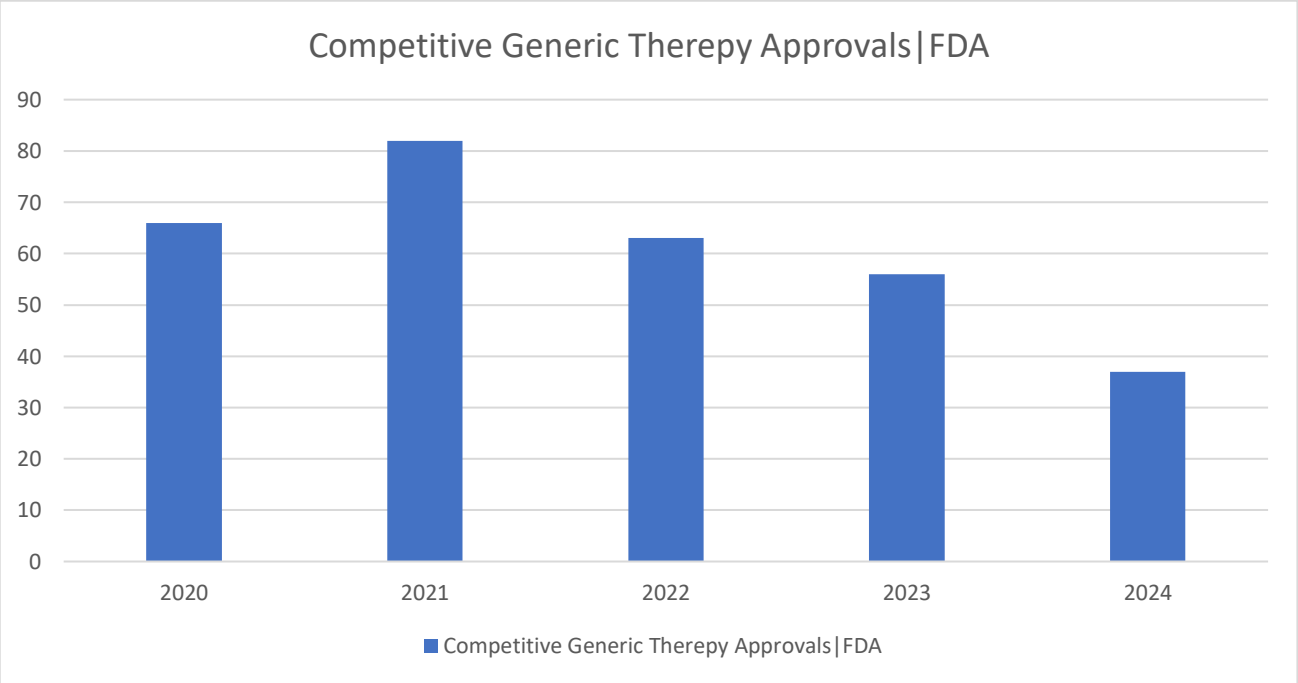

Figure 3 ANDA approvals since the year 2020 to 2024

CAGR: -10.93%

Interpretation:

Over the course of 5-year time period initially the ANDA approval number increased till the year 2021, then it gradually decreased and the CAGR value was found to be -10.93%.

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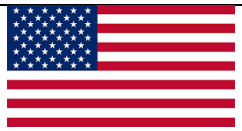
3. Comparative studies:

Table 1 Comparative study of regulatory frameworks of complex generics in USA and EU.

Parameters	USA	EU
		
Drug Regulatory Authority (DRA)	FDA U.S. FOOD & DRUG ADMINISTRATION	EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH
Head of DRA	Commissioner	Executive Director
Definition	The drug products that may have complex active ingredient, complex formulation, complex route of delivery, or complex drug-device combinations are complex generics.	EMA refers to complex generics as "hybrid medicines," whose "authorization depends partly on the results of tests on the reference medicine and partly on new data from clinical trials."
Sub-office of Complex generics	Office of Research and Standards (ORS) within the Office of Generics Drugs	Committee for Medicinal Products for Human Use (CHMP)
Examples of Complex generics	Inhalers, liposomal formulations, drug-device combinations (e.g., EpiPen).	Products, such as liposomal drugs, injectables, and inhalers.
Approval Pathway	Abbreviated New Drug Application (ANDA) process under the Hatch-Waxman Act, 505(j) ANDA pathway.	The Hybrid Marketing Authorization Application (MAA) process is under Directive 2001/83/EC, Article 10(3).
Application Fees	ANDA fees (approx. $240,000)	Varies by country; Centralized EMA fees (approx. €300,000)
Pre-clinical Data Requirements	Depends on the complexity of the products.	Similar to the FDA, but determined on a case-by-case basis.
Clinical Data Requirements	May require additional clinical trials or comparative studies for complex formulations or delivery systems.	May require clinical trials, especially for biological complexity.
Bioequivalence Requirements	Stricter requirements, often demand in vitro and in vivo studies to demonstrate equivalence.	Stricter requirements, often demand in vitro and in vivo studies to demonstrate equivalence.
GMP Standards	Compliance with FDA GMP regulations (21 CFR 210/211)	Compliance with EU GMP guidelines.
Data Requirements	May require additional data for complex formulations, such as in vitro dissolution studies or in vivo PK/PD studies.	May require more detailed pharmacokinetic studies to assess drug release profiles and steady-state concentrations.
Biological Complexity	Complex biologics often follow the 351(k)	Follow specific biosimilar pathways
Combination Products	Requires interaction with FDA's Combination Products Review Group	Requires interaction under EMA's CHMP for product review

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Patent Exclusivity	180-day exclusivity for the first generic approved under the Hatch-Waxman Act, 5 years for the innovator.	10 years of market exclusivity for reference products in most cases.
Market Authorization Timeline	Median approval time for ANDA's is 8-10 months	1-2 years of centralized procedure, varies by country
Post-Approval Changes	The US FDA imposes various post-approval requirements for complex generics, including risk management plans, post-marketing surveillance, periodic safety reports, adverse event reporting, inspections, and product recalls, to ensure their safety and efficacy.	The EMA requires complex generics to adhere to post-approval requirements such as risk management plans, post-marketing surveillance, periodic safety reports, adverse event reporting, inspections, and product recalls.
Regulatory Flexibility	Offers more flexibility in the approval process for complex generics	Maintains strict standards throughout the approval process
Labeling Requirements	Same labeling as the reference drug, unless deviations are necessary for safety.	Labeling is similar to reference products with some allowances for generics.
REMs v/s RMPs	REMS for certain complex generics.	RMPs for risker generics especially for biologicals.
Regulatory Harmonization	Ongoing collaboration with EMA on scientific, technical, and regulatory matters	Ongoing collaboration with FDA on scientific, technical, and regulatory matters
Scientific Advice and Support	Sponsors can seek guidance through the FDA's Pre-ANDA Program for Complex Products.	EMA offers Scientific Advice procedures to support the development of complex generics.
User Fee Programs	PDUFA, and GDUFA fees for applications and inspections.	EMA charges centralized user fees, varies for member states.

Table 2 User Fee Rates in USA

Fee Category	Fee Rates for FY 2024	Fee Rates or FY 2025
Application	-	-
Requiring Clinical Data	$ 4,048,695	$ 4,310,002
Not requiring Clinical Data	$ 2,024,348	$ 2,155,001
Program	$ 416,429	$ 403,889

Table 3 Fees for Marketing Authorization in EU

Fee Type	Fees
Marketing-authorisation application (single strength, one pharmaceutical form, one presentation)	From €357,600
Extension of marketing authorisation (level I)	€107,300
Type-II variation (major variation)	€107,300
Scientific advice	From €53,600 to €107,300
Annual fee (level I)	€128,100

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4. Case Studies:

Lanreotide Acetate:

Lanreotide Acetate is mainly used for the treatment of acromegaly and neuroendocrine tumors by administering subcutaneous injections of a somatostatin analog. Producing this injectable medication with a sustained effect is difficult. For generic versions to be approved under 21 CFR 314.94(a)(9)(iii), they must match the original product in terms of quality (Q1) and quantity (Q2). Two methods exist to demonstrate bioequivalence.

Option 1 offers a biowaiver, granted when the generic matches the reference product in molecular, structural, and thermodynamic characteristics. A comprehensive knowledge of lanreotide's morphology, nanotube composition, and heat resistance is required, in addition to performing equivalent in vitro testing on drug release rates using at least three batches of each reference and test products.

Option 2 involves a bioequivalence study that is carried out in vivo under fasting conditions. This investigation includes both men and women who are in good health, participating in a random, single-dose, parallel design using EQ 120 mg base. The injection is administered in the upper outer quadrant of the buttock subcutaneously, and bioequivalence is assessed by determining lanreotide levels in plasma with a 90% confidence interval. Waivers for in vivo testing of EQ 60 mg and EQ 90 mg strengths can be requested if bioequivalence studies for EQ 120 mg strength, proportionate formulation similarity, and in vitro dissolution testing all meet the requirements. To sum up, it is important to develop an appropriate dissolution testing method and perform comparative dissolution testing on 12 units of both the test and reference products at different strengths, based on the criteria set after reviewing the application[20].

Sacubtitril/ Valsartan:

Sacubitril/Valsartan is a tablet form oral medication prescribed for the treatment of heart failure. The FDA requires two bioequivalence studies for bringing a generic version of this drug to market: a fasting study and a fed study, both with single-dose, two-way crossover designs and involving healthy nonpregnant male and female subjects. Bioequivalence of Sacubitril and Valsartan in plasma is determined by measuring the main analytes with a 90% confidence interval. Requests for waiving in vivo testing on lower strengths (24 mg/26 mg and 49 mg/51 mg) may be made, provided that bioequivalence studies for the 97 mg/103 mg strength are acceptable, dissolution testing is comparable, and formulation similarity is proportional across all strengths. Information and methods for dissolution can be located on the FDA-Recommended Dissolution Methods site, with testing of 12 dosage units for each strength needed for both test and reference products[21].

5. Conclusion:

As a result, regulatory frameworks for complex generics have been put in place to tackle the problems arising from the complexities of these products in the course of the approval process. It is approved by the U.S. FDA through ANDA application and in Europe through Hybrid Marketing Authorization in terms of its requirements for the quality, safety, and efficacy of complex generics. It is therefore important to harmonize these regulations to provide a common base for the complex generics approval process to provide quality products to patients. The US and EU frameworks stress the importance of the regulations for the development of complex generics. The regulatory authorities have to continue their cooperation to align the approval process and stimulate the development of new products in the industry as the demand for complex generics has risen because of the expiry of the reference product's patent. Differences in the regulations of the two regions are important for the pharmaceutical industries to know, it is crucial for appreciating the regulatory environment to allow the approval of intricate generics into the market promptly. The number of ANDA approvals was studied for the year 2020 to 2024 and it was found that the number of approvals initially increased form 2020 to 2021, but later it declined steadily with CAGR of -10.93% over the five years period.

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