Review Article

Navigating Complex Generics Regulations: A Comparative Analysis of US, EU and BRICS Countries

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ABSTRACT

Introduction: Complex generics constitute a technical order of pharmaceutical products distinguished by intricate phrasings, new delivery mechanisms, or integration with medical bias. Unlike conventional generics, which generally establish parity through standard bioequivalence studies, complex generics frequently bear fresh in vitro, in vivo, or clinical evaluations to demonstrate remedial parity. This study provides a relative analysis of the nonsupervisory fabrics and blessing trends for complex generics in the United States, European Union (EU), and BRICS countries (Brazil, Russia, India, China, and South Africa).

Methodology: In the United States, the Food and Drug Administration (FDA) facilitates the development of complex generics through Product-Specific Guidances (PSGs), which delineate the bioequivalence and other supporting study conditions necessary for demonstrating parity to the Reference Listed medicine (RLD). In the EU, similar products are distributed as Hybrid Medicines, and the European Medicines Agency (EMA) has developed similar PSGs to guide their evaluation. Within BRICS nations, nonsupervisory prospects remain different, constantly taking fresh bioequivalence or clinical studies for complex phrasings similar as liposomal products, medicine – device combinations, and non-systemically acting medicines.

Results: Elucidative exemplifications include the FDA blessing of Mylan Laboratories generic Glatiramer acetate, following compliance with PSG criteria, and ANVISA's blessing of a liposomal Cyclosporin expression for Sigma Pharma, supported by Radioimmunoassay (RIA) and concentrated luminescence Immunoassay (PFIA) data.

Discussion: In general, even though great progress has been made, regulatory differences persist across all areas.

Conclusion: In order to speed up the global approval process for complex generic drugs, there is an absolute need for more guidance papers and regulatory harmonization.

Keywords: Complex Generics, Product specific guidances, Hybrid medicines, Bioequivalence studies.

1. INTRODUCTION

In the constantly changing pharmaceutical business, generic medications continue to be the most economical way to guarantee access to necessary medications [1,2]. The research and approval of generic medications around the world were greatly aided by the Hatch-Waxman Act of 1984 [3]. Innovator enterprises gradually turned their attention to the creation of more sophisticated and specialized goods as the number of generic pharmaceutical companies grew quickly [4,5]. Complex generics have become a major problem for generic medication manufacturers in recent years, especially since 2016.

Complex generics, in contrast to ordinary generics, have particular challenges in their clinical application, manufacturing procedures, regulatory approval processes, and development. These products are often described using terms such as specialty generics, super generics, hybrid drugs, value-added generics, or off-patent medicines [3,6]. After reaching about USD 90.68 billion in 2025, the global market for complex generics is expected to increase at a compound annual growth rate (CAGR) of about 8.1% to reach USD 197.59 billion by 2035 [7].

BRICS, informal grouping of countries that has developed into an intergovernmental organization. The acronym derived from the names of the early members Brazil, Russia, India, China, and South Africa [8].

1.1 Classification of Complex Generics

The US FDA has categorized complex generics into four principal categories based on the nature and source of their complexity. This classification, summarized in Table 1, informs the regulatory requirements and development strategies applied to each product type [2].

1.2 Problem statement

When the Hatch-Waxman Amendments created the current generic drug regulatory framework, many complicated drug products were non-existent. As a result, compared to ordinary generics, the scientific and regulatory processes for proving the equivalency of complicated generics are less developed. In many cases, normal bio-equivalency testing is insufficient because of the inherent complexity of these medicines, which include heterogeneous active ingredients, multiphase formulations, device-dependent distribution, and local routes of administration. Additional clinical, non-clinical, physicochemical, and device performance data must be added to ANDA submissions by manufacturers, greatly raising development costs, schedules, and regulatory uncertainties. Moreover, additional challenges

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are created by regulatory variability among international jurisdictions. The regulatory processes in the BRICS nations-Brazil, Russia, India, China, and South Africa remain unorganized, inconsistent, and opaque, despite the development of systematic, science-driven frameworks by the US FDA and the European Medicines Agency (EMA). In emerging nations, this discrepancy makes it more difficult for patients to obtain complicated generic treatments at reasonable prices.

1.3 Objective of the Study

This study is focused on the comparative analysis of regulatory frameworks for complex generics within the context of the United States (US), European Union. To evaluate regulatory pathways, including application types, data requirements, and review mechanisms specific to complex generics. Thus, this study will help find out what regulations currently exist, and what can be proposed for enhancing global regulation of complex generics.

Table 1: Classification of Complex Generics in USA

Category	Description	Representative Examples
Complex Active Ingredients (APIs)	Peptides, polymeric compounds, complex mixtures of APIs, or naturally sourced ingredients with heterogeneous molecular weight distributions	Glatiramer acetate, enoxaparin sodium, sevelamer carbonate, omega-3 acid ethyl esters
Complex Formulations / Dosage Forms	Non-solution products with multiple discrete states of matter, including nanotechnology-based, liposomal, and long-acting injectable systems	Liposomal doxorubicin, albumin-bound paclitaxel, semisolid preparations, extended-release microspheres
Complex Routes of Delivery	Locally-acting products where site-specific absorption, distribution, and therapeutic consistency present unique challenges	Ophthalmic, otic, topical, transdermal, nasal, buccal, and inhalation products
Complex Drug-Device Combinations	Products incorporating a drug within or co-packaged with a device whose design influences drug delivery, dosing accuracy, or user interaction	Metered-dose inhalers, pre-filled auto-injectors, nasal spray pumps, intrauterine systems

2.METHODOLOGY

2.1 Research Design

A narrative systematic review was performed using PRISMA guidelines for Systematic Reviews and Meta-analyses 2020 to study the differences in the regulation system, process of approval, requirements for product-specific guidance (PSG), and approval pattern of complex generic medicines among the USA, EU, and BRICS countries (Brazil, Russia, India, China, and South Africa). In the present study, no new data were collected from unpublished literature, animals, and clinical studies.

2.2 Regulatory Framework: USA

In the United States, complex generic drug development is regulated by the FDA's Center for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD). The primary approval pathway is the ANDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act, as amended by the Hatch-Waxman Amendments [3]. The 1984 Hatch-Waxman Act was a major legislative accomplishment that introduced the Abbreviated New Drug Application (ANDA) process for the approval of generic medicines [9,10]. However, this law primarily addressed simple generic drugs that show bioequivalence to their reference listed drugs (RLDs). When it comes to complex generic products such as drug-device combinations, transdermal delivery systems, and medicines with complicated formulations or active ingredients the structure of the Hatch-Waxman Act is not sufficient for a number of important reasons [11,12]. Firstly, there are no specific approaches and criteria that would be applicable only to the development of such complex products, as the approach is mainly focused on traditional bioequivalence studies, which cannot guarantee the actual therapeutic equivalence of the generic drug compared to its reference product. In this way, additional studies may have to be conducted by the manufacturer in order to provide enough evidence for the approval of a new drug application. Moreover, such drugs face specific challenges in proving their equivalence and meeting the required criteria regarding the proper functioning of the delivery system. The FDA introduced the concept of Product-Specific Guidances (PSG), which outlines the specific development pathway for simple and complex drugs alike. With regard to the complex generics, PSG offers a thorough guide on bioequivalence testing, analysis, and testing approaches. [13]

2.2.1 Product Specific Guidance for each class of Complex generics in USA

The FDA uses Product Specific Guidance **(**PSGs) as one of its most important tools to make complex generic development easier. The FDA PSG requirements for each difficulty category are shown below

Complex API: Glatiramer Acetate Injection (20 mg/mL and 40 mg/mL)

For **Glatiramer Acetate injection**, intended for subcutaneous administration and available in strengths of 20 mg/mL and 40 mg/mL, the FDA has proposed the Comparative characterization research to validate active component equivalence and petition for exemption from in vivo bioequivalence study obligations [14.]

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Guidelines for establishing active component equivalence: Glatiramer acetate consists of a blend of peptide copolymers that incorporate four particular amino acids in a specified proportion. Active component equivalence may be confirmed by demonstrating comparability between the test formulation and the reference listed drug (RLD) according to four criteria outlined in detail below. These four standards should be applied to verify active component equivalence: Comparability of basic reaction methodology, Comparability of physicochemical characteristics including compositional elements, Comparability of structural markers for polymerization and depolymerization processes and Comparability of biological testing outcomes. To rigorously verify these standards, manufacturers of generic medications are recommended to conduct parallel comparative analyses utilizing the test active component and the active component derived from the RLD [15].

Complex Formulation: Doxorubicin Hydrochloride Liposomal Injection

For **Liposomal Doxorubicin Hydrochloride Injection,** the FDA has issued Product-Specific Guidance recommending one in-vivo bioequivalence study along with an in-vitro evaluation of liposome size distribution as part of the bioequivalence assessment.

To be eligible for bioequivalence studies under this guidance, the test product must satisfy several stringent criteria designed to ensure meaningful comparison with the Reference Listed Drug (RLD). Fundamentally, the formulation must be qualitatively (Q1) and quantitatively (Q2) identical to the RLD and manufactured using an active liposome loading method employing an ammonium sulfate gradient. Additionally, at least one batch produced at commercial scale must be utilized in the in vivo bioequivalence study to ensure representative results. Crucially, the test product must demonstrate comparable liposome characteristics to the Reference Standard (RS) across multiple critical quality attributes, including formulation composition, the condition of the encapsulated drug, the internal liposomal environment, particle size distribution, number of lamellar layers, presence of surface-grafted PEG, electrical surface potential or charge, and in vitro leakage rates [16].

Complex route of delivery: Sodium Zirconium Cyclosilicate Oral Suspension

The active ingredient is **Sodium Zirconium Cyclosilicate**, formulated as an oral suspension, and its development is supported by findings from two laboratory studies, requires a multifaceted approach to demonstrate equivalence. To establish active pharmaceutical ingredient (API) sameness for the compound with chemical formula Na~1.5H~0.5ZrSi3O9 2–3H2O, characterization must extend beyond standard compendial tests to include evaluation of composition ratios, crystal structure, pore size, particle size distribution, Fourier-transform infrared spectroscopy (FTIR), density, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and potassium-binding capacity, with comparative studies conducted using at least three batches each of the test product and reference standard [17].

Guidelines for Determining Drug Product Bioequivalence

For drug product bioequivalence, the primary endpoint is a laboratory equilibrium binding assessment performed at pH levels 1.2, 4.5, and 6.8 at 37°C using a 10-gram packet dosage;

Notes: The equilibrium binding assessment is the main bioequivalence (BE) test.

This requires subjecting both the Test and Reference formulations to at least eight different potassium concentrations in pH 1. 2, 4. 5, and 6. 8 buffer solutions. To gather the full adsorption curve, including the maximum binding capacity (ensuring the adsorption plateau is fully achieved), the potassium concentrations for each test condition should be carefully chosen. Every test needs to be carried out at 37°C. A minimum of 12 repetitions of each binding test should be performed using a different sodium zirconium cyclosilicate sample (packet). Additionally, proof that the selected potassium exposure duration for the adsorption process to reach equilibrium must be presented. This is complemented by a laboratory kinetic binding assessment conducted under identical pH and temperature conditions, utilizing minimum, maximum, and intermediate potassium concentrations to evaluate binding rates over at least eight time points up to 24 hours, also with 12 replicates and constant gentle stirring.

Notes: The equilibrium binding analysis is supported by the kinetic binding assessment. The minimum and maximum potassium concentrations utilized in the relevant equilibrium analysis, as well as an intermediate concentration that is roughly half of the maximum concentration, must be applied to both the Test and Reference formulations. pH values of 1, 2, 4, 5, and 6 should be used for the evaluation. It is important to assess potassium binding over time. For each testing scenario, at least eight different time points, up to 24 hours, should be chosen to accurately illustrate the binding rate features, including when equilibrium is established. Each binding test should be repeated at least 12 times, and all procedures must be performed at 37°C with constant, gentle stirring.

Target Measurement: Free potassium in the filtered solution (used to calculate potassium bound to sodium zirconium cyclosilicate) For the laboratory equilibrium binding assessment, the Langmuir binding parameters k1 and k2 must be determined. The ratio of test-to-reference for k1 needs to be calculated. The 90% confidence interval (CI) for k2 must be established, with acceptable limits between 80% and 120%. For the laboratory kinetic binding assessment, the test-to-reference ratios of bound potassium at different time points should be assessed, but they do not need to meet the 90% CI standards.

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Bioequivalence Criteria (90% CI): The Langmuir binding parameter k2 obtained from the equilibrium binding assessment [17].

2.3 Regulatory Framework: EU

In the European Union, complex generics are identified as *Hybrid Medicines Medicines* under Article 10(3) of Directive 2001/83/EC. The EMA's Pharmacokinetics Working Party (PKWP) and Multidisciplinary Working Party (MWP) have developed product-specific guidelines for key complex generics. In contrast to generic applications under Article 10(1), hybrid applications require additional preclinical and/or clinical data when the strict definition of a generic medicinal product is not met, bioequivalence cannot be demonstrated through bioavailability studies alone, or there are changes in active substance, indication, strength, pharmaceutical form, or mode of administration. Some examples of these PSGs are listed below.

2.3.1 Product Specific guidance for each class of complex generics

2.3.1.1 Complex Drug Device Combination: Exenatide Extended-Release Suspension for Injection (2 mg)

Extended-release suspension for injection (2 mg) of Exenatide powder and solvent, including the pre-filled pen presentation, is subject to specific bioequivalence guidance to ensure therapeutic equivalence, device performance, and consistent drug delivery. Criteria for demonstrating bioequivalence (PKWP).

Study design for bioequivalence

When a BCS biowaiver is not applicable, bioequivalence should be established through both single-dose and multiple-dose studies. A single-dose study should involve a 2 mg administration in healthy subjects, while the multiple-dose study should use a 2 mg dose in patients. This dual-study approach is necessary for extended-release formulations that demonstrate accumulation. The study may follow either a crossover or parallel design. Bioanalytical assessment may involve a target compound, its primary compound, the metabolic product, or a combined approach, with sample collection using plasma/serum, whole blood, or urine. A stereoselective analytical method should be applied when required.

Bioequivalence evaluation should be based on the following primary pharmacokinetic parameters: for single-dose studies, AUC_0–t, AUC_0–∞, Cmax (early-release phase), and Cmax (sustained-release phase); and for multiple-dose studies, AUC_0–τ, Cmax,ss, and Cτ,ss. In single-dose studies, assessment of both early-release and sustained-release Cmax is essential, with early-release Cmax being especially important due to its safety implications. The 90% confidence interval should fall within 80.00–125.00% for all parameters except Cmax (early release), for which the upper limit must not exceed 125.00% [18].

2.3.1.2 Complex dosage form: Albumin-bound Paclitaxel Nanoparticle powder for infusion Suspension,5mg/ml

Criteria for Demonstrating Bioequivalence (MWP)

Bioequivalence for albumin-bound paclitaxel requires a single-dose study administered at 260 mg/m^2 every three weeks in breast cancer patients, the criteria for demonstrating bioequivalence require an appropriately designed in-vivo study. A single-dose bioequivalence study should involve administration of 260 mg/m^2 every three weeks in breast cancer patients. Although infusion suspensions generally require in-vivo evaluation, an exemption may be granted if specific conditions are fulfilled, as the suspension dissolves rapidly upon entering the bloodstream. A crossover study design is recommended and the sample analysis may focus on the active compound, its metabolic product, or a combined analytical approach. Biological materials suitable for testing include plasma or serum, whole blood, and urine. A stereoselective analytical method should be applied when applicable.

Bioequivalence Evaluation

Primary pharmacokinetics parameters: Maximum concentration (Cmax) and area under curve from zero to final time point. 90% confidence range 80-125%.

Exemption from Bioequivalence Testing

An exemption from in vivo bioequivalence studies may be granted if comprehensive comparability of specific physicochemical properties is rigorously demonstrated. This study shall involve a full composition assessment, such as the paclitaxel-to-albumin ratio, distribution of particles sizes, verification of the non-crystalline nature of paclitaxel, ratio of free to bound paclitaxel, binding behaviour of paclitaxel/HSA, structural aspects of the particle as a whole, in vitro release of the drug after plasma dilution, polymeric nature of albumin in reconstituted form using size exclusion chromatography (SEC) and electric charge in plasma conditions. In order to ensure an accurate and statistically valid comparison, at least three batches of each sample (test and reference) should be considered, with at least ten replicates per batch. All statistical procedures should also be prospectively planned and validated before testing [19].

2.4 The EMA-FDA Concurrent Scientific Guidance Pilot Program

The EMA and FDA's joint pilot program to offer Concurrent Scientific Guidance (CSG) to applicants developing hybrid products (EMA) under Marketing Authorization Applications and complex generic products (FDA) under ANDAs is a noteworthy recent development in international regulatory cooperation. The program creates a framework that enables both agencies to concurrently review and respond to scientific questions during product development, with the goal of improving regulatory communication from the earliest stages of a complex product's lifecycle. In order to improve regulatory communication from the very beginning of a complicated product's lifetime, the initiative creates a structure that enables both agencies to concurrently

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examine and address scientific questions during product development.

The program comprises three stages of operation. Phase 1 involves applicants submitting a combined request for CSG to both agencies, which includes information on products and reference drugs, scientific questions with data and justification, and formal consent for information sharing between the authorities. Phase 2 involves both agencies confirming the meeting request and the applicant submitting a full meeting package using the FDA's preANDA Help system and the EMA's IRIS portal. Each agency offers independent written input in Phase 3 in accordance with its own standard operating procedures and deadlines. It is crucial to remember that the FDA and EMA have separate regulatory authority and may make different recommendations [14].

2.5 Regulatory Framework: BRICS COUNTRIES

2.5.1 BRAZIL

In Brazil, the regulatory authority for pharmaceuticals is the Agencia Nacional de Vigilancia Sanitaria (ANVISA). For generic medications to be registered in Brazil, pharmaceutical equivalency must be proven, and bioequivalence (BE) studies must be carried out to verify that the product is both stable and therapeutically equivalent to the original (innovator) medication [20].

In the context of generic drug regulation within Brazil and broader Latin American jurisdictions, bioavailability and bioequivalence requirements are governed primarily by RDC No. 60/2014, issued by the Brazilian Health Regulatory Agency (ANVISA), alongside relevant regional criteria [21,22]. For standard bioequivalence assessments, single-dose studies must evaluate critical pharmacokinetic parameters including area under the curve (AUC), maximum plasma concentration (Cmax), and time to reach maximum concentration (Tmax) with a sampling scheme designed to capture the complete pharmacokinetic profile by extending blood collection for a duration equivalent to at least three to five times the elimination half-life of the drug or its active metabolite.

For complex generics, RDC No. 60/2014, Chapter V, imposes additional specific requirements beyond routine administrative and technical documentation: applicants must submit a pharmaceutical equivalence certificate, a dissolution profile certificate, and a comprehensive report detailing the development and validation of the dissolution method, all prepared in strict accordance with applicable legislation. Critically, to ensure internal consistency and scientific reliability across the regulatory submission, bioequivalence or bioavailability studies must be conducted using the exact same batch of drug product employed in the pharmaceutical equivalence study, thereby creating a coherent evidentiary link between critical quality attributes assessed during development, pharmaceutical equivalence testing, and in vivo performance evaluation [23].

2.5.2 RUSSIA

In Russia, complex generic approval is overseen by the Federal Service for Surveillance in Healthcare (Roszdravnadzor).

The registration of standard generic medications fundamentally relies on demonstrating bioequivalence to the reference listed drug. These products must be qualitatively (Q1) and quantitatively (Q2) identical in active ingredient, dosage form, strength, and route of administration, and must establish through appropriate clinical studies that they are therapeutically or bioequivalent to the reference product. Bioequivalence research typically involves pharmacokinetic analysis following single-dose administration, requiring individual measurements of critical parameters including area under the concentration time curve (AUC, encompassing both AUCt and AUC∞), peak plasma concentration (Cmax), and time to reach peak concentration (tmax), with study designs applicable to both immediate- and modified-release formulations [24]. For complex generic products, however, conventional bioequivalence paradigms often require adaptation. Liposomal formulations intended for intravenous administration demand specialized pharmacokinetic methodologies to adequately characterize drug release and distribution. Emulsion-based products must match the reference product qualitatively and quantitatively in composition, with supporting evidence demonstrating close similarity in critical physicochemical attributes such as dispersed phase size distribution, surface properties (e.g., ζ-potential), and rheological behaviour. Similarly, injectable micelle-based medications classified as "advanced" formulations must replicate the reference product's composition at the time of administration and provide comparative data on key characteristics including critical micelle concentration, solubilizing capacity (including Maximum Additive Concentration), the ratio of free to bound active ingredient, and micellar size. For dermatological products intended for local or external application, systemic exposure assessment becomes essential when absorption may lead to systemic adverse effects; in such cases, bioequivalence is demonstrated by ensuring that the upper bound of the 90% confidence interval for systemic exposure metrics remains within the accepted threshold of 125.00%, confirming that the test product does not exceed the reference product's systemic exposure. Notably, due to their hybrid nature combining drug and device-like or formulation-specific complexities, all topical dermatological products are excluded from classification as ordinary generic medications and instead follow tailored regulatory pathways [24].

2.5.3 INDIA

In India, the Central Drugs Standard Control Organization (CDSCO) governs generic drug approvals. To prove therapeutic equivalency between a pharmaceutically equivalent generic product and its reference (innovator) product, regulatory bodies require Bioavailability (BA) and Bioequivalence (BE) studies. These investigations use both

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in vitro and in vivo techniques to assess the drug product's performance and quality.

Requirements for bioavailability and bioequivalence studies are structured around distinct statistical and methodological standards tailored to product complexity. For conventional single-dose studies, bioequivalence is established when the 90% confidence interval (CI) for the ratio of test-to-reference product for two critical pharmacokinetic metrics Area Under the Concentration–Time Curve (AUC) and Maximum Plasma Concentration (Cmax) falls entirely within the accepted range of 80.00% to 125.00%.

For drugs characterized by a long terminal elimination half-life, where single-dose monitoring is impractical, steady-state studies are required to adequately assess pharmacokinetic behaviour under conditions of repeated dosing [25]. However, for complex generic products and specific dosage forms, in vivo evidence of equivalence often necessitates approaches beyond traditional pharmacokinetic endpoints. This includes non-oral and non-parenteral formulations intended for systemic absorption (e.g., transdermal patches, suppositories), modified-release formulations designed for systemic action (e.g., sustained-release tablets), fixed-dose combination (FDC) products with systemic therapeutic effects, and locally acting, non-systemic dosage forms (e.g., nasal sprays, ophthalmic solutions, dermal applications, or rectal and vaginal preparations) where systemic absorption is not the intended mechanism. In these scenarios, conventional bioequivalence assessments based solely on plasma concentration measurements may be inappropriate or infeasible; instead, comparative clinical pharmacodynamic (PD) studies or full comparative clinical trials are often required to robustly demonstrate therapeutic equivalence. Importantly, even for locally acting products, targeted drug concentration measurements remain essential to detect and quantify any unintended systemic absorption, thereby safeguarding patient safety and reinforcing the overall equivalence assessment [25].

2.5.4 CHINA

In China, the National Medical Products Administration (NMPA) regulates generic drug approvals. For standard generic drugs, bioavailability and bioequivalence studies must adhere to well-defined statistical and methodological criteria to ensure therapeutic interchangeability with the reference listed drug. In single-dose studies, bioequivalence is demonstrated when the 90% confidence interval for the test-to-reference ratio of the area under the concentration–time curve (AUC) a key metric of relative bioavailability falls entirely within the accepted regulatory range of 80.00% to 125.00%. For drugs requiring multiple-dose administration, steady-state studies are employed, and it is essential to empirically verify that steady-state conditions have been achieved prior to pharmacokinetic sampling; this ensures that drug accumulation, elimination, and exposure profiles are accurately characterized under conditions reflective of clinical use [22].

Complex Generic Drugs:

Complex generics must meet all requirements applicable to both complex and non-complex generic drugs, in addition to their specific guidelines and regulatory requirements. Given the intricate nature of these product characteristics, researchers must perform comparative studies following a sequential approach was given in table 2.

Table 2: Sequential approach for comparative studies of Complex generics in China

Phase	Research type
Phase 1	Comparative CMC and non-clinical research
Phase 2	In vivo bioequivalence (BE) research
Phase 3	Clinical research
Phase 4 (required only if CMC research and /or non-clinical research indicate the product does not match the RLD)	The sponsor must enhance the formulation enhancing procedures, then repeat the studies the studies from phase 1 [26].

2.5.5 SOUTH AFRICA

In South Africa, the South African Health Products Regulatory Authority (SAHPRA) governs pharmaceutical approvals.

Standard Generic Products:

Bioavailability and bioequivalence assessments rely on specific pharmacokinetic standards. For single-dose evaluations, the primary parameters include AUC_t, AUC_∞, and Cmax. At steady state, immediate-release formulations follow approval criteria similar to those used in single-dose studies, with AUC_∞ applied in place of AUC_t. For controlled or modified-release formulations, the 90% confidence interval for the Test/Reference ratio of AUC_∞ must fall within the accepted bioequivalence range of 0.80–1.25 (80%–125%) [22].

Complex Generic Products:

Alternative source and generic submissions, as well as original manufacturer product extension submissions, may rely on clinical data to support the effectiveness and safety of a formulation, dosage form, indicated therapeutic use(s), or dosing schedule. In addition to clinical evidence, such submissions may demonstrate effectiveness through comparative dissolution evaluations, which serve as a critical surrogate marker for in vivo performance, or through additional comparative evaluations such as physicochemical, pharmacodynamic, or device-functionality assessments that further substantiate therapeutic equivalence. This regulatory framework also accommodates other product categories not explicitly covered above, including liquids and solutions, where conventional bioequivalence paradigms may not apply and alternative evidentiary approaches are justified [27].

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3. RESULTS

Following below are some examples of case studies that have been collected and found from some articles, websites and some internet sources.

3.1 Case studies of complex generic drugs approved across the USA, EU, and BRICS countries

The following case studies highlight regulatory approvals of complex generics in different regions. To begin with, the approvals granted by the US FDA are discussed below.

3.1.1Complex generics of various categories approved in USA (FDA)

The United States Food and Drug Administration (FDA) has approved complex generics across multiple therapeutic categories. These approvals reflect the agency's emphasis on ensuring equivalence in safety, efficacy, and quality for products with advanced formulations and delivery systems.

Category of Complex API

A complex API is a substance composed of multiple components with a molecular weight distribution. Such APIs are considered complex when the labelling indicates a mixture of active constituents or when the chemical structure contains repeating units or a specified molecular weight range.

Sevelamer carbonate- Case study 1

Renvela® is the brand name for Sevelamer carbonate, available as an 800 mg oral tablet. It is primarily indicated for the management of chronic kidney disease. The Abbreviated New Drug Application (ANDA) No. 207179 for this product was approved by the U.S. FDA for Aurobindo Pharma, with the Product-Specific Guidance (PSG) number 22127.

Renvela®'s molecular structure shows that it has an identical polymeric structure like that of Sevelamer hydrochloride but differs in terms of the counter ion, which is carbonate for Renvela® compared to chloride in the case of Sevelamer. Due to this, it is mandatory under FDA regulations for any generic manufacturer producing drugs to prove equivalence of the API used with that of the reference listed drug.

According to the given polymer structure, a and b represent the number of primary amine groups whose total sum is strictly limited to nine (a + b = 9). On the other hand, the variable c refers to the number of crosslinking groups, which is always equal to one (c = 1). Additionally, m refers to a very large number.

In 2015 the FDA issued product-specific guidance for sevelamer carbonate, providing instructions for API characterization and equivalence demonstration. Generic manufacturers are expected to follow the synthetic reaction specified in the RLD label.

Bioequivalence:

Bioequivalence for certain complex generics may be established through complementary in-vitro studies: an equilibrium binding assessment to compare maximum adsorption capacity and affinity, and a binding kinetics study to evaluate the rate and temporal profile of drug binding. Together, these mechanistic approaches demonstrate functional equivalence when systemic pharmacokinetic measures are not applicable or informative.

Following FDA recommendations, the first generic sevelamer carbonate received approval in 2017. It demonstrates that comprehensive API characterization, supported by appropriate analytical methodologies and PSG, is key to gaining FDA approval for complex generic products. A proposed generic formulation achieves Q1/Q2 status with the RLD when it contains identical inactive ingredients (qualitative Q1) at equivalent concentrations (quantitative Q2) [28, 29]. The sevelamer carbonate chemical structure is shown in figure 1[28].

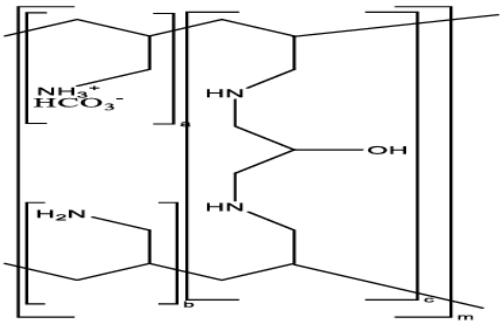

Figure 1: Sevelamer carbonate polymeric structure.

Enoxaparin-Case study 2

Lovenox® is the brand name for Enoxaparin, available as a 100 mg/1 mL subcutaneous injectable formulation. It is used as an anticoagulant to prevent and treat blood clots. The Abbreviated New Drug Application (ANDA) No. 77857 for this product was approved by the U.S. FDA for Sandoz Inc., under Product-Specific Guidance (PSG) number 20164.

Enoxaparin is a low molecular weight heparin (LMWH) that functions by enhancing the activity of antithrombin III, thereby inhibiting factor Xa and thrombin, which play crucial roles in the blood coagulation process. Generic manufacturers are required to demonstrate pharmaceutical equivalence and similar anticoagulant activity to the reference listed drug to ensure safety and efficacy. [29.]

The innovator drug Lovenox (SANOFI AVENTIS US LLC), containing enoxaparin, was approved by the FDA in 1993 (NDA 20164). The generic version was subsequently approved in 2003 (ANDA 77857, Amphastar Pharmaceuticals).

Five important conditions should be fulfilled in order to show API bioequivalence of enoxaparin sodium products apart from the traditional compendial criteria. First of all, it is necessary to show similarity between the tested product and the original one with respect to physical-chemical characteristics; then, the same source of heparin as well as the type of depolymerization have to be proven, because these factors determine the structure of the drug. It is also

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necessary to prove identical disaccharides, fragments, and oligosaccharides sequence. Finally, a biological activity of the tested product has to be shown using biological and biochemical tests and proved to be identical to that of the original one by showing its similar pharmacodynamics profile in vivo.

Since the proposed product fully complies with all the five conditions mentioned above, its sameness with the original is qualitative (Q1) and quantitative (Q2), which means that a waiver for bioequivalence studies has been granted for all dosages.

These five requirements are outlined in the FDA's response to a citizen petition (Docket No. FDA-2003-P-0273) and should be considered alongside the Draft Guidance on Enoxaparin Sodium (October 2011) [30].

In the EU, hybrid medicines are authorized under Article 10(3) of Directive 2001/83/EC. They require additional studies apart from that of traditional generics, usually when changes in strength, route, dosage form, or indication for use. Such approvals expand therapeutic options while maintaining safety and efficacy standards.

3.1.2 Hybrid medicines approved in EU

Category of Complex API

Glatiramer acetate -Case study 3

Glatiramer acetate is classified under the complex API category, as it is a non-biological complex drug (NBCD) composed of a heterogeneous mixture of synthetic polypeptides. In the case study of Glatiramer Acetate, the brand product Copaxone® is indicated for the treatment of multiple sclerosis (MS) and is available in injection dosage form. A generic version of this complex API received authorization on 12 April 2016, manufactured by Synthon [31].

Although the precise mechanism of action and the specific active components responsible for Copaxone's clinical effects remain unclear, the entire composition of Copaxone is considered the active pharmaceutical ingredient (API). Regulatory approval for Synthon's follow-on glatiramer acetate was supported by the GATE study (Glatiramer Acetate Clinical Trial to Assess Equivalence to Copaxone), a large, multi-center Phase III clinical trial. The study demonstrated equivalent safety and efficacy between Synthon's product and Copaxone, supporting its use as an alternative therapy. To date, Synthon is the only company to have conducted such a study and obtained regulatory approval in Europe for a glatiramer acetate product.

On April 12, 2016, the Netherlands-based biotechnology firm Synthon announced the favourable completion of distributed regulatory processes for their subsequent version of glatiramer acetate medication. This medicine, equivalent to the approved multiple sclerosis treatment Copaxone manufactured by Teva Pharmaceuticals, gained support from all 29 Member States involved in the decentralized procedures [32].

Category of Complex formulation

Ciclosporin-Case study 4

Sandimmun Neoral® is the brand name for Cyclosporine, which is used for the prevention of transplanted organ rejection. It is available as a 100 mg oral capsule. The product is manufactured by Alpharma ApS.

Cyclosporine is considered a complex drug because it is a narrow therapeutic index (NTI) drug with a highly variable absorption profile, requiring careful monitoring to ensure therapeutic effectiveness and safety. Generic versions must demonstrate bioequivalence, consistent pharmacokinetics, and therapeutic equivalence to the reference product before regulatory approval.

Background: Neoral, the branded version of ciclosporin, was made available in the EU through national approval processes, which initially caused variations in the information provided about the product across different member states.

To resolve these differences, the European Medicines Agency (EMA) started a referral process, which led to a more consistent approach in the approved uses and guidelines for the product throughout the EU (European Medicines Agency, 2020) [33].

Bioequivalence Recommendations:

The product is a generic medicine, meaning it is developed by showing that it has the same effect in the body as the original branded product, Neoral Capsules. In order to avoid using animals in unnecessary experiments, the developer is not required to repeat the non-clinical (animal-based) studies that were already done by the original manufacturer.

The marketing authorization for the product was granted based on Study 008/00, which was a two-way crossover, single-dose, open bioequivalence study. This study compared the test ciclosporin with Sandimmun Neoral® both in the form of 100 mg soft capsules. Twenty-four healthy volunteers took part in the study [34].

3.1.3 Complex generics in emerging markets: approved products in BRICS countries

Emerging markets such as the BRICS countries have increasingly recognized the importance of complex generics in improving access to advanced therapies. Notable approvals from Brazil, Russia, India, China, and South Africa are highlighted in this section, which reflects regional regulatory strategies and market demands.

3.1.3.1Case studies of complex generics approved by ANVISA in BRAZIL

Some authorized complicated generics in Brazil are shown in the case studies that follow.

Category of Complex route of delivery

Due to the difficulties with site-specific absorption, distribution, and therapeutic consistency, a local drug

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delivery method is typically considered complex. On the other hand, because of their more predictable pharmacokinetic and bioequivalency profiles, systemic modes of delivery are often not regarded as complex.

Buprenorphine-Case study 5

Buprenorphine, an opioid analgesic used to treat moderate to severe pain, is marketed under the trade name Restiva®. It comes in strengths of 5 µg/h, 10 µg/h, and 20 µg/h and is designed as a transdermal patch. The manufacturer of the product is ADIUM S.A. In order to support regulatory approval for a generic version in Brazil, this case study compares the bioequivalency, skin adhesion non-inferiority, and tolerability of a test buprenorphine transdermal patch with the reference product Restiva® [35].

Bioequivalence:

To verify that both patches exhibit similar pharmacokinetic characteristics, bioequivalency experiments were carried out. The findings showed that the test formulation met the bioequivalency standards set by the Brazilian regulatory body, ANVISA. Cmax, AUC_0–t (area under the concentration–time curve from zero to the last measurement point), and partial AUC values all had 90% confidence intervals that fell within the recognized bioequivalency range of 80% to 125%. These results verify that the test product's absorption and elimination properties are similar to those of the reference product.

Skin Adhesion Non-Inferiority:

It was discovered that the test formulation's skin adherence was not worse than that of the reference formulation. Over the course of the seven-day application period, both patches showed sufficient adhesion, guaranteeing that they stayed firmly in place throughout the dosage time. To assess the comfort and safety of the test formulation, a tolerability evaluation was conducted as part of a two-period, single-dose, randomized crossover study employing two treatment sequences. Of the 76 healthy male and female volunteers initially recruited, 52 successfully completed the entire study protocol. Throughout the trial, neither the test nor the reference formulation was associated with any serious safety concerns or adverse events, and all participants demonstrated good acceptance of both products. Overall, the findings confirm that the test formulation was well tolerated, exhibiting a favourable safety and comfort profile suitable for continued clinical development.

The test formulation of the buprenorphine transdermal patch was determined to be bioequivalent to the reference product, Restiva®, based on the results of the study. Additionally, when compared to the reference, the test patch demonstrated comparable tolerability and non-inferior skin adherence. These results met ANVISA's regulatory requirements for the approval and registration of the generic product in Brazil [35].

3.1.3.2 Complex generics approved in RUSSIA

The Federal Service for Surveillance in Healthcare is in charge of approving complicated generics in Russia. The nation's focus on increasing access to cutting-edge treatments while adhering to changing regulatory norms is evident in recent approvals.

Category of Complex formulation

Complex dosage forms, which frequently consist of several states of matter, are non-solution products for non-oral routes. Parenteral liposomes, long-acting polymeric microspheres, and semisolid formulations are a few examples of how their properties and delivery rates vary depending on the production method.

Glatiramer acetate-Case Study 6

Glatiramer Acetate is marketed under the brand name Copaxone® and is used to treat multiple sclerosis. It was approved in May 2016 and is given as an injectable. R-Pharm JSC is the manufacturer of the product. Glatirat, a generic form of glatiramer acetate, was introduced in May 2016 by R-Pharm JSC, a major Russian pharmaceutical business [36].

The primary goal was to demonstrate that Glatirat was equally safe and effective as Copaxone. In order to bolster this claim, R-Pharm carried out clinical research called GATE (Glatiramer Acetate clinical Trial to evaluate Equivalence to Copaxone®), which contrasted Glatirat with the original Copaxone.

The GATE Study:

One significant clinical experiment that assisted in determining whether Glatirat was bioequivalent to Copaxone was the GATE study. The study examined a number of significant factors:

Efficacy: In comparison to Copaxone, it assessed how well Glatirat prevented the disease from getting worse and decreased the number of relapses.

Safety: To ensure that using Glatirat was equally safe as using Copaxone, it looked for any new or different adverse effects

Immunological Response: To make sure that Glatirat's immuno-modifying effects were comparable to those of Copaxone, the study looked at how it affected the immune system, particularly the cells that assault myelin. Glatirat was approved as a generic medication in Russia since the study's findings demonstrated that it was therapeutically equal to Copaxone in terms of safety and efficacy [36].

3.1.3.3 Complex generics approved in INDIA

Complex generic approvals in India are managed by the Central Drugs Standard Control Organization (CDSCO). While guaranteeing a thorough assessment of quality and bioequivalency, the regulatory framework makes advanced medicines more accessible [37].

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Category of Complex formulation

Amphotericin B-Case Study 7

AmphoTLTM (Amphotericin B), a generic antifungal medicine used to treat severe fungal infections, is a component of AmBisome®. It comes in a liposomal injectable dose form and is administered as a 50 mg intravenous injection. In May 2021, the product was authorized.

In order to satisfy public demands, the Central Drugs Standard Control Organization (CDSCO) decided in May 2021 to commercialize AmphoTLTM. The first complex generic that CDSCO approved and that is therapeutically bioequivalent to Gilead's AmBisome is AmphoTLCTM. A license supply and marketing deal has been inked by Taiwan-based specialized pharmaceutical business TLC and internationally renowned pharmaceutical company Zydus to introduce Amphotericin B Liposome for Injection 50mg to the Indian market [38].

Amphotericin B in conventional formulations can seriously harm the kidneys, making treatment challenging, particularly for people who already have kidney issues. Liposomal amphotericin B was created to lessen renal toxicity while preserving the medication's efficacy in order to address this. Mucormycosis infections sharply increased in India during the pandemic, underscoring the critical need for affordable and safe antifungal therapies. AmphoTLCTM is just as safe and effective as the branded medicine AmBisome, according to bioequivalency tests. Additionally, patients who might not have the money to purchase the branded version can use it more easily due to its affordability [38].

3.1.3.4 Complex generic products approved in CHINA

In China, the National Medical Products Administration (NMPA) governs the approval of complex generics. Recent approvals reflect the country's drive to enhance patient access to innovative and high-quality medicines.

Table 3: Global Trends in Complex Generic Approvals: A Cross-Regional Case Study Analysis (USFDA, EMA, BRICS)"

S. No	Category of Complex Generic	Brand Name	Generic Name	Authority approved	Company got Approval
1.	Complex API	Renvela	Sevelamer carbonate	USFDA	Aurobindo Pharma
2.	Complex API	Lovenox	Enoxaparin	USFDA	Amphastar Pharmaceuticals
3.	Complex API	Copaxone	Glatiramer Acetate	USFDA	Mylan Laboratories
4.	Complex Formulation	Doxil	Doxorubicin Hydrochloride	USFDA	Dr.Reddy's Laboratories
5.	Complex route of delivery	Zovirax	Acyclovir	USFDA	Paddock Laboratories
6.	Complex route of delivery	Lidoderm patch	Lidocaine patch	USFDA	Mylan Laboratories
7.	Complex drug–device combination	ProAir HFA	Albuterol Sulfate	USFDA	Perrigo Pharmaceuticals
8.	Complex API	Lovenox	Enoxaparin sodium	EMA	Laboratories ROVI
9.	Complex API	Copaxone	Glatiramer Acetate	EMA	Synthon
10.	Complex Formulation	Bydureon®	Exenatide	EMA	AstraZeneca
11.	Complex Formulation	Sandimmum Neoral	Ciclosporin	EMA	Alpharma ApS
12.	Complex Formulation	Adriamycin	Doxorubicin Hydrochloride	EMA	Pfizer
13.	Complex Formulation	Neoral	Cyclosporin	ANVISA	Sigma pharma
14.	Complex Formulation	Neoparin	Enoxaparin	ANVISA	Eurofarma
15.	Complex route of delivery	Restiva®	Buprenorphine	ANVISA	ADIUM S.A
16.	Complex Formulation	Copaxone®	Glatiramer Acetate	FSSH	R-Pharm JSC
17.	Complex Formulation	AmBisome	Amphotericin B	CDSCO	Zydus (Import)
18.	Complex Formulation	Caelyx®	Doxorubicin Hydrochloride	NMPA	Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co., Ltd.
19.	Complex Formulation	AmBisome	Amphotericin B	NMPA	Sichuan Huiyu Pharmaceutical Co., Ltd
20.	Complex route of delivery	Voltaren	Diclofenac sodium gel	NMPA	Nanjing Chang Ao Pharmaceutical Co., Ltd
21.	Complex route of delivery	Lidoderm®	Lidocaine	NMPA	Teikoku Pharma
22.	Complex drug–device combination	MP-AzeFlu (Dymista®)	AzeFlu	NMPA	Changfeng Pharmaceutical Co.Ltd.
23.	Complex drug–device combination	Faslodex	Fulvestrant	NMPA	Sino Biopharmaceutical Limited

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Category of Complex route of delivery

Lidocaine Patch-Case study 8

Lidoderm® is the brand name for lidocaine; an analgesic used for the management of localized pain. It is formulated as a 5% topical transdermal patch, allowing the drug to be delivered directly through the skin for localized therapeutic action. Teikoku Pharma USA, Inc. is the manufacturer of the product, which was granted marketing permission in May 2024[39].

Clinical assessment and bioequivalency: To ensure that the generic lidocaine patch provides lidocaine at a rate and extent similar to the reference product, Lidoderm®, bioequivalency studies were conducted. Comparable treatment performance and safety were confirmed by the findings. Clinical trials were carried out to show the generic formulation's safety and effectiveness in conditions such post-herpetic neuralgia (PHN) and other localized pain indications in accordance with NMPA regulations. In China, these investigations played a crucial role in the approval process. Because of China's stringent regulations, the approval of generic drugs may take a long time. To demonstrate similarities with the branded reference product, bioequivalency data and clinical efficacy evidence are needed for items like the lidocaine patch[39]. For those with localized neuropathic pain and post-herpetic neuralgia (PHN), the licensing of generic lidocaine patches in China is a major step toward expanding access to pain relief. The generic drug has the potential to enhance patient outcomes, lower healthcare costs, and expand access to therapy by offering a more reasonably priced substitute for the branded Lidoderm®[39].

3.1.3.4 SOUTH AFRICA

The publicly accessible literature and regulatory databases investigated during this study did not contain any particular approvals of complicated generics in South Africa.

4. DISCUSSION

Case studies analysis from the above Table 2

4.1 Bar graph of Number of approved Complex Generics from case studies by country

The bar graph in figure 2 illustrates the number of approvals granted across various regions. The total number of approvals were 23 from the case studies that have been collected. The United States recorded the highest number of approvals (**7**) which was observed due to PSG availability for complex generics [40], followed by China (**6**) and the European Union (**5**). Brazil reported **3** approvals, whereas Russia and India had only **1** approval each. Notably, South Africa had **no approvals** within the observed category. Overall, the data highlights that the USA, China, and the EU are leading regions in terms of complex generic approvals compared to other countries.

4.2 Pie chart of distribution of selected Complex Generics by complexity type

The pie chart figure 3 describes the distribution of selected complex generics based on their type of complexity. Complex formulations represent the largest share (**39%**, 9 products), followed by complex APIs (**26%**, 6 products) and complex routes of delivery (**22%**, 5 products). Complicated drug-device combos make up the least amount (**13%,** 3 items). This suggests that among the chosen approvals, formulation-related difficulty is the most common

4.3 Pie chart for demonstration of proportion of Complex Generics by Dosage form

The distribution of complicated generics by dose form is shown in the following pie chart, figure 4. The highest percentage (52%) is made up of injectables, with transdermal patches and nasal sprays coming in second and third, respectively, at 13%. Suspensions account for 5% and capsules for 9%. With 4% each, tablets and gels are the least popular dosage types. This demonstrates that, in comparison to other dosage forms, injectable formulations predominate among complex generic approvals.

4.4 Bar graph on Year-wise approval of complex Generics in USA and EU

A comparison of complex generic approvals in the US and the EU by year from 2003 to 2022 is shown in Figure 5. Overall, there weren't many approvals throughout this time. With three items approved in 2017, the US saw its highest number of approvals; in contrast, the EU displayed a more stable pattern, with just a few chosen years seeing single approvals.

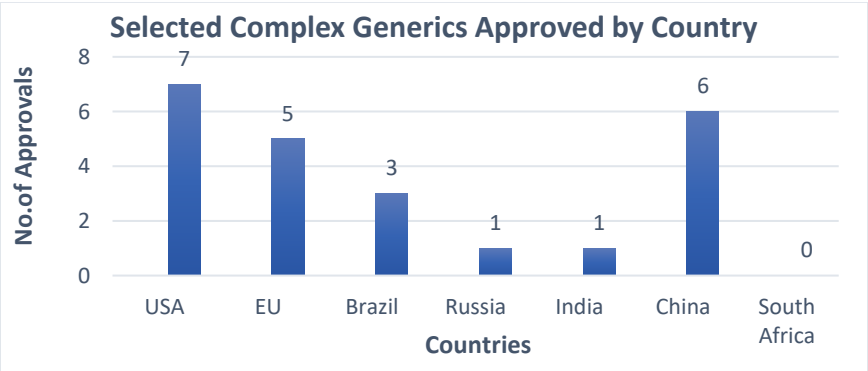

Figure 2: Number of Selected Complex Generics Approved by Country

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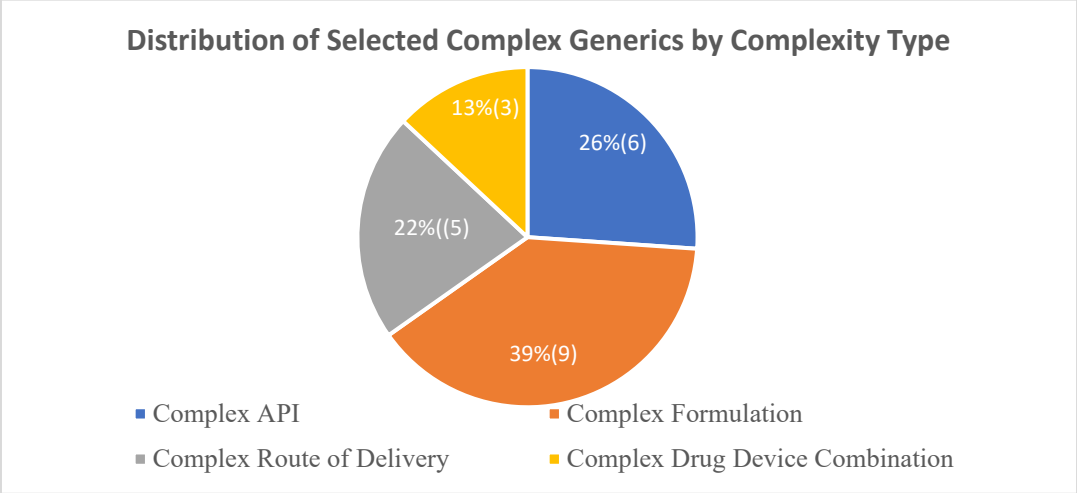

Figure 3: Distribution of selected complex generics by complexity type

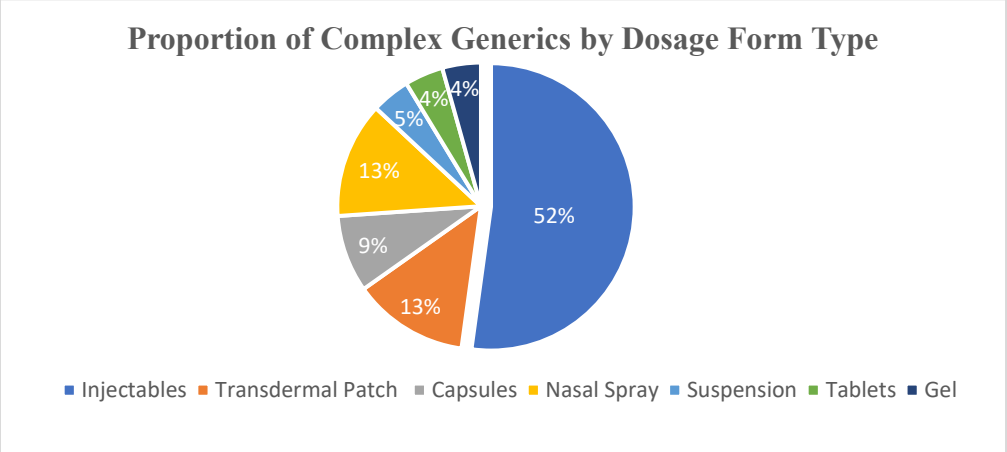

Figure 4: Percentage Share of Complex Generics by Dosage Forms

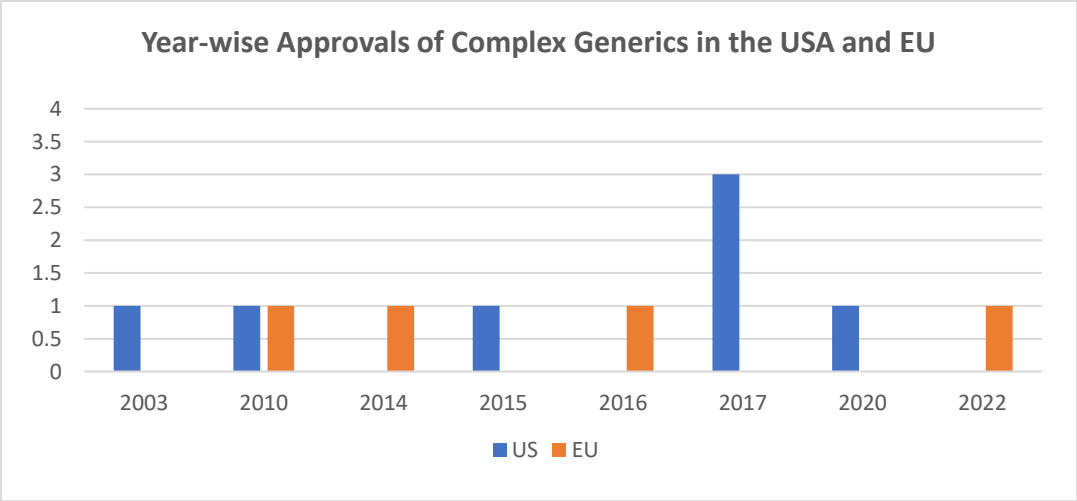

Figure 5: Year-wise Approvals of Complex Generics in the US and EU (2003–2022)

CONCLUSION

The increasing popularity of complex generics, which are distinct from ordinary generics because of their complicated structures, sophisticated formulations, and specific delivery systems, is causing the global pharmaceutical industry to change quickly. Additional non-clinical, in vitro, and clinical research is frequently needed for their evaluation in order to guarantee safety and equivalency. However, despite such regulatory challenges, complex generics play an important role in providing greater access to superior and affordable medicines in the global context.

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This research aimed to compare regulatory approaches and practices concerning complex generics in the USA, EU, and BRICS countries. The findings indicate that there are quite effective scientific-based approaches used by the US FDA and EMA in their approval process – Product-Specific Guidances (PSGs) for the former and the Hybrid Medicine pathway for the latter. At the moment, the collaboration in Product-Specific Assessment (PSA) has become a major breakthrough in terms of regulatory cooperation.

BRICS nations, however, demonstrated somewhat inconsistent progress in this area. In South Africa, India, and Russia, certain deficiencies in regulation and development remain due to their insufficient infrastructure and legislation. Meanwhile, China and Brazil have achieved considerable success due to various reform efforts and positive approvals. The approvals of injectable and formulation-based pharmaceuticals prevail in the field, and BRICS countries are dominated by the USA, EU, and China, as the statistics provided through bar and pie charts suggest. Some examples of these drugs include liposomal doxorubicin (Doxil®), lidocaine patch (Lidoderm®), and glatiramer acetate (Copaxone®).

Overall, the study comes to the conclusion that the greatest obstacle to worldwide complicated generic access is still regulatory heterogeneity. Accelerating approvals requires strengthening international cooperation, standardizing product-specific guidelines, and developing regulatory capability in new areas. Enhanced convergence and reliance frameworks will help ensure that complex generics achieve their full potential in providing equitable and affordable therapies worldwide.

LIST OF ABBREVIATIONS

ANDA	Abbreviated New Drug Application
GDUFA	Generic Drug User Fee Amendments
RLD	Reference Listed Drug
API	Active pharmaceutical ingredient
DCAP	Drug Competition Action Plan
NBCDs	Non -Biologic Complex Drugs
FDA	Food and Drug Administration
EMA	European Medicine Agency
NMPA	National Medical Products Administration
CDSCO	Central Drugs Standard Control Organization
SAHPRA	South African Health Products Regulatory Authority
BCS	Biopharmaceutical Classification Scheme

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