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REVIEW ARTICLE

Current Regulatory Framework and Challenges for the Approval of Complex Generics in the US and the EU

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Abstract:

The pharmaceutical industry is witnessing a growing demand for complex generic products, which are generic versions of drugs that possess complex formulations, delivery systems, or active ingredients. However, the approval process for these complex generic products poses unique challenges compared to traditional generics. There is no specific regulatory procedure available for the approval of complex generics, unlike small-molecule generics and biosimilars. This led to controversial arguments in the past about the scientific evidence needed for applications, which led to lengthy approval processes. The regulatory frameworks that are currently being used for complex generics are debatable and unclear. Complexity in the molecular structure, mechanism of action, route of delivery, and complex manufacturing process makes proving bioequivalence and pharmaceutical equivalence difficult. There is a need for harmonization of the regulatory framework by the agencies to help the generic manufacturers by providing scientific advice, defining the submission requirements for complex products, and fastening the approval process.

This review begins by discussing the regulatory landscape surrounding complex generic products in various regions, including the United States and Europe. It examines the specific guidelines and requirements set forth by regulatory authorities to ensure the safety, efficacy, and quality of these products. Additionally, the review explores the differences in terminology and definitions used to classify complex generics across different jurisdictions. Furthermore, it delves into the challenges faced by both regulatory agencies and pharmaceutical companies in evaluating and approving complex generic products. These challenges include establishing appropriate bioequivalence criteria, determining interchangeability with the reference product, addressing patent and exclusivity issues, and ensuring consistent quality throughout the product lifecycle. The impact of these challenges on market entry and competition is also discussed. The review highlights the need for harmonization and streamlining of regulations for complex generic products worldwide. It emphasizes the importance of clear and consistent guidelines to enable timely approvals, foster innovation, and facilitate patient access to affordable alternatives.

Keywords: Complex drugs, Complex generics, Harmonization, Follow-on generics, Regulatory framework, Low molecular weight heparins.

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1. INTRODUCTION

Complex generics is the term used for generic copies of drug products with complex formulations, complex active pharmaceutical ingredients (APIs), complex routes of administration, complex drug-device combination products, and complex dosage forms or other characteristics that make it difficult to demonstrate bioequivalence [1].

According to the Generic Drug User Fee Amendments (GDUFA III) commitment letter, 2022, the USFDA defined complex generics as:

• Complex active ingredients, *e.g.*, complex mixtures of APIs, polymeric compounds, and peptides.

• Complex formulations, *e.g.*, liposomes, suspensions, emulsions, and gels.

• Complex routes of delivery, *e.g.*, locally acting, such as ophthalmic, otic, dermatological, and inhalational drugs.

• Complex dosage forms, *e.g.*, long-acting injectable and implantable.

• Complex drug-device combinations, *e.g.*, metered dose inhalers and transdermal.

European Medicines Agency (EMA) uses the term "non-biological complex drugs" (NBCDs) instead of "complex generics" or "complex drugs." NBCDs are large, highly complex, synthetic compounds made of complex API and excipients but differ from biological products [2].

While regulatory guidelines for small molecule generics

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are well established, it is still evolving for complex generics. Complex generics involve supramolecular drugs [3], such as nanotherapeutics, for which establishing similarity to the reference product is difficult [4 - 6]. "Drug Price Competition and Patent Term Restoration Act," also known as the Hatch-Waxman Act of 1984, established a scientific and regulatory framework for the development of generics for branded drugs. These amendments outlined a pathway for generic applicants submitting an abbreviated new drug application (ANDA) to the US Food and Drug Administration (USFDA) that includes chemistry manufacturing and control (CMC) information and evidence to support bioequivalence to Reference Listed Drug (RLD) for the approval of an ANDA [7]. However, advancements in pharmaceutical science and the scientific complexity of drugs have made establishing pharmaceutical equivalence (PE) and bioequivalence (BE) difficult [8]. Complex generics can be difficult to develop, which can put patients at risk for drug shortages and restrict their access to cost-effective, high-quality medications [9].

There is a need to create generic versions of these complex drugs because they are utilized to treat chronic and fatal conditions like diabetes mellitus, hepatitis C, malignancies, central nervous system disorders, *etc*. The animal studies, clinical studies, and BA studies conducted for New Drug Application (NDA) are substituted by bioequivalence (BE) testing in the ANDA [10]. Therapeutic equivalence (TE) to the innovator product should be demonstrated through pharmaceutical equivalence (PE) and BE for generics to be approved for marketing [11]. The majority of small molecule generics are fully characterized by homomolecular, low-molecular-weight drugs. As a result, demonstrating TE for such drugs is relatively simple [12]. However, scientific challenges are related to demonstrating PE and BE for complex generics for which the ANDA pathway is applied. This necessitates a stepwise approach to compare the RLD and complex generic drugs to establish therapeutic equivalence. Table **1** describes the differences between the small molecule, non-biological complex drugs, and biologicals based on their characteristics.

Table 1. Comparison between small molecules, biologicals, and NBCDs.

-	Small Molecule	Biologicals	NBCDs
Synthesis	Chemically	Biological source	Chemically
Molecular weight	Has a low molecular weight	Has a high molecular weight	Has a high molecular weight
Structural characteristics	Well-characterized	Not well-characterized, heterogeneous	Not well-characterized, heterogeneous
Manufacturing process	Independent of process variables	Strongly dependent on process variables	Strongly dependent on process variables
Immunogenicity	Not immunogenic	Immunogenic	Immunogenic
Stability	Stable	Relatively unstable	Partly stable

For small molecules, the demonstration of bioequivalence and pharmaceutical equivalence to RLD is relatively straightforward, and established regulatory guidelines are available. Due to the complex molecular structure and novelty, it is challenging to show PE and BE to the RLD for complex generics [13]. Therefore, more research is needed to prove this similarity. Fig. (**1**) provides an overview of the challenges for demonstrating BE and PE and the increase in product complexity ranging from simple small molecules to complex inhalers.

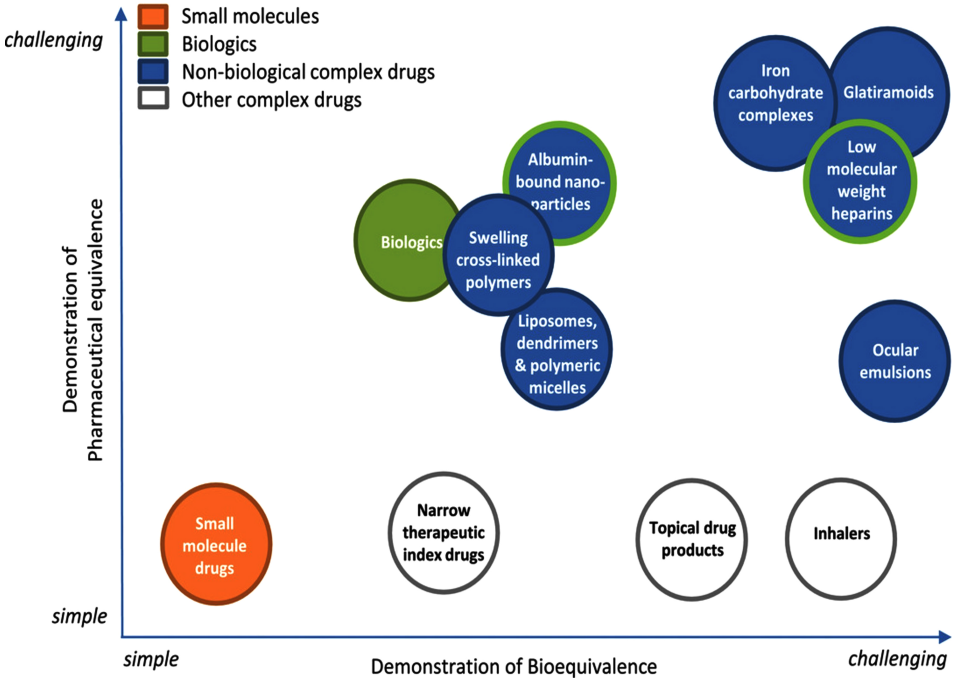

Fig. (1). Overview of challenges for demonstrating bioequivalence and pharmaceutical equivalence to RLD [12].

Table 2. Branded complex drugs for which the first generic drug is approved (FDA, Orange Book Database, 2023).

Brand Name	Generic Name	Indication	First Generic Approved	Number of Generic Approved	References
Lovenox	Enoxaparin sodium injection	Blood clots	2010	3	[21]
Ferrlecit	Sodium ferric gluconate complex	Anaemia	2011	1	[21]
Copaxone	Glatiramer acetate injection	Multiple sclerosis	2015	4	[21]
Venofer	Iron sucrose complex	Iron deficiency anemia	-	0	[17]
Eligard	Leuprolide acetate	Prostate cancer	-	0	[19]
Bydureon	Exenatide	Diabetes mellitus	-	0	[22]
Sandostatin	Octreotide acetate	Acromegaly	-	0	[17]
NuvaRing	Ethinyl estradiol, Etonogestrel	Female contraceptive	2019	2	[14]
Restasis	Cyclosporine	Tear production	2022	2	[17]
Forteo	Teriparatide	Osteoporosis	-	0	[17]
Abraxane	Paclitaxel	Breast, lung cancer	-	0	[17]
Risperdal Consta	Risperidone	Schizophrenia	-	0	[17]

There are a few guidelines published by the FDA that can assist generic companies in developing complex generic products.

• "Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA" [14].

• "Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs" [15].

• "Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs" [16].

• "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin" [17].

• "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" [18].

For many complex drug products, patent coverage or exclusivity has expired, but still, there are few or no approved generic products available (Table **2**). The complexity associated with these products ultimately limits the scope of generic companies to manufacture and prove sameness to RLD. However, the knowledge and capabilities in research and manufacturing cannot be widely used as a platform technology [19]. Also, due to the lengthy timelines for the development, complicated BE research designs, and demand for manufacturing process similarity, there is a high-risk, high magnitude of investment for developing complex generics [20]. An overview of branded complex drugs is presented in Table **2** for which the patent protection has expired, but currently, very few or no generic drug has been approved by the USFDA.

Most of these complex drugs are used to treat severe and life-threatening diseases. Currently, only a few generic products are available for these complex products, increasing the treatment cost and load on the healthcare industry. Bringing complex generics can save the cost of the healthcare system and benefit society. In 2019, the FDA approved a complex generic version of Advair Diskus®, which is used for the treatment of asthma and chronic obstructive pulmonary disease. The out-of-pocket expense for generic Advair Diskus® was less than half that of the brand medicine, based on the FDA's Office of Generic Drugs Annual Report, 2019. According to GlaxoSmithKline, sales of Advair Diskus® dropped from $1.4 billion in 2018 to $641 million in 2019. Within a year of its release, generic versions of Advair Diskus® managed to take over half of the market, according to IQVIA data [17].

The developmental and regulatory requirements of complex generics vary case to case basis. There is an urgent requirement for faster approval of complex generics with affordable medicines to benefit patients [15, 23]. Therefore, it is essential to streamline the regulations for complex generic drug products to ensure a sustainable and balanced healthcare system and to accelerate the approval process for complex generics.

More background information about complex generics is described in the following sections, and case studies regarding complex generics and their approval processes in the EU and the US are discussed, along with developmental and regulatory problems encountered for the approval of complex generics.

2. REGULATORY FRAMEWORK

The approval of complex generics remains ambiguous, and the scientific basis for approval has yet to be established. These are complex molecules, a complex mixture of API and peptides prepared by the synthetic route. However, as they are not biologics, the biosimilar approval pathway does not appear to be relevant [15]. They are, therefore, intended to be approved *via* the generic approval pathway. The challenge is due to their complexity and the difficulties in showing bioequivalence. As a result, regulatory authorities are required to set up procedures and offer product-specific guidance for the approval of complex generics.

2.1. Regulatory Framework in Europe

2.1.1. Article 10(1): Generic Medicinal Product Application

For a generic drug having the same pharmaceutical form and active ingredient composition, both qualitatively and quantitatively, as the reference listed drug, the applicant can apply for Article 10(1). The complete data on pharmaceutical

quality (CMC), as well as bioequivalence (BE) data between the RLD and generic medicinal products, should be provided. Nonclinical and clinical testing results are not usually required.

2.1.2. Article 10(3): Hybrid Medicinal Product Application

When the active ingredient, strengths, indication, pharmaceutical form, or method of administration differs from the RLD, the hybrid application approach is used. The applicant relies on nonclinical and clinical data from the reference product to some extent, and to establish equivalence, appropriate preclinical and clinical trials are required.

2.1.3. Article 10(4): Biologic Product Application

Due to inherent variability in biological sources, biosimilars are not considered generics of a biological reference product. Although they are not exactly the same as the RLD, biosimilars are regarded to be substantially comparable to them. To make sure that minute variations do not adversely affect safety or efficacy, biosimilars need more investigation than generic drugs. A comparison of the biological activity and structure of the biosimilar to the RLD, as well as information on the biosimilar's pharmaceutical quality, must be provided. The biological function, effectiveness, safety, and immunogenicity data may be necessary to show similarity. Fig. (**2**) provides an overview of the regulatory pathways used for approval in the EU.

2.2. Regulatory Framework in the US

2.2.1. 505(b)(1) Application

This route is for new drug applications with active ingredients that have never been studied or approved. In the 505(b)(1) pathway, the sponsor conducts all necessary studies to show the drug's safety and efficacy. All clinical and nonclinical studies must be carried out by or on behalf of the drug development sponsor. These submissions necessitate extensive research and may take years to complete. They also require a significant investment in order to gain approval. The original developer owns the right of reference for any data or findings gathered during the original investigation in 505(b)(1) applications.

2.2.2. 505(b)(2) Application

The applicant submits in parts full reports on safety and efficacy data but also relies on literature and the FDA's finding of safety and effectiveness for an approved drug. 505(b)(2) application is used when there are changes in the dose, formulation, route of delivery, new combination and new indication compared to RLD.

2.2.3. 505(j) Abbreviated New Drug Application

The ANDA applicant needs enough data to show that the generic drug product has the same API, route of administration, dosage form, strength, and generally the same labelling as RLD. They need not provide nonclinical and clinical data for the generic drug product. The generic medicine product's bioequivalence to the RLD must also be shown by the applicant.

2.2.4. 351(k) Biosimilar Application

FDA defines biosimilars as "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and also, "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the pro-

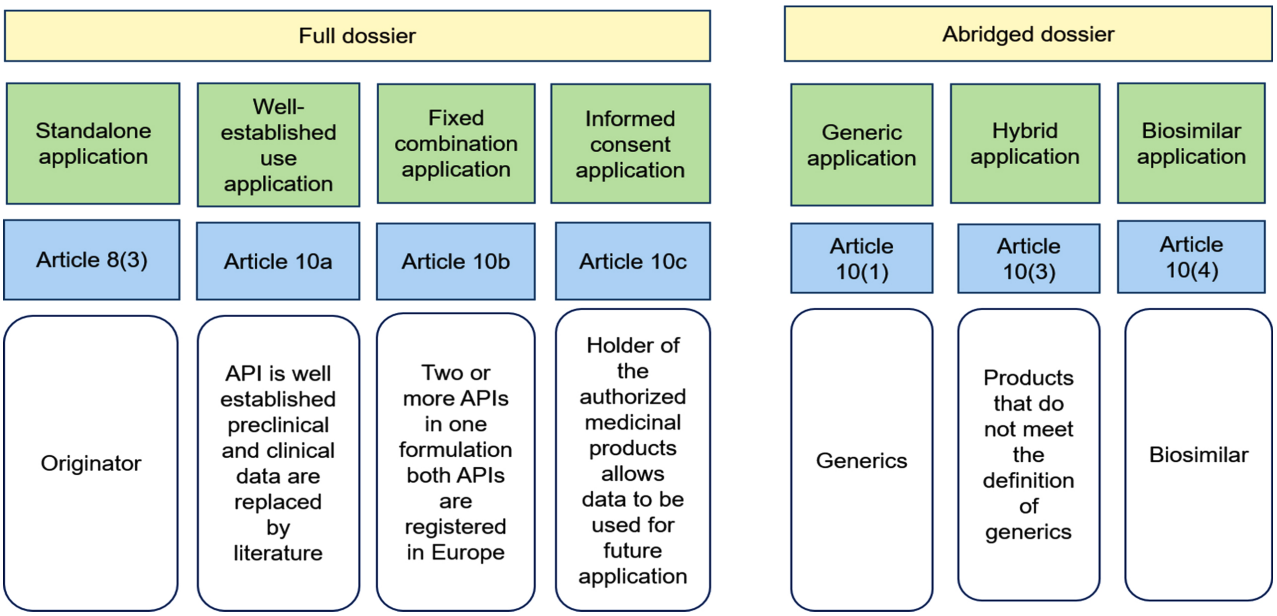

Fig. (2). Overview of the regulatory framework of the EU.

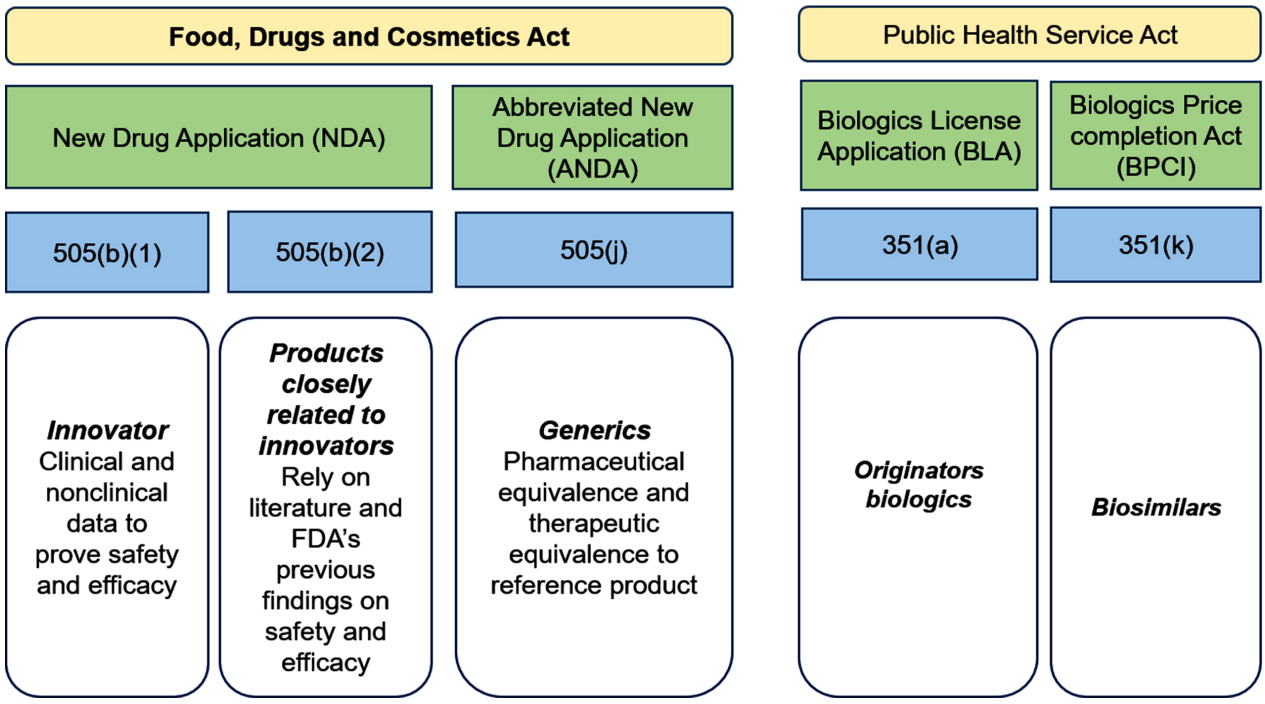

Fig. (3). Overview of the regulatory framework in the US.

duct." A step-by-step process begins with a thorough analytical characterization and is followed by clinical studies comparing the RLD and biosimilar for safety and efficacy using both preclinical studies and human trials. FDA evaluates biosimilars using a "total-of-the-evidence" approach that compares structure, function, human pharmacokinetics and pharmacodynamics, animal toxicity, and clinical immunogenicity.

Fig. (**3**) provides an overview of the regulatory pathways used for the approval of products in the US.

3. CHALLENGES FOR APPROVAL OF COMPLEX GENERICS

Most simple generics are fully characterized by homomolecular, low-molecular-weight drugs. As a result, demonstrating TE for such drugs is relatively simple. A problem arises when it comes to complex products, which require characterizing a mixture of complex APIs, complex excipients, impurities, clinical effects, and safety profiles [16]. It is also difficult to establish bioequivalence because the products have complex mechanisms of drug release, and some of the products act locally, so measuring systemic concentrations of the drug does not prove equivalence.

FDA uses a weight-of-evidence approach, in which the amount of evidence required for the authorization of a specific complex drug product is assessed on a case-to-case basis. This results in uncertainty in the amount of data that should be submitted for approval of complex products. Information required to demonstrate sameness for generic product to be submitted as ANDA faces several challenges as given below:

3.1. Demonstrating API Sameness

When submitting a product through ANDA, it is necessary to show API in a proposed generic is the same as RLD. FDA recommended applicants use the same API as used in the RLD and fully evaluate the changes in the API during the manufacturing process. FDA will reject an ANDA if it lacks sufficient information to demonstrate API sameness [24].

Complex APIs include peptides (liraglutide, dulaglutide, exenatide), polymers (sevelamer carbonate, colesevelam hydrochloride), naturally obtained complex mixtures, and other complex drug substances, such as synthetic nucleotides and iron sucrose complexes [25]. Demonstrating API sameness for small molecules is simple by using characterization tools like HPLC, TLC, laser diffraction analysis, electron microscopy, NMR, and other analytical tools. However, for complex API, it becomes a problem due to a lack of sophisticated analytical techniques and the complexity of the molecules.

4. CASE STUDY

Sevelamer carbonate (Renvela®) was approved in 2007 as a phosphate binder prescribed to control serum phosphorus in patients with chronic kidney disease [26].

According to the label of Renvela®, sevelamer carbonate has a polymeric structure the same as sevelamer hydrochloride, where carbonate replaces chloride as a counter ion [27]. As sevelamer hydrochloride is poly (allylamine hydrochloride) crosslinked with epichlorohydrin, the FDA recommends generic applicants to prove API sameness. The structure of the sevelamer carbonate polymer is shown in Fig. (**4**).

a, b= number of primary amine groups (a+b=9)

c= number of crosslinking groups (c=1)

m= large number indicates extended polymer network

More than 20 ANDAs were submitted but failed to get approval due to a lack of specific techniques to characterize the API and prove sameness to the RLD. Pharmaceutical characterization of the polymeric sevelamer is complicated by its high molecular weight, amorphous composition, and insolubility. Traditional solution-based techniques like high-performance liquid chromatography-mass spectrometry (HPLC-MS) or liquid-state nuclear magnetic resonance (NMR) spectroscopy could not be employed because sevelamer is insoluble in both water and organic solvents.

FDA released product-specific guidance for sevelamer carbonate in 2015, which assisted the generic applicant in successfully characterizing the API and proving sameness. FDA recommended the use of the same reaction scheme as on the RLD label for synthesis 28.

The characterizations of sevelamer carbonate should include the following to prove sameness:

• Degree of crosslinking (C13 solid-state NMR)

• Degree of protonation

• Total titratable amine

• Particle size

• Elemental analysis

• Swelling index

• Additional characterizations by using FTIR, Raman, XRD, DSC

Bioequivalence

– *In-vitro* equilibrium binding study

– *In-vitro* kinetic binding study

Based on the recommendations of the FDA, in 2017, the first generic sevelamer carbonate received approval. This indicates the need for proper analytical tools and PSG for characterization and faster approval of complex APIs.

FDA published draft guidance in 2022 on "Sameness Evaluation in ANDA for active ingredients" to assist applicants by giving suggestions on demonstrating API sameness between the RLD and generic product. Synthetic peptides consisting of 40 or a few amino acids are considered drugs and not biologics. API sameness should be demonstrated using appropriate orthogonal analytical techniques for characterizing [24]:

• Primary amino acid sequence

• Secondary and higher order structure

• Aggregation of peptides

• Biological activity

4.1. Complexity in Q1/ Q2 Requirement

A proposed generic formulation is Q1/Q2 to RLD if it contains the same inactive ingredients (qualitatively Q1) and in the same concentration (quantitatively Q2). The proposed product's inactive substances must be identified and described by the application, along with proof that they do not affect the product's safety or effectiveness.

4.2. Q1: The Identity of an Inactive Ingredient

Each inactive ingredient's chemistry and grade, as well as any necessary characterization data, must be provided in detail.

4.3. Q2: Quantity of an Inactive Ingredient

Determine the percentage difference (%) between a generic (T) and reference product I (*i.e*., [(T-R)/R] x100). Differences of less than 5% are considered acceptable.

Q1/Q2 sameness is mostly sufficient to prove sameness to 'LD's performance, but it may not always be adequate for complex generics. Certain complex ANDAs, such as topicals and inhalational products, require consideration of Q3 similarity.

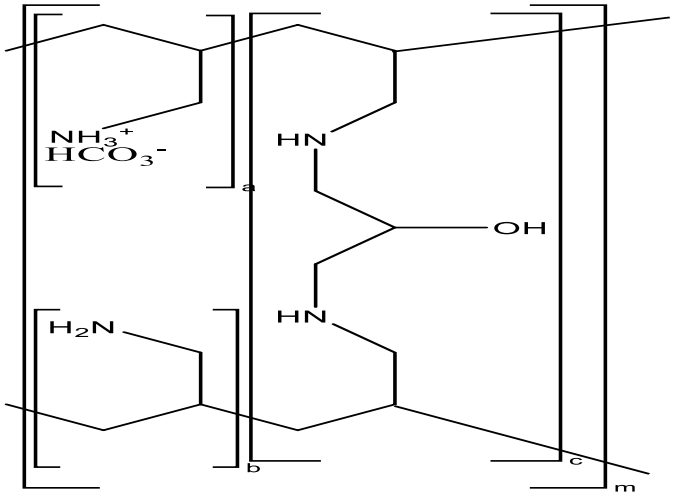

Fig. (4). Sevelamer carbonate polymeric structure.

4.4. Q3: Physicochemical Sameness

The matter arrangement (physical and structural properties) is comparable to the RLD. Q3: Similarity reduces the risk of physicochemical variations in a generic drug product, such as:

- Differences in a drug's polymorphism
- Differences in rheology
- Differences in crystallinity that can affect drug diffusion

These properties show a significant impact on the performance of a generic drug product when evaluating products, such as ophthalmic suspensions and multi-phase creams. As a result, many PSGs, particularly those for topical ANDAs, advise Q3 evaluation.

Complex generics, such as long-acting injectable, generally uses poly-lactic glycolic acid (PLGA) polymer due to their composition and physicochemical properties, which allows controlled API release and polymer degradation [29, 30]. A detailed knowledge of the PLGA in RLD is necessary to develop a generic PLGA-based product with equal clinical effect and quality [22]. Due to PLGA's inherent heterogeneity and the product-specific modifications that result from the manufacturing process and storage conditions, it is challenging to evaluate and achieve Q1/Q2 sameness for generic products.

4.5. Constitution

PLGA is a copolymer with a random sequence of lactic and glycolic acid that is typically produced by ring-opening polymerization of lactic acid and glycolic acid cyclic dimers. Due to the methyl group on the ß-carbon of lactic acid (L), it is more hydrophobic and less crystalline than glycolic acid (G) [19]. The polymer with a high lactic acid ratio will be more hydrophobic than the low ratio polymer. The less hydrophobic polymer will absorb water quickly and hydrolyze faster, resulting in faster drug release [31]. Many lots of each product must be tested to detect variability and any potential deviations from the theoretical ratio to ensure an accurate comparison between a proposed generic and RLD.

4.6. Molecular Weight

It is crucial to understand that the molecular weight of the PLGA in the RLD may be much lower than the initial raw material [32]. Variable PLGA degradation may be caused by changes in the production process (such as exposure to heat and water). During manufacture, tertiary amine-containing APIs like risperidone and naltrexone will hasten PLGA's hydrolytic breakdown. As a result, to evaluate the qualitative sameness of PLGA in a proposed generic product, the molecular weight of the PLGA in the finished formulation should be evaluated [19, 33].

5. BIOEQUIVALENCE OF COMPLEX GENERICS

Demonstration of therapeutic equivalence is very challenging for complex generics compared to small molecules due to the complex route of delivery, complex formulation, and complex API.

5.1. Complex Route of Delivery

Traditional BE studies focus on the systemic exposure of active moiety to compare the proposed generic and RLD. This approach is insufficient to detect very low levels of a drug in the systemic circulation after ophthalmic administration. FDA recommends two approaches in this case: *in-vitro* or *in-vivo* patient studies. If the test and reference formulations are Q1/Q2 identical, extensive *in-vitro* comparative physicochemical (Q3) characterization will suffice to prove bioequivalence. Medications that are not Q1/Q2, pharmacokinetic (PK) studies in patients are suggested alternatively [33].

5.2. Complex Formulation

Comparable tissue exposure may not always reflect similar systemic exposure in terms of total drug concentration for complex generics. The parenteral solutions, such as pegylated liposomal doxorubicin or protein-bound paclitaxel particles for injectable suspension, show formulation-dependent target site drug distribution [34]. Hence, choosing the relevant therapeutic surrogate endpoint to eliminate discrepancies between systemic exposure and target site disposition is the most challenging aspect of proving BE for complex formulations. Hence, the evaluation of total and unbound or free and encapsulated drug concentrations is typically part of the BE demonstration. Also, it is advised to compare the size distribution of *in-vitro* particles and liposomal size using the population BE technique and show compositional equivalence.

5.3. Complex Active Ingredient

The main issue is the demonstration of the sameness of API obtained from different manufacturers. The best example of this is glatiramer acetate. While the formulation is simple, a prefilled syringe containing 1 ml of a solution containing 20 mg of glatiramer acetate and 40 mg of mannitol, demonstrating that peptide copolymer mixture is the same in the proposed generic and RLD is difficult [33]. The most recent research recommends using four-stage criteria that focus on demonstrating: "the equivalence of fundamental reaction scheme, equivalence of physicochemical properties, including compositions, equivalence of structural signatures for polymerization and depolymerization, and equivalence of biological assay results" suggested by FDA guidance for generic glatiramer injection [2]. Despite being synthetic, it is subject to the same regulatory standards as biosimilars. The similar target binding/affinity and, hence, similar API structure/composition are determined from a similar pharmacodynamic (PD) response.

This category also includes iron-based products [34 - 40] that have a colloidal structure that is nanometer-sized and stabilized by a complex carbohydrate. Finding the most appropriate surrogate on which BE would be based is the key challenge [35]. The amount of iron available for biological processes is commonly determined by measuring the drug-bound iron in the blood, that is, evaluating the difference in AUC between total iron and transferrin-bound iron [36]. However, similar PK profiles do not distinguish between drug-bound iron *in vivo* because it is cleared through reticuloendothelial system (RES) uptake. As a result, it is

insufficient to guarantee comparability of these products' toxicological and pharmacological effects. Consequently, regulatory authorities recommend extensive *in vitro* product characterization and animal tissue bio-distribution studies [34].

6. CHARACTERIZATION OF COMPLEX API AND EXCIPIENTS

The production of peptides presents many difficulties despite the fact that peptides play a significant role in public healthcare medications for curing chronic diseases [37, 38]. In addition, it has been particularly challenging to manufacture generic peptides that are comparable to their innovator counterparts [17]. There are a number of obstacles to overcome in order to guarantee quality, safety and equivalence of generic and innovator peptide drug products, and these obstacles vary based on the type of peptide drug product [39]. Peptide-related impurities are particularly hard to identify, investigate, and control since they are generally comparable to amino acid sequences present in actual medication [22]. It is not methodologically simple to know whether a proposed generic product contains the same active ingredient as the innovator peptide products with varying amino acid lengths and sequences [40]. This requires advanced analytical methods and novel statistical methods to determine pharmaceutical equivalence based on a large dataset of characterizations.

FDA suggested the following characterization requirements for the peptide containing complex generics:

1. Comparative structural analysis for peptides and oligonucleotides involves evaluation of the primary structure, secondary structure, and tertiary structure.

2. Comparative physicochemical property analysis, which includes spectroscopic and molecular weight analysis.

3. Comparison of impurity profiles includes peptide-related impurities for synthetic peptides and (N+1) and (N-1) impurities for oligonucleotides.

4. Comparative biological activity analyses are required to confirm biological activity *in vitro* and/or *in vivo* for biosimilars.

6.1. Manufacturing Complexity Complicates Reverse Engineering

Multi-vesicular liposomes have a complex structure accomplished through an intensive manufacturing process. Generic product manufacturers face the challenge of undertaking extensive reverse engineering and process development in order to produce a product with structural and functional "equivalence" and quantitative and qualitative similarity in composition to the RLD41. Companies can learn more about the reference product from patents, scientific articles, package leaflets or other publicly available documents before beginning reverse engineering. They can plan well-informed Quality Target Product Profiles (QTPPs) with the assistance of PSGs and meetings with the agencies. The unit operations are scale-dependent. At a large scale, the process and equipment used may bring about varying forces or time scales that affect the finished product; *e.g.*, the physical stability of the emulsion is critical at larger scales. However, the same process does not require scientific attention at a laboratory scale [31]. Another challenge in the production of complex parenteral drug products is the final dosage form's sterility. Aseptic processing makes it easier to make sterile parenteral drug products by sterilizing the ingredients used, like lipids, polymers, aqueous buffers, and organic solvents, through 0.22-particle size filters. The aseptic filling should be monitored for potential contaminants like primary packaging materials, operating staff, air pollution in the environment, and water drainage systems [41, 42]. The stability of the formulation can be affected by conventional sterilization procedures like gamma radiation, autoclaving, and ionizing radiation due to the distinct physical characteristics and chemical composition of the materials used to make complex injectables.

6.2. Lack of Compendial *In-vitro In-vivo* Correlation (IVIVC) Method

IVIVC is a scientific method for describing the relationship between an *in-vitro* property of a dosage form, like the extent or rate of drug release, and its relevance *in-vivo* response, like plasma drug concentration or amount of drug absorbed. IVIVC model makes it easier to develop and evaluate modified-release and other complex dosage forms rationally. An IVIVC can be validated and then utilized for *in-vivo* BA and BE testing, formulation screening, and creating dissolution/drug release acceptance criteria [43].

6.2.1. IVIVC for Parenteral Polymeric Microspheres/ Implants

Designing *in-vitro* release studies that effectively mimic the *in-vivo* behaviour of the medication is the challenging part of designing IVIVC models for complex products like PLGA-based polymeric microspheres or implants injected directly or subcutaneously. Drugs are slowly released after injection or implantation into tissue fluids *via* complex release processes, such as diffusion or polymer erosion and delivered into the systemic circulation [44]. In order to evaluate drug release and create IVIVC methodologies, a number of *in-vitro* release techniques, such as sample-and-separate, membrane dialysis, and flow-through, are used. *In-vivo* data should be deconvolved and correlated with *in-vitro* release data. Due to the complex release characteristics, deconvoluted *in-vivo* data may be difficult to correlate with multi-phasic *in-vitro* release data using a simple mathematical model [45]. The crucial factor to take into account while building a reliable IVIVC is physiologic reactions to biomaterials because they could alter the *in-vivo* polymer breakdown pathway [46]. Changing the PLGA microspheres' degradation mechanism to surface erosion can hasten polymer degradation and boost *in vivo* drug release [45]. On the other hand, fibrosis and persistent inflammation caused by microspheres at the interstitial location may generate and isolate microspheres, reducing *in vivo* absorption or release.

6.2.2. IVIVC for Transdermal Delivery System

Three processes are involved in transdermal drug delivery: the release of the drug from the formulation, the penetration or diffusion of the drug into or through the skin, and the delivery

of the drug at the site of action to start a pharmacological action [41]. Developing an IVIVC for transdermal delivery systems that mimics the penetration of drugs through human skin is challenging. Several *in-vitro* dissolution techniques are suggested as quality control methods for topical or transdermal medicinal products. These dissolution techniques, however, might not completely reflect the complex mechanism(s) underlying drug diffusion or permeation over the skin [45].

For most complex generics, there are currently few or no literature reports on IVIVC. To assure product performance and safety, as well as aiding in product development, IVIVCs must be developed for the commercialization of novel and complex generics.

It became evident that the regulatory framework established for small molecules and biologics may not be sufficient to address the regulatory requirements for complex generics. There is no defined regulatory pathway for complex generics approval, creating a dilemma for regulators and scientists [48]. Also, there are many challenges related to manufacturing, proving API sameness, PE and BE related to complex generics. Pharmaceutical companies manufacturing innovator drugs believe that a generic pathway is insufficient and that a therapeutic equivalency study, similar to that used for biosimilars, is required to ensure interchangeability. On the other side, companies manufacturing generics argue that it is preferable to avoid unnecessary clinical trials in order to provide patients with accessible medications. The requirement for more efficacy and safety studies can delay the development of generics [49].

As complex generics are chemical compounds, they can be approved by a generic or a hybrid pathway since there is no specific regulatory framework for their approval. Researchers argue that a biosimilar strategy should be used because of the complex structure and mechanism of action [50]. The issue is whether the current regulatory pathways can approve complex generics and can take into account the specific needs of these drugs. Also, it appears that the US and the EU take different approaches to the approval of complex generics, which raises the question of whether different scientific standards are followed and whether complex generics approved by both agencies are equally safe and effective.

The approval processes for a few NBCDs and complex generics in the US and the EU are reviewed and discussed in the sections of case studies given below.

7. CASE STUDIES: APPROVAL OF COMPLEX GENERICS/ NBCDS

7.1. Low-molecular-weight Heparin (LMWH)

Heparin is a carbohydrate that is often isolated from the pig's intestinal mucosa, highly sulfated glycosaminoglycan. Heparin is a combination of repeating disaccharide molecules and ranges in molecular weight from 5 to 40 kDa. The typical disaccharide unit consists of an L-iduronic acid linked to D-glucosamine *via* 1-4 glycosidic bonds, with C2 of the iduronic acid and C6 of the glucosamine being O-sulfated and C2 of the glucosamine being N-sulfated. The crucial component of the binding ability of heparin to antithrombin III is due to a unique pentasaccharide sequence containing 3-O-sulfated glucosamine residue. The antithrombin molecule undergoes a conformational shift as a result of this interaction 51. The structure of heparin is shown in Fig. (**5**) below:

Heparin acts by activating the antithrombin III (enzyme inhibitor), subsequently inactivating coagulation factors, including thrombin and factor Xa. It is the preferred anticoagulant, typically administered to hospitalized patients *via* intravenous injection or infusion. Heparin has some drawbacks, including unintentional bleeding and the inability to inactivate surface-bound factor IIa or factor Xa, which lowers effectiveness. Heparin-induced thrombocytopenia (HIT) is a significant risk related to the drug [51, 52]. Due to the short half-life of heparin, infusions must be given frequently or continuously. Patients respond differently to heparin; thus, the anticoagulant action should be monitored closely.

LMWH is synthesized by using chemical or enzymatic de-polymerization of unfractionated heparin. LMWHs are marketed in the US and Europe, *e.g.*, dalteparin, enoxaparin, tinzaparin, and reviparin. FDA has approved four NDAs for LMWHs: Fragmin® (dalteparin sodium) (NDA 20287), Lovenox® (enoxaparin sodium) (NDA 20164), Normiflo® (ardeparin sodium) (NDA 20227) withdrawn in 2001, and Innohep® (tinzaparin sodium) (NDA 20-484).

One of the most popular anticoagulants, enoxaparin, is approved and marketed in the US and Europe under the brand names Lovenox® and Clexane®, respectively. Heparin from the intestinal mucosa of pigs is converted to enoxaparin sodium

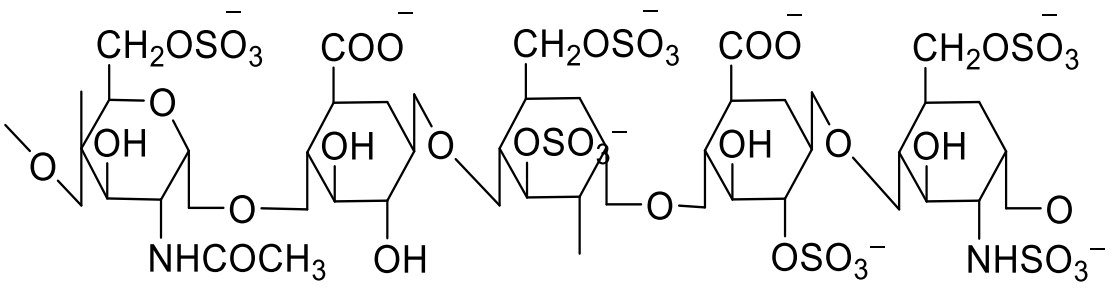

Fig. (5). Heparin structure.

using an alkaline depolymerization process. It is an oligosaccharide mixture that is heterogeneous in nature and primarily composed of less than 18 monosaccharide units. Three crucial factors contribute to the heterogeneity of enoxaparin:

• varying chain lengths,

• disaccharide units and its sequences in the chain

• variability in the modified terminal end of the oligosaccharide chain

Enoxaparin has a higher antithrombotic and anticoagulant activity than unfractionated heparin due to its shorter chain length [53]. Based on the various classifications of pharmaceuticals produced from animal sources, the FDA and the EMA adopt various approaches for approval of their generic versions. The FDA defines generic LMWH as synthetic products; thus, if active ingredient sameness can be demonstrated, they can be approved through the ANDA pathway. Since LMWH is regarded by the EMA as a biological product, all generic LMWH products must be approved as biosimilars.

7.2. US approval of Generic Enoxaparin

The FDA granted approval to Lovenox® (SANOFI AVENTIS US LLC), the originator of enoxaparin and, consequently, the reference product, in 1993 (NDA 20164). The first generic enoxaparin was filed in 2003 (ANDA 76684 by Amphastar Pharmaceuticals). However, it was approved in 2010 (ANDA 77857, Sandoz Inc.) by the ANDA pathway, which is typically used for small molecule generics. The heterogeneous character of enoxaparin sodium and the complexity of LMWH are both acknowledged by the FDA. Therefore, in addition to compendial standards for enoxaparin sodium, the following five criteria must be met to demonstrate "active ingredient sameness":

1. Equivalence of physicochemical properties

2. Equivalence of heparin source material and mode of depolymerization

3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species

4. Equivalence in biological and biochemical assays

5. Equivalence of *in-vivo* pharmacodynamic (PD) profile

If the proposed generic product qualifies the above-mentioned criteria for demonstrating API sameness and is both Q1/Q2 same as the RLD, the waiver request for the *in-vivo* BE study for all strengths may be approved. These five requirements are outlined in the FDA's response to a citizen petition (Docket No. FDA-2003-P-0273), which must be read in conjunction with the "Draft Guidance on Enoxaparin sodium", released in October, 2011 [54]. FDA provides its perspective on what is meant by the "same" active ingredient in this response document, highlighting the discretion that they have in evaluating what data must be considered in order to establish that two active ingredients are identical [61]. The FDA considers an API in a generic product identical to RLD if it satisfies the same identity standards. The pharmacopoeial requirements for identification are typically used, but in some circumstances, additional standards are required to assure the API sameness. FDA's answer to the citizen petition offers a thorough knowledge of Criteria 1-4, explaining why these criteria are deemed essential and providing instructions to carry them out [54, 55].

7.3. Criteria 1

Equivalence of physicochemical properties gives a broad overview of the chemical structure as a whole and the distribution of molecular weights, ensuring a consistent distribution of oligosaccharide chain lengths. The extent and pattern of heparin depolymerization in the generic enoxaparin are equal to RLD by demonstrating molecular weight distribution equivalence using both conventional, complementary high-resolution chain mapping and size exclusion chromatography.

7.4. Criteria 2

The disaccharide sequence in enoxaparin depends on the sequences found in the heparin as well as the cleavage locations. Hence, it is vital that the heparin source and mechanism of depolymerization be equivalent to RLD. Cleavage reaction also results in the introduction of novel chemical structures at the ends of the broken oligosaccharide chains. Since the originator and the generic product must have identical structures, only an equivalent mode of depolymerization can guarantee equivalence to RLD.

7.5. Criteria 3

Detailed structural analysis is conducted to evaluate the fragment mapping, disaccharide building blocks, and sequence of oligosaccharide species. Information on the distribution of disaccharide unit sequences in oligosaccharide chains is obtained through fragment mapping. Direct sequencing of oligosaccharides can provide further details on the distribution of disaccharide units in sequence.

7.6. Criteria 4

Measurements of significant anticoagulant activity markers, such as Heptest prolongation time and activated partial thromboplastin time, are made using an *in-vitro* biological assay. The biochemical assay measures the coagulation cascade's inhibitory effect on factors IIa and Xa. A comparison of these biochemical characteristics offers additional support, proving the active ingredient sameness and equivalent pharmacological activity.

7.7. Criteria 5

Assessments of *in-vivo* anti-Xa and anti-IIa profiles are used to compare *in-vivo* PD profiles. Factors anti-Xa and anti-IIa are assessed as part of a single dose in a two-way crossover *in-vivo* PD investigation. Equivalence is based on the comparison of AUC data for the anti-Xa and anti-IIa peak effect for RLD and generic products.

To ensure that the raw materials, chemical processes throughout the depolymerization process, and structures are equivalent, the first three criteria must be satisfied. The FDA

believes that when the first two requirements are satisfied, the third requirement offers vital proof of equivalent molecular diversity of the original product and generic version. The biological and biochemical characteristics of enoxaparin are the basis for the fourth and fifth criteria, which offer additional significant proof of the active ingredient's similarity. FDA concludes that the generic enoxaparin is the same as the RLD only if all the five criteria are satisfied. The FDA discusses the issue of immunogenicity in the Answer to Citizen Petition. Thrombocytopenia is a well-known adverse reaction to heparin and LMWH. So, it is expected that a generic product having the same molecular diversity as the innovator does not stimulate the immune response [56].

7.8. EU Approval of Follow-on Enoxaparin

As LMWH is regarded by EMA and the WHO as a biological product, any follow-up drugs must obtain approval through the biosimilar pathway. A biological substance requires a combination of physicochemical and biological testing, along with the CMC data for characterization and the evaluation of its quality. Since they are derived from biological sources and have complex characterizations, heparin and LMWH are considered biological substances in Europe [57].

A product-specific guideline is provided by EMA on "Guideline for nonclinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins" (EMEA/CHMP/BMWP/118264/2007 Ver. 1). The recommendation, which was most recently revised in November, 2016, clearly describes the various quality aspects that are compared for LMWH in addition to the European Pharmacopeia requirements:

• Molecular weight distribution and overall chemical composition.

• Starting material and mode of depolymerization.

• Disaccharide building blocks, fragment mapping profiles, and sequences of selected unfragmented oligosaccharides.

• Biological and biochemical assays.

A risk-based approach is used for the preclinical studies; therefore, the type and details of such studies are dependent on how firmly similarity was shown during the physicochemical and biological characterization. To compare any differences in response between the biosimilar and reference LMWH, preclinical studies (*in-vitro* and *in-vivo* PD studies) should be carried out. Studies on *in-vitro* pharmacodynamics should at least assess the anti-Xa and anti-IIa factors. A comparative PD study is conducted to examine the tissue factor pathway inhibitor (TFPI) and anti-FXa and anti-FIIa activities in clinical studies.

7.9. Comparison of European and US Approach

The FDA considers LMWH follow-on drugs as chemicals and approves them under the ANDA 505(j) procedure, whereas, in Europe, they are considered biosimilars under Article 10(4). The dossier content and scientific requirements in both jurisdictions seem to be mostly in line despite different regulatory approval pathways. To establish the sameness of active ingredients, the FDA established five criteria.

The US requirements, however, strictly demand equivalence for criteria 4 that is part of a quality or nonclinical dossier, whereas, in Europe, a risk-based approach, along with additional *in-vivo* PD study, may be conducted to support similarity. A key distinction between the two agencies is that, under the FDA's "active ingredient sameness" approach, a generic product that convincingly does not show equivalence in criteria 1 to 4 is not considered for further evaluation, whereas according to EMA for the demonstration of "active ingredient similarity", the risk-based approach is applied. Additional nonclinical study requirements depend on the similar results obtained.

The comparative *in-vivo* PD study of anti-FXa and anti-FIIa factors conforms to the clinical data standards according to criteria 5 of FDA product-specific guidance. The FDA suggests further *in-vitro* and *in-vivo* assays to assess impurities in immunogenicity testing. EMA guidance states that since animal studies are not thought to be predictive of human immunogenicity, immunogenicity has to be compared in the appropriate nonclinical tests.

EMA has established guidelines for LMWH products that contain an active component that is comparable to LMWH product that is currently in the market. The active ingredient in the proposed product in Europe will be comparable (as opposed to identical according to the FDA); therefore, it might behave very differently from the active ingredient in the LMWH medication that is already in the market. As a result, there may be questions about the efficacy and safety of the proposed identical product. Therefore, sponsors are required to submit clinical trials that demonstrate comparable efficacy to the proposed similar LMWH product as well as clinical data that demonstrate comparable safety, including with regard to Heparin-induced Thrombocytopenia (HIT), within the EMA framework [52]. This is contrary to the FDA's strategy, which has outlined the rationale for determining that the generic form of enoxaparin contains the same active ingredient as the RLD (Tables **3** and **4**).

7.9.1. Exenatide (incretin mimetics)

Exenatide is incretin mimetics used to treat diabetes mellitus. When blood sugar levels are high, it causes the pancreas to release insulin, which aids in the transfer of blood sugar to different body tissues, where it is used as an energy source.

After release into the systemic circulation, similar to glucagon-like peptide-1 (GLP-1), it boosts glucose-dependent insulin secretion and exhibits antihyperglycemic effects. It also controls excessively increased glucagon secretion and slows down gastric emptying [58].

An amino acid sequence of exenatide and the amino acid sequence of human GLP-1 partially overlap. *In-vitro* studies have demonstrated that exenatide binds to and activates the human GLP-1 receptor. It involves cAMP and intracellular signaling pathways to increase both the pancreatic beta cell's *in-vivo* production of insulin and their glucose-dependent insulin synthesis [59].

Table 3. Comparison of the US and the EU approach.

-	US Approach	European Approach
Approval pathway	ANDA 505(j)	Biosimilar application Article 10(4)
Justification	Active ingredient **sameness** based on five criteria	LMWH is considered a biological substance Active ingredient **similarity**
Quality data	1. Equivalence of physicochemical properties 2. Equivalence of heparin source material and mode of depolymerization 3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species 4. Equivalence in biological and biochemical assays	• Molecular weight distribution and overall chemical composition • Starting material (tissue type and species) and mode of depolymerization • Disaccharide building blocks, fragment mapping profiles, and sequences of selected unfragmented oligosaccharides • Biological and biochemical assays
Nonclinical data	Equivalence of biochemical assay (Criteria 4) Comparative measurement of anti-Fxa and anti-FIIa	**Risk-based approach** − *In-vitro* PD studies: comparative bioassays (evaluations of anti-FXa and anti-FIIa) may already be part of the quality dossier − *In-vivo* PD studies: not routinely required if similarity already convincingly demonstrated. Otherwise: *In-vivo* pharmacodynamic model for clinically relevant pharmacodynamic effects for LMWH or animal thrombosis model
Clinical data	Equivalence of *in-vivo* PD profile: (Criterion 5) Fasting, single-dose, two-way crossover *in-vivo* in healthy subjects (endpoints: anti-FXa and anti-FIIa)	Comparative *in-vivo* PD study: Randomized, single-dose, two-way crossover in healthy volunteers (assessment of anti-FXa and anti-FIIa, Tissue Factor Pathway Inhibitor (TFPI) activity) Comparative efficacy trial not necessary
Immunogenicity data	*In-vitro* and *in-vivo* assays to address immunogenicity of LMWH and impurities	*In-vitro* immunogenicity Clinical immunogenicity assessment depends on the impurity profile.
Guidance	FDA Draft Guidance on Enoxaparin Sodium, Oct 2011 FDA Guidance for Industries: Immunogenicity-Related Considerations for Low Molecular Weight Heparin, Feb 2016	Guideline on the nonclinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins (EMEA/CHMP/BMWP/118264/2007/Rev. 1, 10th Nov, 2016)

Table 4. Branded exenatide approved in the US (FDA, Orange Book Database, 2023).

-	BYETTA®	BYDUREON®	BYDUREON BCise®
Approval date	28th April 2005	27th January 2012	20th October, 2017
Indication	To improve glycemic control in patients with Type 2 Diabetes mellitus		
Route of administration	subcutaneously injection	subcutaneously injection	subcutaneously injection
Formulation	no microsphere	extended-release aqueous suspension formulation contains biodegradable polymeric microspheres; provided as a powder to be combined with an aqueous vehicle to form a suspension for injection	extended-release non-aqueous suspension formulation contains the same drug substance but with a non-aqueous medium-chain triglycerides (MCT) vehicle
Device Combination	prefilled pen	single-dose tray or dual-chamber pen	autoinjector

Exenatide is a 39-amino acid peptide amide. Exenatide has the empirical formula C184H282N50O60S and a molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below. H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-ValArg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-SerNH2 [60] (Fig. **6**).

Due to the complexity in the API structure, it becomes very difficult to develop a generic version of exenatide having the same pharmaceutical and bioequivalence compared to RLD, complexity in the characterization of API, impurities, immunogenicity data, and sameness in the device interface.

7.10. US Approval for Generic Exenatide

Product-specific guidance for exenatide was published in May 2022, indicating studies to be conducted by the applicant for approval of generic exenatide [61].

FDA recommends two studies

(1) One *in-vivo* single-dose bioequivalence study with pharmacokinetic endpoints in healthy subjects or

(2) One *in-vivo* multiple-dose steady-state bioequivalence study with pharmacokinetic endpoints in patients

Biowaiver is not applicable for *in-vivo* testing.

Additionally, the RLD product is designed as a prefilled, single-use, single-dose autoinjector. The autoinjector is the device constituent. FDA suggests that the generic applicants evaluate the size and shape, external operating principles and external critical design attributes of the RLD devices when

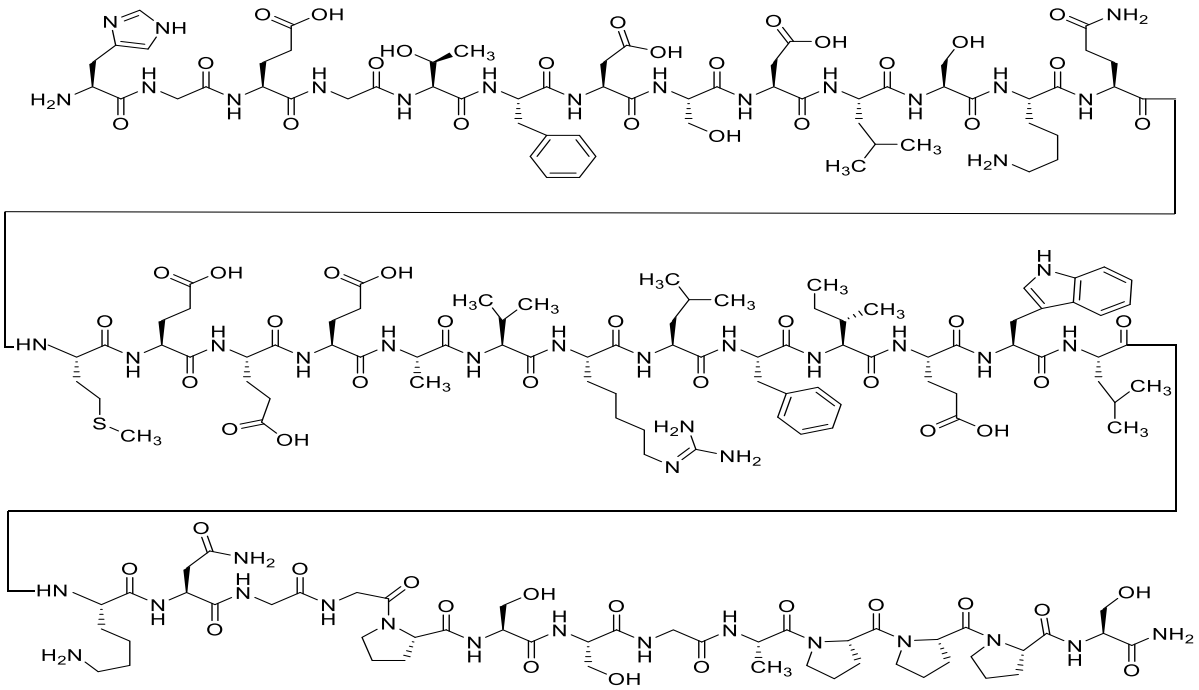

Fig. (6). Exenatide structure.

designing the test device. In addition, test device design should take into consideration the following characteristics of the RLD devices:

- Single-dose, fixed-dose format of the RLD device.
- Needle gauge and length.

FDA recommends user interface assessment, including comparative analysis, in order to determine whether any changes in the proposed generic product's user interface and RLD are acceptable and ensure the same clinical and safety profile.

7.11. European Approval of Generic Exenatide

The originator product Bydureon® with active ingredient exenatide has been marketed in European members since 2011 with marketing authorization holder AstraZeneca. Bioequivalence guidance for approval of generic exenatide was published in 2017. The guidance recommended a single-dose, crossover study in healthy individuals. Even though the requirements set by the agency for generic exenatide approval are less, to date, there is no generic exenatide approved, indicating the complexity of developing a similar product to RLD [62].

7.12. Problem Statement

Bydureon (Bdn) consists of microspheres made from polylactic glycolic acid from which exenatide is released over weeks and helps simplify the dosing regimen for the patients [63]. There is a lot of research on PLGA microspheres and peptide medications, but very little is known about the physical and chemical properties of exenatide. The immune response is influenced by the size and size distribution of the peptide-loaded PLGA microparticles. Furthermore, there is a scientific gap between our present knowledge of what occurs during the production and storage of long-acting injectables and how they function when given to patients [22]. This gap affects generic drug manufacturers who attempt to create generic versions of exenatide, define important criteria for regulatory approval, and manufacture products for clinical trials and post-marketing approval [63, 64]. When considering regulatory submissions, the agency faces severe uncertainties due to developmental and regulatory complexities. Hence, to precisely evaluate the complex PLGA-encapsulated peptide, additional and rigorous characterization approaches are required.

Medisorb® polymer microsphere technology is used for manufacturing Bydureon. With the help of the Medisorb technology, a drug is encapsulated in injectable microspheres that gradually break down in the body and release the drug over time. Poly- (D, L-lactide-co-glycolide) (PLG), a medical-grade biodegradable polymer, makes up the structural matrix of the microsphere. By selecting the proper sort of PLG matrix, the length of the extended-release can be modified [65]. Decreasing the overall hydrophilicity of the microspheres and reducing the rate of biodegradation can be achieved by increasing the lactide-to-glycolide ratio in the matrix. On the other hand, increasing the hydrophilicity of the microspheres by adding carboxylic acid end groups to the PLG polymers favors quicker release [66].

The rate of biodegradation can be reduced or increased by modifying the molecular weight of the polymer. Hence, one may control the amount of medicine released from the PLG matrix by selecting the ideal lactide-to-glycolide ratio,

molecular weight and functional group of the end polymer. Together with choosing the right polymer, it is crucial to make sure the peptide is stable before and after it forms the depot *in vivo*. The development of an appropriate *in-vitro* release test method posed a significant problem, as an *in-vitro* release is a crucial quality characteristic for assessing and proving acceptable product performance [44]. With parenteral microsphere products, unlike oral formulations, there are no standardized techniques (such as USP methods); therefore, the process of establishing acceptance criteria becomes more complicated.

AstraZeneca introduced a dual-chamber pen of Bydureon® in 2014 to enhance patient compliance. The microsphere powder formulation is present in one chamber, while a diluent for suspension is present in the other. The challenging manufacturing processes required filing and assembling a dual-chamber pen served as significant barriers to the entry of generic products. AstraZeneca then launched Bydureon® BCise®, a ready-to-use autoinjector with the same API and microspheres as Bydureon® in 2018; however, it used a non-aqueous medium-chain triglycerides carrier [63]. After the launch of the autoinjector, AstraZeneca discontinued the supply of a vial and dual chamber pen. In order to market a generic product, ambitious generic product companies most commonly choose Bydureon® vial or dual-chamber pen as their target RLD. However, after discontinuation of the RLD, generic product manufacturer must gather sufficient new RLD data, produce a new formulation, find and develop a new device, repeat all supporting studies, and change their production process in order to prove *in-vitro* sameness and *in-vivo* PK BE with the new RLD [19].

This reflects the challenges faced by generic companies developing generic exenatide and the need for research on developing analytical techniques for the characterization of API. To date, there is no generic exenatide approved by USFDA.

8. DISCUSSION

Complex generics create unique problems regarding proving the therapeutic equivalence with the originators because of their complicated structure, mechanism of action, and reliance on the manufacturing process for the determination of their quality profile. In contrast to the US, where generic drugs are approved through the traditional ANDA pathway, European authorities expressly use the Article 10(3) hybrid pathway with data criteria comparable to those for biosimilars. There is no specific regulatory framework or clear direction for the approval of complex generics, which creates uncertainty for generic companies who want to commercialize generics.

8.1. Appropriate Legal Basis for the Approval of Complex Generics

According to EMA, two regulatory pathways are available for the approval of complex generics:

a. Generic pathway: When the generic has the same active ingredient's qualitative and quantitative composition and pharmaceutical form, bioequivalence to the RLD is established.

b. Hybrid pathway: When bioequivalence to RLD cannot be proven or when the active ingredient, indications, strengths, dosage form, or method of administration have only minor modifications. Further preclinical and clinical data must be provided in this pathway.

The complex generics discussed above in the thesis are approved *via* the generic ANDA pathway [505 (j)] by the FDA. FDA's regulatory approach diverges from the European perspective. The FDA makes a lot of effort to verify the sameness of the API and may require an equivalent manufacturing process as the originator's product. The FDA devised a thorough scientific strategy for showing API sameness for generic enoxaparin and specified the equivalence requirements as well as the order in which they must be satisfied. The product is only taken into consideration for further assessment in the second criterion if it effectively demonstrates equivalency in the first criterion. Risk-based approaches, as used in Europe for enoxaparin, are not accepted by the FDA; instead, the scope and details of non-clinical research are determined by how convincingly similarity was shown in the earlier stages. The product would not be considered for further examination if equivalency could not be convincingly established. In contrast to clinical efficacy trials in Europe, the FDA claims that quality equivalency criteria are more sensitive to detect differences in product. Both agencies have disparities in approval requirements for complex generics, making it difficult for the industry stakeholders to come up with well-established submission data. Therefore, it is crucial that regulatory bodies develop well-defined guidelines to approve complex generics. Harmonizing regulations is crucial to creating a consistent basis for approval and ensuring that patients receive medications of the highest quality, safety, and efficacy.

8.2. Steps Taken by the FDA and EMA to Address Challenges Related to Complex Generics

In an attempt to support applicants of complex generics in creating proper submissions containing the required data for proving similarity with the RLD, the FDA makes a lot of effort to release product-specific guidance every quarterly. ICH reflection paper was published suggesting the need to develop a series of ICH guidelines to demonstrate bioequivalence for complex generics like inhalational, dermatological, otic, and long-acting parenteral [64 - 68]. This will help the generic manufacturers overcome the challenges faced while conducting BE studies for complex products.

The GDUFA science and research program promotes the development of novel approaches and more effective tools to assist the development of drug equivalency criteria that enable the development of high-quality, safe, and effective generics. GDUFA science and research report published in 2023 suggested various steps taken by the FDA to increase access to generic versions of complex drugs and improve effectiveness and global harmonization of complex generic development [68].

After several years of GDUFA research to provide the rationale for BE evaluations of ophthalmic drugs, the FDA

approved the first generic cyclosporine ophthalmic emulsion product in 2022 (FDA, Orange Book Database, 2023). The innovator product Restasis® got approval in 2002 (N050790) but there was no generic cyclosporine available due to the difficulty in assessing bioequivalence. FDA started undertaking research to provide bioequivalence recommendations for cyclosporine ophthalmic emulsion under the GDUFA Science and Research Program. It published guidance on cyclosporine ophthalmic emulsion 0.05% in 2016. FDA collaborated with Absorption System Inc. to gain important insights into how characteristics of ophthalmic suspension products, such as particle size distribution and viscosity, affect PK/PD of highly complex ophthalmics [68]. The significant issues with the analytical and statistical evaluation of a proposed generic Restasis were also addressed. FDA's efforts helped the generic company to get approval for the first generic cyclosporine ophthalmic emulsion in 2022.

Another initiative taken by the FDA and EMA to assist complex generics approval is the establishment of a Parallel Scientific Advise (PSA) pilot in 2022. With the pilot initiative, prospective ANDA and MAA applicants to the FDA and EMA can submit a request for a meeting with both organizations to discuss specific concerns regarding the development of complex generic drugs and hybrid products [69]. The PSA pilot program's objective is to give FDA and EMA reviewers a way to converse with applicants concurrently about scientific issues faced for the development of complex generic and hybrid products, which are typically more difficult to develop using conventional bioequivalence methods [70, 71]. Applicants would learn about both agencies' recommendations through the PSA procedure. This will help the applicant resolve any challenges faced during the development of complex generics and get detailed information about the submission data required for approval.

CONCLUSION

The approval of complex generics has demonstrated that each product has to be evaluated on a case-to-case basis. In the past, the approval processes for complex products involved prolonged discussions and controversy between different agencies' opinions. Harmonization of the regulatory framework can help overcome challenges related to PE, BE, and TE of complex products. More research needs to be conducted to develop sophisticated analytical techniques for the characterization of active ingredients. FDA and EMA initiative on PSA pilot can enhance communication between the industry and agencies helping to develop a well-defined basis for approval. It will reduce challenges and studies required for approval and bring about adequate access to quality, cost-effective, and safe complex generics.

LIST OF ABBREVIATIONS

ANDA	=	Abbreviated new drug application
API	=	Active pharmaceutical ingredient
BA	=	Bioavailability
BE	=	Bioequivalence
BLA	=	Biologic License application
CMC	=	Chemistry Manufacturing Control
EMA	=	European Medicines Agency
EU	=	European Union
GDUFA	=	Generic Drug User Fee Amendment
HIT	=	Heparin-induced thrombocytopenia
IVIVC	=	*In-vitro In-vivo* correlation
LMWH	=	Low molecular weight Heparin
MAA	=	Marketing Authorization Application
NBCD	=	Non-biological complex drugs
NDA	=	New drug application
OGD	=	Office of Generic Drugs
PD	=	Pharmacodynamics
PE	=	Pharmaceutical equivalence
Ph. Eur.	=	European Pharmacopeia
PK	=	Pharmacokinetics
PLGA	=	Polylactic glycolic acid
PSA	=	Parallel Scientific Advise
PSG	=	Product-specific guidance
RLD	=	Reference listed drug
TE	=	Therapeutic equivalence
US	=	United States
USFDA	=	United States Food and Drug Administration
USP	=	United States Pharmacopeia

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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