

DDE Whitepaper
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The Challenges of Complex Generics

Complex Generics

Generic combination drug products are broadly characterized in the GDUFA II guidance and refer to oral products with more than one active, complex formulations such as liposomes, suspensions, emulsions, and gels, complex routes of administration such as locally acting products (topical creams and gels, nasal spray, and inhalation products), drug combinations with devices, long-acting injectables. REF 1. There is a nice list of complex generic product guidances which are going to take effect soon. REF 2

Generic complex drug products in the injectable space refer to the combination of an approved drug and a device for synthetically produced drugs, including small molecules, peptides, and oligonucleotides. For large peptides, proteins, and antibodies, which are produced by recombinant methods, the biosimilar guidelines apply in the US and Europe. REF 3

Complexity for solution injectables ranges from vial and syringe to pre-filled syringe to more complicated systems including pen and cartridge, or auto-injector systems and cartridge container closure systems. For these immediate release solution injectables, the

About Drug Delivery Experts: Drug Delivery Experts (DDE) is a drug product research and development company that specializes in drug delivery systems from preclinical to clinical development and commercialization. DDE has specific expertise with peptides, proteins, and oligonucleotides along with formulation, process, and combination drug product development. With over 200 years of pharmaceutical development experience at a broad range of companies, the leadership team at DDE has worked on products across many routes of administration and dosage forms including various non-invasive and sustained release injection products. DDE is located at 11494 Sorrento Valley Road, Suite J, San Diego, California.



Figure 1. Complex Generic Product Examples
1a. Cinvanti (aprepitant) injectable emulsion for intravenous use
1b. Primatene mist epinephrine inhalation aerosol
1c. Lidocaine generic Lidoderm 5% patch

generic bioequivalence guidance written for oral tablet and capsule generics can be applied to establish physical and chemical comparability and bioequivalence in the clinic. REF 4 This is true for small molecules and peptides in the US (up to 40 amino acids) which are produced by synthetic processes REF 5



Figure 2. Complex injectable product configurations.

2a. Vial and syringe

2b. Pre-filled syringe

2c. Injection pen and cartridge

2d. Auto-injector

If the generic is a biologic or macromolecule produced by recombinant methods, it will be considered a biosimilar, and the US and EU have developed guidances for approval of these products. The European biosimilar market is more mature than the US with the first product approved by EMA in 2006 (Omnitrope, Novartis) and 63 products approved up to July 2019. REF 4 The US FDA approved the first biosimilar in Mar 2015 (Zarxio, Filgrastim-sndz), with 23 total biosimilars introduced up to July 2019. REF 6

Complex Generic Combination Drug Products

Complex combination generic drug products can be much more challenging and require much more data to convince the regulatory agencies of comparability of the two drug products. The approval requirements are much closer to that for biosimilars than to that for generic products. For example, Copaxone (glatiramer acetate) which was originally developed by Teva and approved in the US in 1997 is a complex mixture of amino acid polymers. While it is considered a peptide by many, it is a mixture of synthetic peptides produced through a polymerization reaction and includes a very specific molecular weight fractionation and

purification process. In this case, the process used to manufacture the product has a dramatic impact on the quality and performance of the product. The resulting regulatory package for the generic products is much closer to that for biosimilars, as seen in the regulatory guidance for glatiramer acetate ANDAs. REF 7

Long-Acting Injectables and Implantables

Similarly, long-acting injectables and implantables are considered complex combination drug products. These products are composed of an active ingredient (typically a small molecule or peptide) and a functional excipient, formulation, or device, which controls the rate of release of the drug from the product. As a result, the approval process requires a typical full clinical program, although the magnitude of clinical safety data is typically reduced compared to the original application for the solution injectable product. The regulatory program for a long-acting injectable or implantable system follows the 505(b)2 NDA approval process because they reference clinical and safety data from the original NDA for the immediate release product, whether oral or injection.

Complex Generic Pathway for Long-Acting Products?

Due to the complexity of the long-acting systems, it is not surprising that there is no generic product or pathway for long-acting injectables or implantables. On the surface, long-acting products might appear to be appropriate for a complex injectable generic drug product approval process. However, to date, there has been no generic approval of a long-acting injectable.

The complexity of replicating the clinical PK profile and the formulation make these products very difficult to copy as a generic formulation. In addition, the amount of clinical and CMC work required is sub-

stantial and appears to be greater than many generic companies wish to undertake.

The long-acting delivery system space is a maturing technology area and the generic pathway may open up at some point once more experience has been gained with the specific types of dosage forms. However, all long-acting systems cannot be treated equally since they are made from various release-controlling mechanisms which are drug molecule and formulation specific. It is probable that each long-acting product will have to be considered individually for the development pathway and the hope for a generic process is likely some years off.

References

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