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Demonstration of equivalence of a generic glatiramer acetate (Glatopa™)

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ABSTRACT

Glatiramer acetate (GA) has been available under the brand name Copaxone® for nearly two decades. Recently, the US Food and Drug Administration (FDA) approved the first generic GA, Glatopa™, as fully substitutable for all indications for which Copaxone 20 mg is approved; Glatopa also represents the first FDA-approved "AP-rated," substitutable generic for treating patients with MS. Glatiramer acetate is a complex mixture of polypeptides and, consequently, its characterization presented challenges not generally encountered in drug development. Despite its complexity, and without requiring any clinical data, approval was accomplished through an Abbreviated New Drug Application in which equivalence to Copaxone was evaluated across four criteria: starting materials and basic chemistry; structural signatures for polymerization, depolymerization, and purification; physicochemical properties; and biological and immunological properties. This article describes the rigorous overall scientific approach used to successfully establish equivalence between Glatopa and Copaxone, and presents key representative data from several of the comprehensive sets of physicochemical (structural) and biological (functional) assays that were conducted.

1. Introduction

Glatiramer acetate (GA; Copaxone®, Teva Pharmaceuticals USA Inc., North Wales, PA, USA) is approved for the treatment of relapsing forms of multiple sclerosis (MS) [1]. Its mechanism of action is complex and involves immunomodulation of both the innate and adaptive immune systems [2]. Known mechanisms include alteration of regulatory T-cell function [3–5], with induction of a T-helper 1 (Th1) to Th2 cell shift resulting in a more anti-inflammatory cytokine profile [6–10], alteration of antigen-presenting cell (APC) function [3], and modulation of B-cell function [2]. The possible neuroprotective effects of GA, which are mediated by neurotrophic factors, include the ability to reduce demyelination and promote remyelination [2]. Glatiramer acetate is considered a disease-modifying therapy that is dosed as a baseline immunomodulatory agent administered for extended periods of time [11,12]. Glatiramer acetate and similar therapies are indicated to reduce the frequency of exacerbations in patients with relapsing MS [1,12–16], and are commonly initiated when patients show signs of relapsing MS [12].

Due to the widespread use and relatively high cost of Copaxone, there is increasing interest in the development of generic versions of GA to reduce costs and increase access to this medication for patients with MS. Recently, the US Food and Drug Administration (FDA) approved the first generic GA, Glatopa™, which has been approved as a fully substitutable generic for all indications for which Copaxone 20 mg is approved [17].

In the United States, a generic drug is approved under an Abbreviated New Drug Application (ANDA). Using this process, preclinical or clinical data are generally not required to establish safety and effectiveness of the generic drug [18]. Instead, generics must demonstrate therapeutic equivalence (i.e., pharmaceutical equivalence and bioequivalence) to the innovator drug product [19]. Bioequivalence is defined by the Code of Federal Regulations, 21CFR320.1, as the "absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives

Abbreviations: ANDA, Abbreviated New Drug Application; APC, antigen-presenting cell; CNS, central nervous system; DEA, diethylamine; EAE, experimental autoimmune encephalomyelitis; ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug Administration; GA, glatiramer acetate; MHC, major histocompatibility complex; mAbs, monoclonal antibodies; MS, multiple sclerosis; MOG, myelin oligodendrocyte glycoprotein; NCAs, N-carboxyanhydrides; PLP, proteolipid peptide.

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becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study [19]." Per Code of Federal Regulations 21CFR320.22 [20], and as is routinely determined for injectable products, the bioequivalence of Glatopa has been deemed self-evident based on the fact that it is a parenteral solution intended solely for administration by injection and that it contains the same active and inactive ingredients in the same concentrations as the approved drug product, Copaxone. Although GA is a mixture of polypeptides, it is produced by a completely chemical synthesis and is not a biologic; therefore, the ANDA process was the appropriate regulatory pathway.

Establishing pharmaceutical equivalence involves demonstrating "sameness" of the active ingredient, as well as other product characteristics, such as dosage form and concentration. While the latter qualities are easily verified, demonstrating "sameness" of the active ingredient requires both detailed characterization of the active ingredient and development of a process that reproducibly yields an equivalent material. Most generic medicines approved to date consist of small-molecule, one-component active ingredients, where the demonstration of sameness can be achieved through first-principle chemical analysis and the chemical connections can be fully ascribed. The development of the process to produce a generic is typically designed to make the correct end product, while minimizing the levels of side-products and impurities. These processes need not be similar to the brand process, and the characterization of the process is not a critical component of the demonstration of sameness of the active ingredient. While the size and complexity of the generics approved in recent years has increased, most generics still follow this simple model of proof of structure and quality via direct chemical analysis.

Glatiramer acetate, however, is a complex mixture of synthetic polypeptides with a range of molecular weights and sequences, manufactured from the copolymerization of the amino acids L-alanine, L-glutamic acid, L-lysine, and L-tyrosine in a specific molar ratio [1,6,10]. Therefore, due to the large number of possible components, structural elucidation by complete component analysis is not possible. However, the exact analysis of each component is neither practical nor necessary, and the equivalence of Glatopa to Copaxone was demonstrated by a comprehensive set of physicochemical and biological characterization techniques, in combination with a thorough understanding of the process used to make GA. The combination of thorough product characterization and process understanding was utilized to achieve and demonstrate equivalence of the GA in Glatopa and Copaxone, the reference listed drug.

2. Materials and methods

A strategy was developed to establish equivalence based on an understanding of the chemistry, manufacturing process, and biology of GA. The following four-point criteria were employed for evaluating the equivalence of Glatopa to Copaxone.

- Equivalence of starting materials and basic chemistry
- Equivalence of structural signatures for polymerization, depolymerization, and purification
- Equivalence of physicochemical properties
- Equivalence of biological and immunological properties

Using this framework, this article describes the process of establishing sameness and presents data demonstrating the equivalence of Glatopa to Copaxone 20 mg.

3. Results and discussion

3.1. Characterization of the reference listed drug

To develop an equivalent product and process, a thorough understanding of the brand product was first required. This was accomplished by a review of the available scientific, patent, and regulatory literature on Copaxone and by extensive physicochemical, biological, and immunological characterization of Copaxone. These characterizations involved the use of more than 60 methods, with up to 50 different Copaxone lots being measured for some attributes. In addition to describing Copaxone, the use of multiple-lot testing served to measure and express the diversity and range of the commercial lots of Copaxone for certain quantitative attributes. The data from these analyses are presented as examples of the application of the four equivalence criteria, which are discussed in the following sections.

3.2. Equivalence of starting materials and basic chemistry

The chemical process used to manufacture the drug substance for Copaxone is relatively straightforward and well understood; the basic framework (i.e., identity of reagents, solvents, ratios, and processing steps) have been available in the public literature for many years [21]. It consists of three basic chemical steps, followed by a final purification step (Fig. 1): 1) polymerization of four amino acid N-carboxyanhydrides (NCAs) initiated by diethylamine; 2) depolymerization and deprotection of the initially formed protected polypeptide mixture; and 3) final deprotection of the second intermediate polypeptide mixture, followed by purification and counter ion-exchange.

The same starting materials (NCAs) with the same protecting groups are used for the manufacture of both Glatopa and Copaxone. Similarly, the same solution-phase polymerization, HBr-based depolymerization, and deprotection chemistry are applied in the synthesis of both Glatopa and Copaxone. The identities of the starting materials, reagents, and solvents have been previously described [1,22] and were confirmed through the detection of residual materials, such as protecting groups in the brand product (i.e., Lys[TFA] and Glu[OBn]). The starting materials were extensively investigated with several conventional analytical methods (i.e., spectroscopic, chromatographic, and chiral purity and impurity analysis), and the effects of the starting material quality were assessed (e.g., the impact of NCA impurities on product attributes).

3.3. Equivalence of structural signatures for polymerization, depolymerization, and purification

As noted, GA is a complex mixture of polypeptides and its characterization presents challenges not generally encountered in generic drug development. However, while GA is complex, it is not complicated and is produced by a process that is well documented, well understood, and decipherable. Consequently, the impact of process conditions on specific product attributes can be elucidated experimentally. The product attributes that are directly attributable and sensitive to the processes of polymerization, depolymerization, and purification are referred to as *process signatures*. As part of the development of generic GA, a thorough understanding of this process was developed by coupling the analysis of GA process signatures with process development. The demonstration of the equivalence of process signatures for the three steps in both the Glatopa and Copaxone processes ensures that the processes used to manufacture the two materials are equivalent.

It should be noted that process conditions need not be identical to produce equivalent material. In fact, extensive process characterization studies were performed to not only discover the process signatures but to also define the acceptable ranges for all critical process conditions (e.g., reaction temperatures, concentration of reactants) that influenced the corresponding process signatures. The total evaluation comprised developing the analytical methods appropriate for measuring process signatures specific to each of the chemical steps used to produce GA, and defining the range of process conditions that produce equivalent and nonequivalent process signatures. Therefore, comparing different lots of GA on the basis of process signatures can demonstrate whether or not equivalent processes were used to produce the materials. GA