Demonstration of Equivalence between Glatopa™ and Copaxone® 20 mg

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INTRODUCTION AND PURPOSE

Glatopa™ (glatiramer acetate injection; Sandoz, Inc.; M356) has been developed by Momenta and Sandoz as a generic version of Copaxone® 20 mg (glatiramer acetate injection; Teva Pharmaceutical Industries Ltd.) for the treatment of relapsing forms of multiple sclerosis. In the United States, a generic drug is approved under the Abbreviated New Drug Application (ANDA) 505(j) pathway. Clinical data are generally not required to establish safety and effectiveness of the generic drug. To gain FDA approval, a generic drug must: 1) contain the same active ingredients as the innovator drug; 2) be identical in strength, dosage form, and route of administration; 3) have the same use indications; 4) be bioequivalent; 5) meet the same batch requirements for identity, strength, purity, and quality; 6) be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products. Bioequivalence for a parenteral solution intended for administration by injection is based on the fact that it contains the same active and inactive ingredients in the same concentrations as the reference listed drug.

Glatiramer acetate (GA) is a complex mixture of synthetic polypeptides with a range of molecular weights and sequences, comprising the amino acids, L-alanine, L-glutamic acid, L-lysine and L-tyrosine in a specific molar ratio. Due to this complexity, demonstration of equivalence of the active ingredient in a proposed generic versus Copaxone requires a more extensive dataset than is generally required for an ANDA application. A strategy was developed to establish equivalence based upon an understanding of the chemistry, process, and biology of GA.

Four-Point Criteria for Demonstration of Equivalence of Glatopa and Copaxone 20 mg

- 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.

RESULTS AND DISCUSSION

Characterization of Brand Copaxone

- Thorough understanding of reference listed drug (Copaxone) required.
- Review available scientific, patent, and regulatory literature on Copaxone.
- Characterization by more than 60 physicochemical, biological, and immunological methods.
- Multiple lots (up to 50 for some attributes) were studied over several years probing the range and diversity of the commercial lots, as well as evaluating the effects of lot aging.

Equivalence of Starting Materials and Basic Chemistry

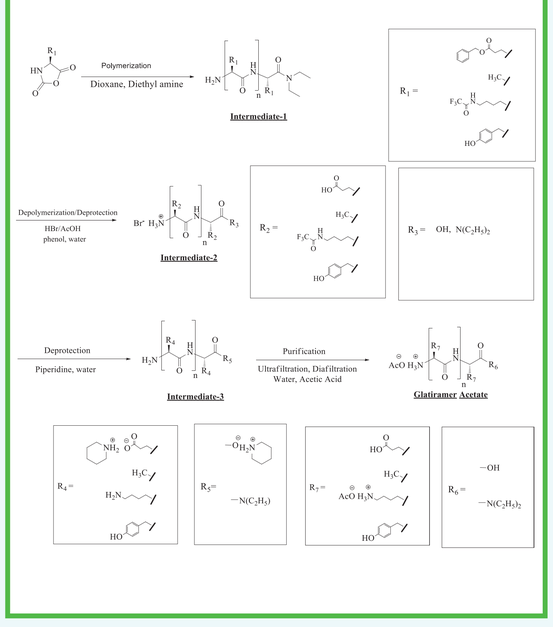
- Straightforward, well understood process whose details are publicly available.
- Known starting materials.
- Same starting materials employed as with the brand process.
- Identity of starting materials confirmed by residual analysis of brand product.

Process

The process (Figure 1) consists of three basic chemical steps, followed by a final purification step:

- Polymerization of four amino acid N-carboxyanhydrides (NCAs) initiated by diethylamine.
- Depolymerization and deprotection of the initially formed protected polypeptide mixture.
- Final deprotection of the second intermediate polypeptide mixture.
- Purification and counter ion-exchange.

Figure 1. General Synthetic Scheme for Glatiramer Acetate.



Equivalence of Structural Signatures for Polymerization, Depolymerization, and Purification

- GA is a complex mixture of polypeptides and its characterization presents challenges not generally encountered in drug development. However, while GA is complex, it is not *complicated*, and it 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 experimentally elucidated.
- 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 Glatopa, a thorough understanding of this process was developed by a coupling of the analysis of Copaxone process signatures with process development. The demonstration of the equivalence of process signatures for the three steps ensures that the process used to manufacture Glatopa is equivalent to the process used for Copaxone.

Example of Process Signature for Step-1: Polymerization of NCAs

- The polymerization is initiated by the reaction of one NCA with diethylamine (DEA), yielding a product with a (primary) amine at the N-terminus and a diethylamide at the C-terminus (Figure 2).
- Polymerization is propagated by reaction of the N-terminal amine with a subsequent NCA.
- The abundance of amino acids at the beginning of the chain (near the DEA) is governed by the relative amount of each NCA present and the differential reaction kinetics between each NCA and the growing polymer, with the most reactive and abundant amino acids dominating.
- As the chains propagate and NCAs are depleted, the ratio of amino acids available for reaction changes, so that the ends of the chains have proportionally more of the less reactive amino acids.
- The proportion of each amino acid that is adjacent to diethylamine in the final GA (defined as a diethylamide) is different from the bulk ratio of the amino acids in the product and subsequently the ratio of diethylamides can be monitored as a reflection of the initiation kinetics of the Step-1 reaction (Figure 3).
- Polymerization is NOT random; all aspects of the NCA polymerization are determined by the chemistry – specifically the chemical kinetics – of the individual reactions.

Figure 2. Pictorial Representation of the Reactions in Step-1 (NCA Polymerization) and Step-2 (Intermediate-1 Depolymerization), which are Controlled by Reaction Kinetics.

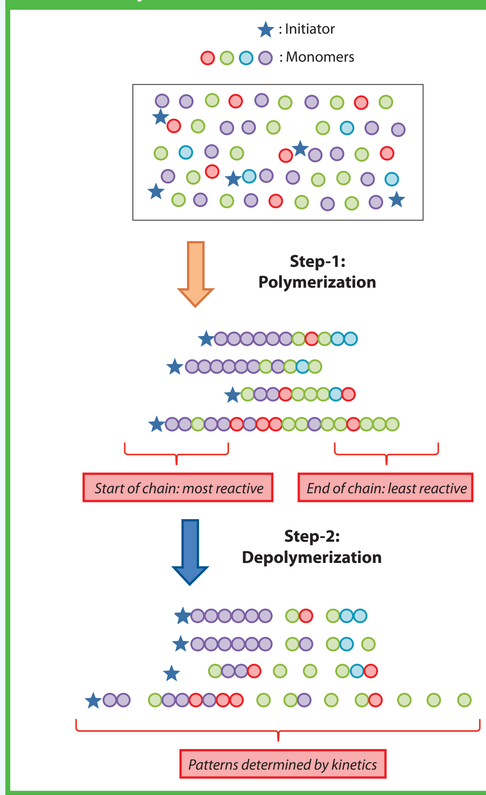
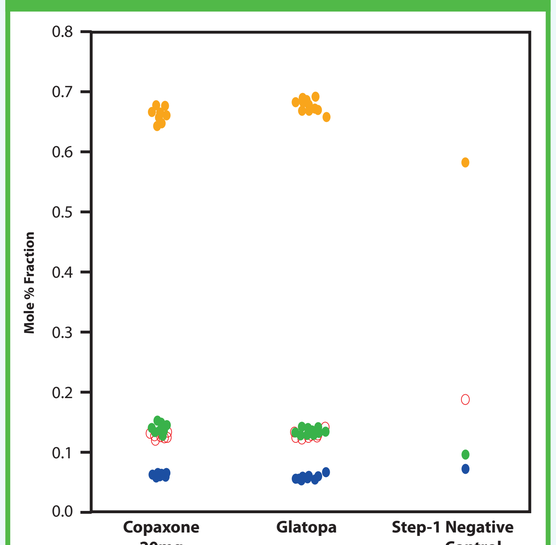


Figure 3. Relative Level of Amino Acid Adjacent to Diethylamine in Final GA. Several lots of Glatopa, Copaxone, and a Step-1 negative control are shown. The reaction was run in a different solvent resulting in different relative reaction kinetics.



Example of Process Signature for Step-2: Depolymerization of Intermediate

- In Step-2 of the process, the polyamide backbones of the long chain polypeptides created in Step-1 are cleaved to create smaller peptides (Figure 2), and the benzyl protecting group on glutamic acid is removed.
- The extent and sites of the chain cleavages are governed by reaction conditions (time, temperature, etc.), and also by cleavage preferences (kinetics) of individual bonds.
- These cleavage preferences are reflected in the C- and N-termini observed in the final GA (Figures 4 and 5).

Figure 4. Relative Amino Acid Levels at the N-Termini of GA for the First 5 Cycles of N-Terminal Analysis by Edman Degradation. The red lines represent the Copaxone-based specifications for each amino acid for each cycle. Within these lines are the results for four representative Glatopa lots (blue). Also shown are 2 negative controls: one is a Step-1 reaction negative control (orange) where the reaction was run with a different solvent; the other is a Step-2 negative control (green), in which the depolymerization reaction was altered.

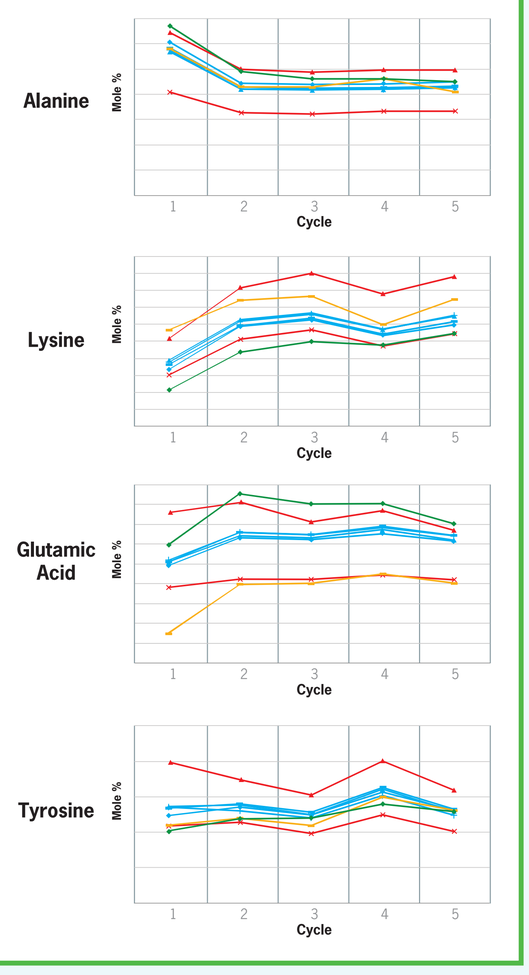
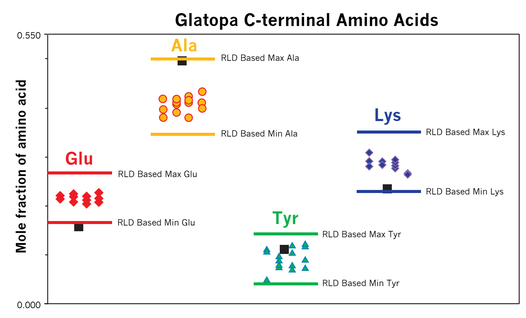


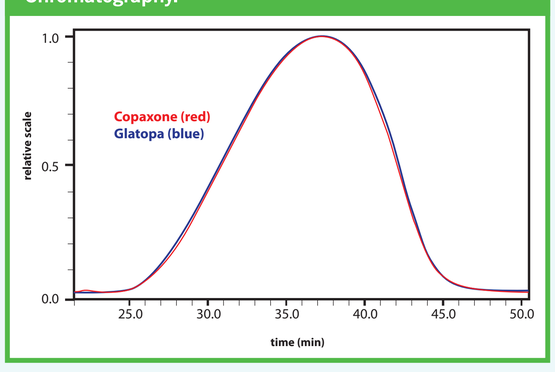
Figure 5. Relative Amino Acid Levels at the C-termini of Glatiramer Acetate. The solid lines for each amino acid represent the Copaxone-based specifications for that amino acid. Within these lines are the results for multiple Glatopa lots. Also shown is a Step-2 negative control, in which the depolymerization reaction was altered (black squares). Note: This method quantifies the C-termini that end in COOH, and does not include the peptides that terminate in diethylamide (See Fig 3).



Example of Process Signature for Step-3: Final Deprotection, Purification, and Salt Exchange

- Step-3 of the process is a final deprotection of the lysine residues followed by purification and final acetate salt exchange.
- An example of a process signature of this step is the final molar mass distribution.
- While the molar mass is in part determined by the Step-2 cleavage, the final distribution is governed by Step-3, wherein removal of small peptides is achieved via diafiltration (Figure 6).

Figure 6. Overlay of the Molar Mass Distributions of Glatopa and Copaxone, as Measured by Size Exclusion Chromatography.



Equivalence of Physicochemical Properties

- In addition to the methods used to detect process signatures, approximately 45 different methods were employed to characterize the drug substance and drug product and to ensure the quality of the product.
- These include many methods that are orthogonal to the ones previously described, as well as methods that probe additional physicochemical attributes (such as secondary structure and chirality), bulk composition properties (such as amino acid content, NMR and IR spectral properties), as well as many that define general quality attributes (such as impurities, concentration, and potency).
- Examples included total amino acid composition (Figure 7) and circular dichroism (Figure 8).

Figure 7. Amino Acid Compositions as Mole Fractions for Several Lots of Glatopa and Copaxone.

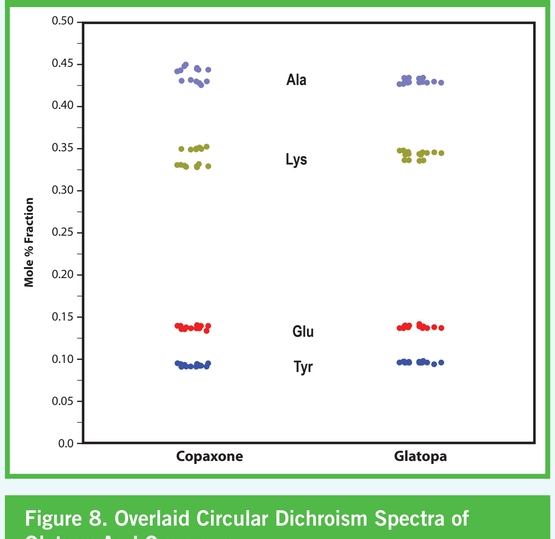


Figure 8. Overlaid Circular Dichroism Spectra of Glatopa And Copaxone.

Equivalence of Biological and Immunological Properties

- A detailed understanding of the biological functions of GA were examined in order to demonstrate the equivalence of Glatopa and Copaxone both in aggregate biological function as well as in the key aspects of its biology described in the literature (see Poster P647).
- This strategy employed multiple, redundant, and orthogonal biological and immunological assays, including MHC II class binding, antigen presenting cell function, T cell proliferation, T cell polarization, B cell biology, antibody response, immunorecognition, genome-wide gene expression effects (see Poster P641), anti-inflammatory effects, and neuroprotection (see Ref. 1 and Poster P647).

CONCLUSIONS

- A rigorous scientific approach enabled determination of equivalence for Glatopa™ with Copaxone® 20 mg.
- Active ingredient sameness was demonstrated using a four-point criteria framework. These criteria included equivalence of starting materials, process signatures, physicochemical properties, and biological and immunological attributes.
- The selected methods and data presented here represent a small portion of the comprehensive set of physicochemical (structural) and biological (functional) assays that were conducted. No differences were observed in structure or function between Glatopa and Copaxone 20 mg, as measured using more than 45 physicochemical methods and more than 15 biological and immunological assays (e.g., multiple methods for amino acid composition, molar mass distribution, N- and C-terminal analysis, and potency, T cell, B cell, APC biology, gene expression profile (see Posters P641 and P647.)

REFERENCES

1. Honan C, Ganguly TC, Fier I, Kaundinya GV. Comparative efficacy between a generic (M356) and brand Copaxone® (glatiramer acetate injection) in an animal model of multiple sclerosis. Presented at the 2014 Joint ACTRIMS-ECTRIMS Meeting; September 12, 2014, Boston, MA.

DISCLOSURES: All authors are employees of Momenta Pharmaceuticals, Inc.

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