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Draft Guidance on Glatiramer Acetate

November 2023

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Glatiramer acetate
Dosage Form:	Injectable
Route:	Subcutaneous
Strengths:	20 mg/mL, 40 mg/mL
Recommended Studies:	Comparative characterization studies to support active ingredient sameness and request for waiver of in vivo bioequivalence study requirements

Recommendations for demonstrating active ingredient sameness:

Glatiramer acetate is a mixture of peptide copolymers containing four specific amino acids in a defined ratio. The amino acids present in glatiramer acetate are L-glutamic acid, L-lysine, L-alanine and L-tyrosine with an average molar ratio of 0.141, 0.338, 0.427 and 0.095 respectively.[1] Active ingredient sameness can be established by showing equivalence between the test product and the reference listed drug (RLD) as to the four criteria described in detail below.[2] Generic drug sponsors are advised to perform side-by-side comparative studies using the test active ingredient and the active ingredient obtained from the RLD. It is recommended that at least three batches of the test active ingredient and three batches of active ingredient from the RLD should be characterized to assess active ingredient sameness and robustness in the manufacturing process. The following four criteria should be used to demonstrate active ingredient sameness:

[1] See the labeling information of Copaxone (NDA 020622).
[2] For more detailed discussion, see the FDA response to Citizen Petition, Docket No. FDA-2015-P-1050, which is available to the public at: http://www.regulations.gov.

a. Equivalence of fundamental reaction scheme;
b. Equivalence of physicochemical properties including compositions;
c. Equivalence of structural signatures for polymerization and depolymerization; and
d. Equivalence of biological assay results.

1. Equivalence of fundamental reaction scheme

A fundamental reaction scheme for the manufacture of glatiramer acetate has been published which features the polymerization reaction of activated amino acids and initiator, followed by a partial depolymerization of the intermediate copolymers.[3,4] An abbreviated new drug application (ANDA) applicant may satisfy this first criterion of active ingredient sameness by using the same (or equivalent): (1) NCA-amino acids and polymerization initiator to yield the intermediate copolymer; and (2) chemical reagent(s) for acid-catalyzed cleavage conditions. The elements of a fundamental reaction scheme to manufacture glatiramer acetate can be determined and confirmed using publicly available information on the synthesis process[5] in conjunction with diagnostic analysis of the RLD by orthogonal analytical measurements.

2. Equivalence of physicochemical properties, including composition

Physicochemical properties, such as amino acid composition, molecular weight distribution, spectroscopic fingerprints can provide broad and important characterizations in confirming active ingredient sameness and equivalence in underlying reaction schemes. Generic sponsors should perform side-by-side comparative physicochemical characterizations of test active ingredient and the active ingredient from the RLD. Methods and results of the characterizations should be reported to the FDA. The following physicochemical characterizations should be performed to demonstrate active ingredient sameness:

a. Amino acid content and optical purity of the four amino acids;
b. Molecular weight distribution, including the molar mass moments (Mn, Mw, and Mz) and polydispersity (Ip);
c. Spectroscopic fingerprints, including but not limited to, Fourier Transformation Infrared spectroscopy (FT-IR), nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) and circular dichroism (CD).

3. Equivalence of structural signatures for polymerization and depolymerization

The composition and sequence diversity of peptide copolymers in glatiramer acetate are governed by the polymerization and depolymerization reaction kinetics used in the synthesis. Structural signatures refer to certain characteristics in the active ingredient resulting from the underlying reactions, such as initiation chemistry of the peptide chains, coupling between the various amino acids pairs during propagation and any cleavage preference of depolymerization. An important feature of the polymerization step is that the molar fractions of each of the four amino acids in the intermediate copolymer chain vary across the synthesized chain, which is

[3] Teitelbaum D., Meshorer A., Hirshfeld T., Arnon R., Sela M., "Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide". Eur. J. Immunol. 1971, 1 (4), pp. 242-248.
[4] US Patent 7,199,908 describes the synthesis of copolymer-1 (glatiramer acetate).
[5] See notes 2 and 3, for example.

referred to as propagational shift. A generic sponsor should identify and analyze structural signatures that are chemical attributes of glatiramer acetate and correlate to both the polymerization step (including initiation kinetics and propagational shift) and the cleavage step of partial depolymerization. Information should be provided to the Agency to support the validity of the proposed structural signatures and the corresponding methods, which can be supported, for example, by (a) a mechanistic understanding of the synthetic process, (b) published literature, (c) pharmaceutical development studies that link changes in the ANDA manufacturing process to the corresponding structural signature, (d) negative control studies that introduce variations in the process and corresponding variations to the resulting product and structural signatures and (e) the proposed equivalence range/acceptance criteria should be based on the batch-to-batch variations of the RLD. This should include:

a. Structural signatures for polymerization initiation

Two characteristics should be captured: (1) the distribution of the four amino acid-initiator adducts; and (2) the initiator content in the copolymer.

b. Structural signatures for propagational shift during polymerization

A generic sponsor should identify relevant amino acid sequence properties and corresponding analytical procedures, which can quantitatively measure the propagational shift in the generic and RLD, and demonstrate that the propagational shift resulting from its process is the same (or equivalent) as the propagational shift present in the RLD.

c. Structural signatures for cleavage reactions in partial depolymerization

A generic sponsor should characterize any preference at the site of cleavage and average number of cleavages for an intermediate copolymer chain. For example, detailed analysis of N-termini and C-termini of the copolymers and the ratio of "uncapped" C-termini formed by the cleavage reaction versus "capped" C-termini produced by initiation reaction in the test active ingredient and active ingredient from the RLD should be performed. The results and rationale should be provided to the Agency.

4. Equivalence of biological assay results

A biological assay can serve as a confirmatory test of equivalence and provide complementary confirmation of active ingredient sameness. The Agency recommends ANDA applicants to conduct at least the following two experimental autoimmune encephalomyelitis (EAE) assays:[6,7] (1) prophylactic dosing in the active C57BL/6 mouse model induced by immunization with myelin oligodendrocyte glycoprotein peptide 35-55 in adjuvant, and (2) therapeutic dosing in the

[6] Robinson A. P., Harp C.T., Noronha A., Miller S.D. "The experimental autoimmune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment". Handb. Clin. Neurol. 2014, 122, pp. 173-189.

[7] Stern J. N. H., Illés Z., Reddy J., Keskin D. B., Sheu E., Fridkis-Hareli M., Nishimura H., Brosnan C. F., Santambrogio L., Kuchroo V. K., Strominger J. L., "Amelioration of Proteolipid Protein139-151-Induced Encephalomyelitis in SJL Mice by Modified Amino Acid Copolymers and Their Mechanisms". Proc. Natl. Acad. Sci. USA 2004, 101 (32), pp. 11743-11748.

passive SJL mouse model induced by adoptive transfer of encephalitogenic T cells activated in vitro with proteolipid lipoprotein peptide 139 – 151.[8,9]

Waiver of in vivo bioequivalence study requirements:

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), a generic glatiramer acetate subcutaneous injectable product should be qualitatively (Q1)[10] and quantitatively (Q2)[11] the same as the RLD.

An applicant may seek approval of a drug product that differ from the RLD in preservative, buffer or antioxidant if the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[12]

Additional information:

Device:
The RLD is presented as a prefilled syringe. The device constituent is the pre-filled syringe.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- Single-use, single-dose format of the pre-filled syringe
- Needle gauge and length

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

[8] McCarthy D. P., Richards M.H., Miller S.D. "Mouse models of multiple sclerosis: "Experimental autoimmune encephalomyelitis and Theiler's virus-induced demyelinating disease." Methods Mol. Biol. 2012, 900, 99. 381-401.
[9] Miller S.D., Karpus WJ, Davidson TS. "Experimental autoimmune encephalomyelitis in the mouse." Curr. Protoc. Immunol. 2007, Unit–15.1.
[10] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[11] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the reference product.
[12] 21CFR 314.94(a)(9)(iii).

Document History: Recommended April 2016; Revised July 2018, November 2023

Unique Agency Identifier: PSG_020622

[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.