

PL-6

## Same Product Different Regulatory Approach Around the World: Glatiramer Acetate

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### 1. Introduction

Complex drugs may be either biological, if the active ingredients are derived from a biological source, or non-biological, if obtained by chemical synthesis. In both cases, their quality depends considerably on the manufacturing process. For Non Biological Complex Drugs (NBCDs), in particular, complexity may arise either from the active substance, as in the case of glatiramer acetate (GA), or from other sources, such as the formulation, as in the case of liposomes (Figure 1) (1). GA is approved, in the US and the EU, as a disease-modifying treatment for patients with relapsing forms of Multiple Sclerosis. It is a heterogeneous mixture of not fully characterized synthetic polypeptides, containing L-alanine, L-lysine, L-glutamic acid, L-tyrosine in the constant molar ratio 0.43:0.34:0.14:0.09, with an average molecular weight from 5 to 9 kDa and distribution range from 2.5 to 20 kDa (2). The amino acid sequences are not completely random, being the result of both the physicochemical properties of the starting materials and the fundamental reaction scheme. However, they are not completely conserved from batch to batch, even when the process is tightly controlled. Indeed along with conserved characteristics - such as amino acid molar ratio - other characteristics - such as the specific amino acid sequences - will show batch-to-batch variability (1). To address this complexity, for the marketing of GA copies, US and EU regulatory agencies have chosen a generic approach integrated with additional data. However, the implementation is different in the two jurisdictions (Figure 1).

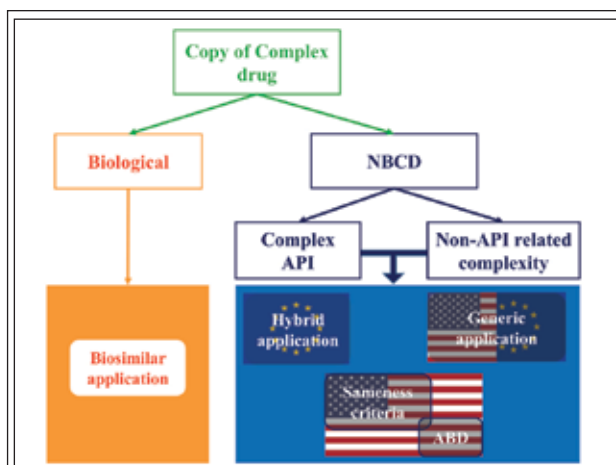
### 2. Results

The originator GA was first authorized in Israel and then in the United States in 1996. In the EU, the 20 mg/ml was initially approved in the UK, in 2000, and then in other Member States by a Mutual Recognition Procedure starting in 2004. Copies are now marketed in many countries. In the USA,

they have been approved following an Abbreviated New Drug Application (ANDA) and are considered generics. In the EU, they have been approved following a hybrid application and are considered as generics in some member states (1,3).

In the United States, the FDA required the demonstration of both pharmaceutical equivalence and bioequivalence. Demonstration of pharmaceutical equivalence, though, relies on the fact the two products contain the same active pharmaceutical ingredients (APIs). Currently, there is no single physicochemical or biological assay that can be used to demonstrate API sameness between the originator and a copy. However, FDA's position has been that API sameness can be demonstrated using a battery of orthogonal methods and an approach based on four criteria, published in product-specific guideline, which may be used to demonstrate API sameness even when the manufacturer of a copy does not entirely know the manufacturing steps used by the manufacturer of the originator (1).

In the EU, the first copy of GA 20 mg/ml was approved in 2016 with a decentralized procedure, following a hybrid application. Unlike the US case, no



**Figure 1.** Marketing Authorisation application routes for copies in the EU and the USA (after 23 March 2020). NBCD = Non-Biological Complex Drug, API = Active Pharmaceutical Ingredient, ABD = Additional Bioequivalence Data.

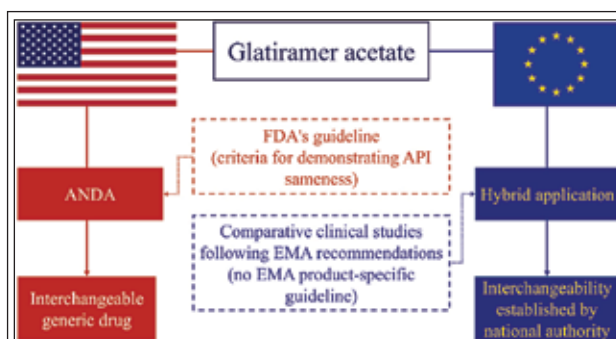
product-specific guideline exists in the EU for the production of GA copies, and the nature and extent of the studies required is determined on a case by case basis. The national regulatory agencies required a comparative characterization study with the originator (1,3). The Applicant, in agreement with the EMA, also provided non-clinical and clinical data in support of similarity. As for the non-clinical aspects, it provided data from an EAE mouse model, two 28-days studies and one 90-days comparative toxicity study performed in rats. As for the clinical aspects, following EMA's recommendation, the applicant performed a comparative clinical trial to assess the efficacy, safety, and tolerability of both prolonged treatment with the copy (GTR) and switching from the originator 20mg OD to GTR 20 mg OD. The 9-month randomized clinical trial on 794 patients, named Glatiramer Acetate Clinical Trial to assess Equivalence with Copaxone® (GATE) (4), was followed by 15 months open label follow-up. To support the hybrid application for GTR 40 mg/ml, which could not be based only an extrapolation of the results from the GATE study, Synthon used bridging scheme which involved GATE clinical study (comparing Copaxone® 20 mg/ml to GTR 20 mg/ml), the GALA clinical study (comparing Copaxone® 40 mg/ml to placebo) and four other published clinical studies (partly used in the application for Copaxone® 40 mg/ml).

#### 4. Conclusions

For the approval of GA copies, regulatory agencies in the US and the EU are currently oriented toward a generic approach supplemented by additional data. However, this path has been implemented differently in the two jurisdictions (**Figure 2**).

In the US, this has immediate consequences on interchangeability, as the decision is taken by the FDA during approval. In the case of GA, the additional data required is listed in a product specific guideline and copies have been approved by the FDA as generics based on an ANDA and assigned and "A" code in the Orange Book.

In the EU, a product approved based on a simplified dossier is automatically considered interchangeable. If, on the other hand, it follows a hybrid application, it is not interchangeable per se and, as in the case of GA copies, EMA leaves the decision about interchangeability and substitution to the individual member states. For GA copies, national regulatory agencies followed a hybrid approach requiring an additional comparative



**Figure 2.** Regulatory pathways for Glatiramer Acetate in the US and EU. ANDA = Abbreviated New Drug Application, API = Active Pharmaceutical Ingredient

study, except for one case where an informed consent application could be used (3).

In conclusion, differences in US and EU policies for NBCD copies still exist. They clearly have an impact on the costs incurred by pharmaceutical companies, but have proven adequate to guarantee Quality, Safety and Efficacy. Moreover, as knowledge of complex drugs and the related technology advance, US and EU policies seem to be undergoing a process of alignment. Indeed, there are points where the approaches in the two jurisdictions have converged: neither the FDA nor the European agencies have introduced an ad hoc regulatory class for NBCDs. The path taken by the FDA, i.e. the development of product specific guidelines for different NBCDs may pave the way to a similar approach by the EMA. At the same time, monographs for NBCDs are being drafted in the European and US Pharmacopoeias.

In view of the above and in the light of current knowledge and technological developments it is important, regardless of the regulatory approach, that the prescribing physician is always able to trace the actual complex drug administered to each patient.

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