

Copies of Non-Biological Complex Drugs: generic, hybrid or biosimilar?

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Teaser: Complex drugs, biological or not, require special care by regulatory authorities. Current regulations, which often require an abbreviated application integrated with additional data, yield different results in the US and Europe.

Conflict of Interest Statement

The authors declare they have no conflict of interest.

Abstract

The experience gained with biosimilars has made clear that copies of complex drugs are more challenging to produce and put on the market than generics. In the case of so-called Non-Biological Complex Drugs (NBCDs), the complexity may arise either from a complex active substance or by other factors, such as formulation or route of delivery.

Regulatory policies in the US and Europe for the marketing of NBCD copies are reviewed, using glatiramer acetate copies as a case study. In the US, they are approved and marketed as generics (though needing additional data), and so they are interchangeable with the originator. In the EU, being managed with a hybrid application, their interchangeability and substitution are established by individual Member States.

Introduction

Pharmaceutical companies may choose to market copies of an approved medicinal product after patent rights and data protection have expired. The required application procedure depends on the type of product. The generic route should be followed in the case of small-molecule synthetic drugs and the biosimilar route in the case of most biological products. The rationale of this distinction is that the quality of biologic drugs depends heavily on the manufacturing process. Therefore, it is affected by a change of manufacturer or manufacturing process, and it may show batch-to-batch variability. Moreover, biological active substances cannot be thoroughly characterized using current analytical methods and, as a consequence, bioequivalence is not sufficient to guarantee therapeutic equivalence as the pharmacodynamics can be different [1].

In the US, the dossier of an abbreviated application may include additional data in the case of more complex products, such as non biological products that does not fall within the definition of generic. In the EU a hybrid application may be used. Those medicinal products, so-called Non Biological Complex Drugs (NBCDs), share their synthetic origin with small molecule drugs, and their complexity with biological drugs.

Patent rights and the data protection period for major NBCDs, such as Copaxone® are now expiring. Therefore, it is important to analyze the different regulatory approaches to NBCDs and their copies in the US and Europe. In this paper, such an analysis is carried out, and the legislative framework for NBCDs is outlined. Glatiramoids are used as a case study, while Low Molecular Weight Heparins (LMWHs), another example of complex drugs already addressed in a previous paper [2], are briefly considered. They represent a borderline case, as they are classified as biologicals in the EU and non-biologics in the USA [3,4].

In this paper, the term “copy” is used to denote any medicinal product manufactured and marketed to be therapeutically equivalent to an already authorized product, while the terms “generic” and “biosimilar” only address specific categories of copies.

NBCDs copies from a regulatory perspective

There is still no consensus on the definition of NBCDs. A NBCD has been defined as: “*a medicinal product, not being a biological medicine, where the active substance is not a homomolecular structure, but consists of different (closely related and often nanoparticulate) structures that cannot be isolated and fully quantitated, characterized and/or described by physico-chemical analytical means*” [5].

Complexity, though, may also arise from other sources, such as the formulation, and not only from the active substance. Indeed, some drugs are considered to be complex by the U.S. Food & Drug Administration (FDA) based on all those sources of complexity. The six complex categories recognized by the FDA are shown in **Table 1** and have been numbered for ease of reference in subsequent tables [6,7].

From a regulatory point of view, the EMA and the FDA do not consider NBCDs to be a distinct category of medicinal products. In the US, NBCD copies are considered to be generics [6] and all NBCDs applications are managed by the FDA. In the EU, on the other hand, most NBCDs

applications are not managed by the EMA, but by national Agencies (there is no provision that NBCDs should be mandatorily evaluated by the EMA).

The U.S. Government Accountability Office (GAO) published a list of 28 drugs, which are considered both nonbiologic and complex by the FDA [6]. The list, based on publications that identified specific drugs as NBCDs, was reviewed by the Non-Biological Complex Drugs Working Group (which consists of experts from industry, academia, and knowledge institutes) and by the National Institutes of Health's Nanotechnology Characterization Lab. However, four of the listed products (propofol, estradiol hemihydrate, paliperidone palmitate and lidocaine/prilocaine combination) are not considered to be NBCDs by the Working Group. Of the 28 products listed by the U.S. GAO, only 10 have been approved following a centralised procedure in the EU, mainly for being innovative, or biological (Enoxaparin sodium) or orphan (liposomal Irinotecan hydrochloride) medicinal products, while most of the others have been granted a MA through a decentralised procedure (**Table 2**) [6,8,9,10].

In the US, with respect to Abbreviated New Drug Applications (ANDAs) for small molecule drugs, additional data may be required to support the equivalence of the generic NBCD to its originator. This may be necessary, as the FDA recognizes that the manufacturing process of a NBCD is complex and, generally, proprietary. As a consequence, the second manufacturer may not know the exact manufacturing steps used by the manufacturer of the originator.

In general, for a medicinal product to be approved as a generic, there are two steps that regulatory agencies and sponsors must complete: the demonstration of pharmaceutical equivalence and the demonstration of bioequivalence. Both of these steps pose particular difficulties in the case of NBCDs.

Demonstrating pharmaceutical equivalence is difficult, particularly in the case of complex active ingredients, as those are generally not identical in the originator and in the copy. Moreover, the drug structure cannot be thoroughly characterized and, as in the case of glatiramer acetate (GA), the actual part of the active substance responsible for the therapeutic response may be

unknown [6] and simple pharmacokinetic studies not appropriate for bridging the copy to the originator [11].

As far as bioequivalence is concerned, in the case of complex active substances and complex formulations measuring plasma concentration of the free active substance may not be enough. This may be due to the properties of the nanocarrier, as in the case of liposomes, or to the local action of the drug, as in the case of Cyclosporine eye drops [6,12]. The FDA has issued regulations on assessing bioequivalence beyond plasma concentration, and it may consider other approaches, if deemed adequate (21 C.F.R. §320.24).

The FDA has issued (draft) product specific guidelines on the assessment of bioequivalence for 19 NBCDs: Paclitaxel, Amphotericin B (liposomal), Daunorubicin citrate, Iron dextran, Estradiol hemihydrate, Ferumoxytol, Dalteparin sodium, Ferric carboxymaltose, Paliperidone palmitate, Lidocaine-prilocaine, Cyclosporine, Iron sucrose, Verteporfin, Doxorubicin hydrochloride (liposomal), Enoxaparin sodium, Glatiramer acetate, Propofol, Sodium ferric gluconate complex in glucose and Sevelamer carbonate. Following the guidelines' publication, generic versions of the last six products listed above have been approved in the US [13].

In Europe, the route followed for the marketing of copies NBCDs varies, depending on the nature of the product. In the case of LMWHs, which are considered biologicals, a biosimilar approach, through a centralised procedure, has been used. In the case of glatiramer acetate copies, a hybrid application path has been followed, through a decentralised procedure (Reference Member State: The Netherlands) [11].

A classification of medicinal products marketed in the US and Europe based on the source of the active substance and on the complexity of the manufacturing process, along with the regulatory approach used in marketing copies, is proposed in **Table 3**. At the two extremes of the spectrum are small molecule drugs and biological products. In the USA, most biological medicinal products are approved with a Biologics License Applications (BLA), regulated in section 351 of the Public Health Service (PHS) Act, as amended by the Biologics Price Competition and Innovation

Act (BPCIA) of 2009 [1]. In the EU, products obtained by means of biotechnological manufacturing processes (biotechnological medicinal products), are approved under the provisions of Regulation (EU) no. 726/2004 (other biological product may be approved by the same route, according to the provisions of Art. 3(2)(b) of Reg. EU no. 726/2004, or the Annex, points 3 and 4).

In between those two extremes, some drugs are regulated differently in the US and Europe. Indeed, for historical reasons, the FDA regulates non-synthetic polypeptides under 40 amino acids as drugs under the Food, Drug and Cosmetic (FD&C) Act, while the EMA regulates the same products, when produced by means of a biotechnological process, under Regulation CE no. 726/2004, together with the other biotechnological medicinal products. However, a rapprochement of the US and EU scenarios has started, due to both technological advances and regulatory alignment.

On the regulatory side, the "Deemed to be a License" provision of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) extended the scope to include any protein (except chemically synthesized polypeptides). It provides that, from March 23rd, 2020, "an application for a biological product approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) will be deemed to be a license for the biological product under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262)" [14]. As a result, products containing (non-synthetic) polypeptides under 40 amino acids now approved with a New Drug Application (NDA) or an ANDA (e.g. insulin and somatropin) will fall under the BPCIA. Therefore, US legislation on polypeptide-based and protein-based products will then be closer to EU legislation.

LMWHs, too, are regulated differently in the EU, where they are considered biologicals and their copies must be authorized following the biosimilar approach, and in the US, where they are considered to be non-biologics. In particular, Enoxaparin sodium is considered to be a complex drug by the FDA, and was approved under the ANDA pathway: LMWH copies that are indistinguishable from originators in structural terms, are considered to have predictably similar

properties in the patient, so that pre-licensing tests in patients are not necessary [2]. However, even for LMWHs FDA and EMA requirements are converging. As advancements in analytical methods allow for better characterization of intermediates and products, and regulatory experience increases, clinical data may be no longer necessary. Indeed, in the last revision of EMA's guideline on LMWHs [15], a clinical efficacy and safety trial is not considered mandatory [16].

Interchangeability, substitution and traceability

Biosimilars are not interchangeable *per se*. The US Public Health Service (PHS) Act (Section 351), as amended, states the conditions for a biological product to be interchangeable with the originator. In Europe, the EMA leaves the decision about interchangeability to individual member states [17]. Automatic substitution, meaning a substitution at the dispensing level without the physician explicit prior consent, can be introduced by local authorities on the basis of interchangeability. So far, no biosimilar has been designated as interchangeable by any regulatory authority, so the automatic substitution of biosimilars is generally not accepted [18].

Generics are interchangeable by definition, and automatic substitution follows logically. Copies of NBCDs, on the other hand, are interchangeable *per se* only in countries where they are approved as generics. In the EU, where they are approved with a hybrid application, interchangeability can only be introduced by local authorities, on a case by case basis, after the medicinal product has received a Marketing Authorisation.

Automatic substitution at the dispensing level, when extended to complex drugs, biologicals or not, makes traceability more difficult to deal with, and the prescribing physician may lose all the information about which medicinal product is being administered to the patient. While this is generally accepted in the case of small molecule generics, it may not be appropriate in the case of complex drugs, which are not unanimously considered to be interchangeable. In the US automatic substitution of NBCDs is generally permitted. In the EU, when complex drugs are biologicals, as in the case of LMWHs, they are not considered interchangeable, while when they are non-biologics

they may be considered interchangeable or not, depending on the decision of national authorities, as in the case of Glatopa and Copaxone[®].

From a products liability perspective, a potential “failure to warn” or “design defect” liability is not ascribable to the generic Marketing Authorization Holder (MAH), since the generic product bears the same labelling as the originator. In general, redesign and/or label modification, as a mean to improve the risk/benefit ratio of a medicinal product are not possible for generics, because the generic drug is required to have the same active ingredients, route of administration, dosage form, strength, and labeling as the originator (21 U.S.C. 355(j)). This limits the extent to which a generic manufacturer could be held liable in failure to warn or design defect claims [19,20,21].

Case study: Glatiramoids

The active substance of glatiramoids is a copolymeric mixture of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, in a constant molar ratio [22]. Glatiramer acetate (GA), contained in the originator Copaxone[®], is marketed as a colloidal suspension in pre-filled syringes for SC injection (20 mg/ml and 40 mg/ml). GA is a heterogeneous mixture of not fully characterized synthetic polypeptides, the size of which ranges from 1 to 500 nm, and the average molecular weight (MW) from 5000 to 9000 Dalton (MW distribution range is 2500 - 20,000). The exact mechanism of action of GA is not fully known, and the peptides responsible for the therapeutic effect have not been identified, which adds to the complexity of the medicinal product [23]. A 60 amino acids (AA) polypeptide (about 7000 Dalton) will contain on average 8 Glutamic Acid, 26 Alanine, 6 Tyrosine and 20 Lysine residues, with 1029 possible AA sequence combinations [24].

As in the case of therapeutic proteins, the quality of GA is mainly defined by the manufacturing process [22,23,25]. This is exemplified by the history of the second generation glatiramoid, known as TV-5010, developed by the same manufacturer of the first-generation GA, after changes in the downstream stages of the manufacturing process. Despite having the same

molar ratio of AA as GA (but a higher average molecular weight) and mostly similar physicochemical parameters, TV-5010 showed a different in vivo safety profile [26].

The sensitivity of GA to changes in the manufacturing process is similar to the case of biological active substances. The analogy does not end here, though, since, as in the case of biologicals, the active substance is difficult to characterize, as no analytical technique developed so far can be used to demonstrate that two glatiramoid mixtures are identical.

According to the FDA's Draft Guidance on Glatiramer Acetate Injection released in 2016 [27], API sameness can be established by showing equivalence between the originator and the generic product according to four criteria:

1. Equivalence of fundamental reaction scheme, as it can be determined using publicly available information.
2. Equivalence of physicochemical properties, including compositions, assessed by: amino acid content and optical purity of the four amino acids; MW distribution, including the molar mass moments and polydispersity; spectroscopic fingerprints, such as Fourier Transformation Infrared spectroscopy (FT-IR), nuclear magnetic resonance spectra (^1H and ^{13}C NMR) and circular dichroism (CD). Other analytical methods, such as Capillary Isoelectric Focusing (IEF), Dynamic Light Scattering (DLS), Atomic Force Microscopy (AFM), Ion Mobility Mass Spectrometry (IMMS), can discriminate among glatiramoids made by different manufacturers [28].
3. Equivalence of structural signatures for polymerization and depolymerization, such as initiation chemistry of the peptide chains, coupling between the various amino acids pairs during propagation and any cleavage preference of depolymerization.
4. Equivalence of biological assay results. The FDA recommends experimental allergic encephalomyelitis (EAE) assay as an animal model for multiple sclerosis.

The FDA does not recommend that any clinical trial be performed. In the United States, Copaxone[®] 20 mg/ml and 40 mg/ml solution for injection, pre-filled syringes and its copies (marketed as Glatiramer acetate Mylan, and Glatopa[®]) are considered to be therapeutically equivalent (AP code in the Orange Book) [29].

In Europe, glatiramer acetate copies have been approved in 2016, under different brand names, with a decentralised procedure. The MA has been granted through a hybrid application under Article 10(3) of Directive 2001/83/EC, claiming similarity with the innovator product Copaxone[®]. The regulatory Agencies recognized that the complexity of the active ingredients posed challenges for the demonstration of equivalence with the originator and for testing production consistency, and that, therefore, a detailed comparative characterization study with Copaxone[®] was needed, including any additional data necessary to prove similarity. Actually, the Applicant (Synthon BV) followed a strategy similar to that of biosimilar applications, providing non-clinical and clinical data in support of similarity, next to quality data. As for the non-clinical aspects, data from an experimental autoimmune encephalitis (EAE) mouse model were provided to demonstrate pharmacological comparability, along with two 28-days studies and one 90-days comparative toxicity studies performed in rats [11].

EMA, in its scientific advice to Synthon, required the conducts of a clinical trial [30]. The study, Glatiramer Acetate Clinical Trial to assess Equivalence with Copaxone[®] (GATE), was a 9-month randomized clinical trial on 794 patients [31] with a 15 months open label follow-up on 729 patients [32], performed to evaluate the efficacy, safety, and tolerability of (1) prolonged generic glatiramer acetate treatment and (2) switching from Copaxone[®] to generic glatiramer acetate treatment. According to the study, the two products have equivalent efficacy, safety and tolerability and switching is safe and well tolerated.

However, the study, developed with input from the EMA, shows, admittedly some limits [31]. The primary end point was Magnetic Resonance Imaging (MRI) activity, expressed as the total number of gadolinium-enhancing lesions during one quarter (months 7-9), which weakly

correlates with clinical activity and was never accepted by the FDA as a primary end point in pivotal Multiple Sclerosis (MS) trials [33]. On the one hand, both drugs were superior to placebo: mean numbers of gadolinium-enhancing lesions were 0.42 for Synthon's product, 0.38 for Teva's, and 0.82 for placebo [31]. On the other hand, annualized relapse rate (ARR) observed for Copaxone[®] (0.41) was essentially the same as for the placebo (0.39) [31], while in a previous study [34] Copaxone[®] was found to decrease the ARR substantially (0.81 for Copaxone[®] versus 1.21 for placebo). The divergence between MRI activity and clinical activity is quite unexpected, as a previous meta-analysis [35] showed higher correlation.

Conclusion

Different regulatory aspects of NBCDs and their copies are still actively debated. The experience gained with LMWHs, liposomes and glatiramoids represents a solid foundation for a much-needed evolution of regulatory policies for NBCDs copies.

The current orientation of regulatory Agencies in the United States and Europe is toward a generic approach, integrated with additional data determined on a case-by-case basis. Even though the specificity of NBCDs is recognized and further studies are required in addition to bioavailability the outcomes may be different in the two jurisdictions.

The case of glatiramer acetate is particularly indicative of this divergence. In the US, copies of Copaxone[®] were approved by the FDA based on equivalence of (1) fundamental reaction scheme, (2) physicochemical properties, (3) structural signatures for polymerization/depolymerization and (4) biological assay results. Those copies are considered interchangeable *per se*. In the EU, regulatory bodies required an additional clinical study, the design of which was based on EMA's recommendations. Interchangeability and substitution schemes have been managed on a case by case basis by national Agencies.

However, an alignment of US and EU regulatory policies has started. On the one hand, on the basis of the "Deemed to be a License" provision of the BPCIA the copies of some biologics,

such as insulins, will be treated similarly. On the other hand, the divergence in regulatory policies for products, such as LMWHs that are considered biologicals in the EU but not in the US, are deemed to converge due to advancements in analytical methods, which allow for a reduction in required clinical data, and to the increased regulatory experience.

From a products liability perspective, if a medicinal product is classified as a generic drug classification manufacturers/MAHs are incapable of modifying either the drug composition in active substances or their warnings, strongly limiting their leeway and, consequently, their liability in case of adverse events. This can be considered adequate in the case of small molecule drugs, but a classification of NBCDs as generics extends those effects to an entire class of complex products, and serious issues may arise in the future. The biosimilar approach, on the other hand, puts much more responsibility on manufacturers/MAHs. No regulatory agency, though, seems oriented toward an approach based on similarity in the case of complex drugs, unless they are biologics, as in the case of LMWHs in Europe. Considering that regulatory agencies are oriented toward the requirement of an abbreviated application integrated with additional data, the issue of liability is probably referred to the Courts.

Apart from liability issues, even where NBCDs copies are approved as generics, they should not be automatically considered in the same class as small molecule bioequivalent medicinal products and regulatory authorities should consider the impact of the generic classification on post-marketing issues, such as traceability and substitution practices.

References

- ¹ Minghetti P, Rocco P, Cilurzo F, Vecchio LD, Locatelli F. The regulatory framework of biosimilars in the European Union. *Drug Discov Today*. 2012 Jan;17(1-2):63-70.
- ² Minghetti P, Cilurzo F, Franzé S, Musazzi UM, Itri M. Low molecular weight heparins copies: are they considered to be generics or biosimilars? *Drug Discov Today*. 2013 Mar;18(5-6):305-11.
- ³ Gray E, Mulloy B. Biosimilar low molecular weight heparin products. *J Thromb Haemost*. 2009;7(7):1218-21.
- ⁴ Rodrigo I, Caruncho S, Alonso C, Gómez-Outes A, Mulloy B. Low Molecular Weight Heparins, Biological Drugs close to Non-Biological Complex Drugs. In *Non-Biological Complex Drugs. The Science and the Regulatory Landscape*, Crommelin DJA and de Vlieger JSB (Eds.), Springer, Cham, 2015.
- ⁵ Crommelin DJ, de Vlieger JS, Weinstein V, Mühlebach S, Shah VP, Schellekens H. Different pharmaceutical products need similar terminology. *AAPS J*. 2014;16(1):11-4.
- ⁶ U.S. Government Accountability Office. Report to Congressional Requesters. Generic Drugs. FDA Should Make Public Its Plans to Issue and Revise Guidance on Nonbiological Complex Drugs. GAO-18-80 (2017). Available at <https://www.gao.gov/products/GAO-18-80>. Last accessed on 8 May 2018.
- ⁷ U.S Food & Drug Administration. Generic Drug User Fee Act reauthorization for Fiscal Years (FYs) 2018-2022 (GDUFA II commitment letter), 2017. Available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>. Last accessed on 2 May 2018.
- ⁸ Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Available at <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004R0726>.
- ⁹ European Medicines Agency. European public assessment reports. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124. Last accessed on 8 May 2018.
- ¹⁰ Heads of Medicines Agencies (HMA). The MRI Product Index. Available at <https://mri.cts-mrp.eu/Human/>. Last accessed on 10 May 2018.
- ¹¹ College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board, CBG/MEB). Public Assessment Report. Scientific discussion. Glatiramer acetate 20 mg/ml solution for injection, pre-filled syringe (2016). Available at https://mri.cts-mrp.eu/Human/Downloads/NL_H_3213_001_PAR.pdf
- ¹² Pita R. The EU Regulatory Landscape of Non-Biological Complex Drugs. In *Non-Biological Complex Drugs. The Science and the Regulatory Landscape*, Crommelin DJA and de Vlieger JSB (Eds.), Springer, Cham, 2015.
- ¹³ U.S. Food and Drug Administration. Product-Specific Guidances for Generic Drug Development. Available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>. Last accessed on 2 February 2018.
- ¹⁴ U.S. Food and Drug Administration. Implementation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry (Draft), March 2016. Available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf>. Last accessed on 12 April 2018.
- ¹⁵ European Medicines Agency. Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins. EMEA/CHMP/BMWP/118264/2007 Rev. 1. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500217126.pdf. Last accessed on 7/29/2018.
- ¹⁶ Husaarts L, Mühlebach S, Shah VP, McNeil S, Borchard G, Flühmann B, Weinstein V, Neervannan S, Griffiths E, Jiang W, Wolff-Holz E, Crommelin DJA, de Vlieger JSB. Equivalence of complex drug products: advances in and challenges for current regulatory frameworks. *Ann N Y Acad Sci*. 2017;1407(1):39-49.
- ¹⁷ Minghetti P, Rocco P, Schellekens H. The constrained prescription, interchangeability and substitution of biosimilars. *Nat Biotechnol*. 2015 Jul;33(7):688-9.
- ¹⁸ Ebbers HC, Crow SA, Vulto AG, Schellekens H (2012). Interchangeability, immunogenicity and biosimilars. *Nat Biotechnol*. 2012 Dec;30(12):1186-90.
- ¹⁹ *Pliva v. Mensing*, 564 U.S. 604 (2011).
- ²⁰ *Mutual Pharmaceutical Co. v. Bartlett*, 133 S. Ct. 2466 (2013).
- ²¹ Rocco P, Selletti S, Minghetti P. Biosimilar switching and related medical liability. *J Forensic Leg Med*, 2018;55:93–94.
- ²² Varkony H, Weinstein V, Klinger E, Sterling J, Cooperman H, Komlos T, Ladkani D, Schwartz R. The glatiramide class of immunomodulator drugs. *Expert Opin Pharmacother*. 2009;10(4):657-68.
- ²³ Borchard G, Crommelin DJA. Equivalence of glatiramer acetate products: challenges in assessing pharmaceutical equivalence and critical clinical performance attributes. *Expert Opin Drug Deliv*. 2017;22:1-13.

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- ²⁴ Carter NJ, Keating GM. Glatiramer acetate: a review of its use in relapsing-remitting multiple sclerosis and in delaying the onset of clinically definite multiple sclerosis. *Drugs*. 2010;70(12):1545-77.
- ²⁵ Schellekens H, Klinger E, Mühlebach S, Brin JF, Storm G, Crommelin DJ. The therapeutic equivalence of complex drugs. *Regul Toxicol Pharmacol*. 2011;59(1):176-83.
- ²⁶ Ramot Y, Rosenstock M, Klinger E, Bursztyn D, Nyska A, Shinar DM. Comparative long-term preclinical safety evaluation of two glatiramoid compounds (glatiramer Acetate, Copaxone(R), and TV-5010, protiramer) in rats and monkeys. *Toxicol Pathol*. 2012;40(1):40-54.
- ²⁷ U.S. Food and Drug Administration. Draft Guidance on Glatiramer Acetate Injection, 2016. Available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>. Last accessed on 2 February 2018.
- ²⁸ Weinstein V, Schwartz R, Grossman I, Zeskind B, Michael Nicholas JM. Glatiramoids. In *Non-Biological Complex Drugs. The Science and the Regulatory Landscape*, Crommelin DJA and de Vlioger JSB (Eds.), Springer, Cham, 2015.
- ²⁹ U.S. Food and Drug Administration. Approved Drug Products With Therapeutic Equivalence Evaluations (Orange Book), 38th Edition. Available at <https://www.accessdata.fda.gov/scripts/cder/ob/>. Last accessed on 12 April 2018.
- ³⁰ Bourdette D, Hartung D. Equivalence of Glatiramer Acetate Generics With Branded Glatiramer Acetate in Efficacy and Cost for the Treatment of Multiple Sclerosis. *JAMA Neurol*. 2015 Dec;72(12):1411-3.
- ³¹ Cohen J, Belova A, Selmaj K, Wolf C, Sormani MP, Oberyé J, van den Tweel E, Mulder R, Koper N, Voortman G, Barkhof F. Glatiramer Acetate Clinical Trial to Assess Equivalence With Copaxone (GATE) Study Group. Equivalence of Generic Glatiramer Acetate in Multiple Sclerosis: A Randomized Clinical Trial. *JAMA Neurol*. 2015;72(12):1433-41.
- ³² Selmaj K, Barkhof F, Belova AN, Wolf C, van den Tweel ERW, Oberyé J, Mulder R, Egging DF, Koper NP, Cohen JA, and on behalf of the GATE study group. Switching from branded to generic glatiramer acetate: 15-month GATE trial extension results. *Mult Scler*. 2017; 23(14): 1909–1917.
- ³³ Sørensen PS. Multiple sclerosis. Generic glatiramer acetate--a step toward cheaper MS drugs? *Nat Rev Neurol*. 2016;12(1):5-6.
- ³⁴ Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. *Ann Neurol*. 2001;49(3):290-7.
- ³⁵ Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. *Lancet Neurol*. 2013;12(7):669-76.