Copies of nonbiological complex drugs: generic, hybrid or biosimilar?

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The experience gained with biosimilars has made it clear that copies of complex drugs are more challenging to produce and put on the market than generics. In the case of so-called nonbiological complex drugs (NBCDs), the complexity can arise either from a complex active substance or by other factors, such as formulation or route of delivery. Regulatory policies in the USA and the EU for the marketing of NBCD copies are reviewed, using glatiramer acetate copies as a case study. In the USA, they are approved and marketed as generics (although needing additional data), and so they are interchangeable with the originator. In the EU, they are managed with a hybrid application, and their interchangeability and substitution are established by individual member states.

Introduction

Pharmaceutical companies can 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 can 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 because the pharmacodynamics can be different [1].

In the USA, the dossier of an abbreviated application can include additional data in the case of more-complex products, such as nonbiological products that do not fall within the definition of generic. In the EU, a hybrid application can be used. Those medicinal products, so-called nonbiological 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 USA and the EU. In this review, such an analysis is carried out, and the legislative framework for NBCDs is outlined. Glatiramoids are used as a case study, whereas 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, because they are classified as biologics in the EU and nonbiologics in the USA [3,4]. Here, the term 'copy' is used to denote any medicinal product manufactured and marketed to be therapeutically equivalent to an already authorized product, whereas the terms 'generic' and 'biosimilar' only address specific categories of copies.

NBCD 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, however, can 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 FDA based on all those sources of complexity. The six complex

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TABLE 1

Categories of drugs considered to be complex by the FDA, as listed in the GAO report [6]

#	Category	Examples
1	Complex active ingredient	Peptides, polymeric compounds, complex mixtures of active pharmaceutical ingredients, naturally sourced ingredients
2	Complex formulations	Liposomes and colloids
3	Complex routes of delivery	Locally acting drugs such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions or gels
4	Complex dosage forms	Transdermals, metered dose inhalers and extended-release injectables
5	Complex drug–device combinations	Autoinjectors, metered-dose inhalers
6	Other	Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement

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 USA, NBCD copies are considered to be generics [6] and all NBCD applications are managed by the FDA. In the EU, by contrast, most NBCD 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 US Government Accountability Office (GAO) published a list of 28 drugs, which are considered 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 US GAO, only ten have been approved following a centralized procedure in the EU, mainly for being innovative, or biological (enoxaparin sodium) or orphan (liposomal irinotecan hydrochloride) medicinal products, whereas most of the others have been granted a marketing authorization (MA) through a decentralized procedure (Table 2) [6,8–10].

In the US, with respect to abbreviated new drug applications (ANDAs) for small-molecule drugs, additional data might be required to support the equivalence of the generic NBCD to its originator. This could be necessary because the FDA recognizes that the manufacturing process of a NBCD is complex and, generally, proprietary. As a consequence, the second manufacturer might not know the exact manufacturing steps used by the manufacturer or 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, because 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 might 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 might not be enough. This could 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 can consider other approaches, if deemed adequate (21C.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 publication of the guidelines, generic versions of the last six products listed above have been approved in the USA [13]. In the EU, the route followed for the marketing of NBCD copies varies, depending on the nature of the product. In the case of LMWHs, which are considered biologics, a biosimilar approach, through a centralized procedure, has been used. In the case of glatiramer acetate copies, a hybrid application path has been followed, through a decentralized procedure (Reference Member State: The Netherlands) [11].

A classification of medicinal products marketed in the USA and the EU 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 biologic products. In the USA, most biologic medicinal products are approved with a biologics license application (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 products can 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 USA and the EU. Indeed, for historical reasons, the FDA regulates nonsynthetic polypeptides under 40 amino acids as drugs under the Food, Drug and Cosmetic (FD&C) Act, whereas 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,

TABLE 2

Originator nonbiological complex drugs marketed in the USA [6] and the corresponding medicinal products marketed in the EU with a centralized procedure (CP) or decentralized/mutual recognition procedure (DCP/MRP) [10]. For Products approved with DCP/MRP name Reference Member State is given. Products approved with a national procedure or first authorized before the establishment of the EMA are omitted

Category #[a]	Active substance	US trade name	EU trade name (CP, MRP/DCP)
2	Paclitaxel	Abraxane®	Abraxane® (CP)
2	Amphotericin B (liposomal)	Ambisome®	Ambisome®[b]
2	Amphotericin B (lipid complex)	[Amphotec® (discontinued[c])]	Abelcet® (MRP/DCP)
1	Glatiramer acetate injection	Copaxone®	Copaxone® (MRP/DCP)
2	Daunorubicin citrate (liposomal)	[DaunoXome® (discontinued[c])]	DaunoXome® (MRP/DCP)
2	Cytarabine (liposomal)	DepoCyt®	DepoCyte® (CP)
2	Morphine sulfate (liposomal)	[Depodur® (discontinued[c])]	–
1	Iron dextran (EU: iron(III)-hydroxide dextran complex)	Dexferrum®, InFed®	Cosmofer® (MRP/DCP)
2	Doxorubicin hydrochloride (liposomal)	Doxil®	Caelyx®, Myocet® (CP)
2	Bupivacaine (liposomal)	Exparel®	–
1	Ferumoxytol	FeraHeme®	[Rienso® (CP, discontinued[c])]
1	Ferumoxides	[Feridex® (discontinued[c])]	Endorem® (MRP/DCP)
1	Sodium ferric gluconate complex in sucrose	Ferrlecit®	–
1	Dalteparin sodium	Fragmin®	Dalteparinnatrium Pfizer (MRP/DCP)
1	Ferric carboxymaltose	Injectafer®	–
1	Tinzaparin sodium	[Innohep® (discontinued[c])]	Innohep® (MRP/DCP)
1	Enoxaparin sodium injection	Lovenox®	Lovenox®, Clexane®, Qualiop® (MRP/DCP)
2	Vincristine sulfate (liposomal)	Marqibo®	–
2	Irinotecan hydrochloride (liposomal)	Onivyde®	Onivyde® (CP)
1	Sevelamer carbonate	Renvela®	Renvela® (CP)
3	Cyclosporine (EU: ciclosporine)	Restasis®	Ikervis® (CP)
1	Iron sucrose	Venofer®	Venofer® (MRP/DCP)
6	Verteporfin	Visudyne®	Visudyne® (CP)
6	Propofol	Diprivan®	Diprivan®[b]
2	Estradiol hemihydrate	[EstrasorbTM (discontinued[c])]	–
4	Paliperidone palmitate	Invega sustenna®	Xeplion® (CP)
1	Lidocaine; prilocaine	Oraqix®	Fortacin® (CP)

[a] With reference to category numbers assigned in Table 1.
[b] Not listed in [10].
[c] ``Discontinued'' may denote an approved product never marketed, or discontinued from marketing, or that has had its approvals withdrawn for reasons other than safety or efficacy.

TABLE 3

Complexity of drugs and related policies

Drug	Biological source	Complex manufacturing	Regulatory approach to copies	Classification of copies	Interchangeable
Small molecule	No	No	Generic	Generic	Yes
NBCD	No	Yes	USA: generic + additional data EU: hybrid or generic	USA: generic EU: variable	USA: yes EU: variable
Biological	Yes	Yes	Biosimilar	Biosimilar	No

Abbreviation: NBCD, nonbiological complex drug.

owing to technological advances and regulatory alignment. On the regulatory side, the 'Deemed to be a License' provision of the Biologics Price Competition and Innovation Act (BPCIA) of 2009 extended the scope to include any protein (except chemically synthesized polypeptides). It provides that, from 23rd March 2020, 'an application for a biological product approved under section 505 of the 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 (nonsynthetic) 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 be closer to EU legislation.

LMWHs are also regulated differently in the EU, where they are considered biologics and their copies must be authorized following the biosimilar approach; in the USA they are considered to be nonbiologics. 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 enable better characterization of intermediates and products, and regulatory experience increases, clinical data might be no longer necessary. Indeed, in the last revision of the 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*, even though the US Public Health Service (PHS) Act (Section 351), as amended, states the conditions for a biological product to be interchangeable with the originator. The EMA leaves the decision about interchangeability to individual member states [17]. Automatic substitution, meaning a substitution at the dispensing level without 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, by contrast, 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 MA.

Automatic substitution at the dispensing level, when extended to complex drugs, biologics or not, makes traceability more difficult to deal with, and the prescribing physician could lose all the information about which medicinal product is being administered to the patient. Although this is generally accepted in the case of small-molecule generics, it might not be appropriate in the case of complex drugs, which are not unanimously considered to be interchangeable. In the USA, automatic substitution of NBCDs is generally permitted. In the EU, when complex drugs are biologics, as in the case of LMWHs, they are not considered interchangeable, whereas when they are nonbiologics they can 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), because the generic product bears the same labeling as the originator. In general, redesign and/or label modification, as a means 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 [19–21].

Case study: glatiramoids

The active substances called glatiramoids are a copolymeric mixture of L-alanine, L-glutamic acid, L-lysine and L-tyrosine, in a constant molar ratio [22]. GA, contained in the originator Copaxone®, is marketed as a colloidal suspension in pre-filled syringes for sub cutaneous (SC) injection (20 mg/ml and 40 mg/ml). GA is a heterogeneous mixture of not fully characterized synthetic polypeptides, with average molecular weight (MW) ranging from 5000 to 9000 Da (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 acid (AA) polypeptide (~7000 Da) will contain on average of eight glutamic acid, 26 alanine, six 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 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, however, because, as in the case of biologics, the active substance is difficult to characterize, and 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], active pharmaceutical ingredient (API) sameness can be established by showing equivalence between the originator and the generic product according to four criteria.

- Equivalence of fundamental reaction scheme, because it can be determined using publicly available information.
- 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), NMR spectra (1H and 13C 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].
- Equivalence of structural signatures for polymerization and depolymerization, such as initiation chemistry of the peptide chains, coupling between the various amino acid pairs during propagation and any cleavage preference of depolymerization.
- Equivalence of biological assay results. The FDA recommends the experimental autoimmune encephalomyelitis (EAE) assay as an animal model for multiple sclerosis (MS).

TABLE 4

Marketing authorisation (MA) holders and trade names of glatiramer acetate 20 mg/ml and 40 mg/ml marketed in the EU. Reference member state (RMS): The Netherlands [10]

Glatiramer acetate 20 mg/ml		
MA holder in RMS	**Trade name in RMS**	**Trade name in CMSs**
Actavis	Glatiramer acetate Actavis	Meglarat, Brabio®, Copemyl, Remurel
Synthon	Sclerthon	Glatoxone, Galtipex
Mylan	Glatsyn	Glatiramyl®, Glatiramer Mylan
Glatiramer acetate 40 mg/ml		
MA holder in RMS	**Trade name in RMS**	**Trade name in CMSs**
Alvogen	Remurel®	Remurel®
Synthon	Sclerthon, Marcyto	Perscleran, Galtipex
Mylan	Glatiramer acetate Mylan	Glatiramyl®, Copemyl, Clift, Glatiramer Mylan

Abbreviation: CMS, concerned member state.

The FDA does not recommend that any clinical trial be performed. In the USA, 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 were approved in 2016, under different brand names, with a decentralized procedure (Table 4). The MA has been granted through a hybrid application under Article 10(3) of Directive 2001/83/EC. 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 nonclinical and clinical data in support of similarity, next to quality data. As for the nonclinical aspects, data from an EAE mouse model were provided to demonstrate pharmacological comparability, along with two 28-day studies and one 90-day comparative toxicity study performed in rats [11]. The EMA, in its scientific advice to Synthon, required the conduct of a clinical trial [30]. Glatiramer Acetate Clinical Trial to assess Equivalence with Copaxone® (GATE) was a 9-month randomized clinical trial on 794 patients [31] with a 15-month open-label follow-up on 729 patients [32], performed to evaluate the efficacy, safety and tolerability of (i) prolonged generic glatiramer acetate treatment and (ii) switching from Copaxone® to generic GA 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, admittedly has some limitations [33]. The primary endpoint was 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 endpoint in pivotal MS trials [34]. Both drugs proved superior to placebo relative to the primary endpoint [31]. However, the annualized relapse rate (ARR) observed for Copaxone® was essentially the same as for the placebo [31], whereas in a previous study [33] Copaxone® was found to decrease the ARR substantially. The divergence between MRI activity and clinical activity is unexpected, because a previous meta-analysis [35] showed higher correlation.

Concluding remarks

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 NBCD copies. The current orientation of regulatory agencies in the USA 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 might be different in the two jurisdictions.

The case of GA is particularly indicative of this divergence. In the USA, copies of Copaxone® were approved by the FDA based on equivalence of (i) the fundamental reaction scheme, (ii) physicochemical properties, (iii) structural signatures for polymerization and depolymerization and (iv) biological assay results. Those copies are considered interchangeable. In the EU, regulatory authorities required an additional clinical study, based on EMA 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 biologics in the EU but not in the USA, are deemed to converge owing to advances in analytical methods, which enable 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, 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 could arise in the future. The biosimilar approach, by contrast, puts much more responsibility on

manufacturers/MAHs. The FDA is not oriented toward an approach based on similarity in the case of complex drugs, while EU regulatory agencies have followed a strategy similar to that of biosimilars in the case of glatiramer acetate. 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 NBCD 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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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