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Regulatory considerations for generic products of non-biological complex drugs

Regulatory considerations for generic products of non-biological complex drugs

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Abstract

The Non-Biological Complex Drug (NBCD) Working Group defines an NBCD as "a medicinal product, not being a biological medicine, where the active substance is not a homo-molecular structure, but consists of different (closely related and often nanoparticulate) structures that cannot be isolated and fully quantitated, characterized and/or described by physicochemical analytical means". There are concerns about the potential clinical differences between the follow-on versions and the originator products and within the individual follow-on versions. In the present study, we compare the regulatory requirements for developing generic products of NBCDs in the European Union (EU) and the United States (US). The NBCDs investigated included nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) injections, liposomal injections, glatiramer acetate injections, iron carbohydrate complexes, and sevelamer oral dosage forms. The demonstration of pharmaceutical comparability between the generic products and the reference products through comprehensive characterization is emphasized for all product categories investigated. However, the approval pathways and detailed requirements in terms of non-clinical and clinical aspects may differ. The general guidelines in combination with product-specific guidelines are considered effective in conveying regulatory considerations. While regulatory uncertainties still prevail, it is anticipated that through the pilot program established by the European Medicines Agency (EMA) and the FDA, harmonization of the regulatory requirements will be achieved, thereby facilitating the development of follow-on versions of NBCDs.

Keywords: Follow-on products, Generic drugs, Nanomedicine, Non-biological complex drugs

1. Introduction

A non-biological complex drug (NBCD) was defined by the NBCD Working Group as "a medicinal product, not being a biological medicine, where the active substance is not a homo-molecular structure, but consists of different (closely related and often nanoparticulate) structures that can't be isolated and fully quantitated, characterized and/or described by physicochemical analytical means" [1–5]. The NBCD Working Group, established in 2009, gathers experts from the academia, industries, and institutions to facilitate the discussion between stakeholders about NBCDs. Their ultimate mission is to facilitate the development of internationally harmonized, science-based approval and post-approval standards for NBCDs so as to ensure patient safety and benefit [4]. While there is no official definition for NBCDs in the European Union (EU) [5], the complex products recognized by the United States Food and Drug Administration (FDA) are products with complex active ingredients, complex formulations, complex routes of delivery, or complex dosage forms, as well as complex drug–device combination products [6]. Moreover, other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement are also included [6]. NBCDs, including many products containing nanomaterials, are highly dependent on the manufacturing processes for consistency in their compositions and properties. Their complicated and heterogeneous nature poses

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challenges in regulating NBCDs, especially with regards to their generic or follow-on versions [1–9]. As stated previously, concerns have been raised about the potential clinical differences between the follow-on versions and the originator products as well as those among the follow-on versions [3,10,11]. For example, the carbohydrate stabilizing the iron core of the iron complexes would affect the metabolic behavior of the complex and the interaction with the innate immune system [11]. A review of clinical and non-clinical studies in chronic heart failure patients demonstrated that the results obtained from one intravenous iron product should not be extrapolated to a different product without head-to-head clinical studies [11].

In the EU, the generic or follow-on versions of NBCDs may be approved through the centralized procedure (CP) or non-centralized procedures depending on the type and the indication of the products, which are related to the eligibility of applications for evaluation under the centralized procedure coordinated by the European Medicines Agency (EMA) [5,7]. A marketing authorization granted under the CP is valid for all EU Member States [7]. Non-centralized procedures include the purely national procedure (NP), the mutual recognition procedure (MRP), and the decentralized procedure (DCP) involving related national competent authorities [5,7]. Regarding the legal basis, although the procedure via Article 10(1) of Directive 2001/83/EC for generic applications was mostly utilized, Klein et al. [5] pointed out the increasing use of the hybrid pathway via Article 10(3), which may require additional pre-clinical tests and clinical trials to support the approval. Their findings revealed the rising concerns about the complexity of the follow-on versions of NBCDs which differentiated them from ordinary generics with greater regulatory uncertainties for applicants [5]. On the other hand, the generic versions of NBCDs were approved as generic products (abbreviated new drug applications, ANDAs) in the United States (US) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C 355(j)) [3,6]. Considering that additional requirements may be required for these products with complicated natures [3,12], the FDA encouraged the discussion between the FDA and ANDA applicants regarding complex products to facilitate the development process [6].

A list of 28 products considered as non-biological and complex by the FDA was published by the US Government Accountability Office (GAO) and further reviewed by the NBCD Working Group and the National Institutes of Health's Nanotechnology Characterization Lab [3,13]. A total of 24 products were recognized as NBCDs by all three parties [3]. Considering the importance in reducing regulatory uncertainties for facilitating the development of the generic products of NBCDs, the aim of the present study was to compare the EU and US regulatory considerations for the generic versions of the NBCDs recognized by all three parties as mentioned above through investigation of the publicly available assessment reports of the concerned regulatory authorities and/or the related guidance documents. It is hoped that the findings would shed light on the similarities and dissimilarities of these stringent regulatory authorities, the implementation of the related guidance documents in the approval process. It is further hoped that the findings will support the possibility of harmonization in the future.

2. Methods

The FDA database, "Drugs@FDA: FDA-Approved Drugs" (last accessed on May 20, 2022) was searched for the availability of generic products and their review reports for the 24 products recognized as NBCDs by the aforementioned three parties [3,14]. For those products or product categories with generic versions approved by the FDA or with available product-specific guidance documents [12], we searched for the guidelines from the websites of the EMA [15] and the availability of the public assessment reports (PARs) of the follow-on products approved through the CP, DCP, or MRP in the EU from the websites of the EMA and the Heads of Medicines Agencies (HMA) [16,17]. Further information for the aforementioned products was then searched from the websites of the European Commission (EC), the Medicines & Healthcare products Regulatory Agency (MHRA), and the national registers of authorized medicines (last accessed on May 20, 2022), if necessary [18–20]. If neither guidelines nor assessment reports for products were publicly available on the websites mentioned above, the products were excluded from the present study. Products containing low-molecular-weight heparins were excluded from the present study since they are currently considered as biological products in the EU [21]. Products approved through purely national procedures were not within the scope of the present study.

3. Results

3.1. Products analyzed in the present study

Among 24 products recognized as NBCDs by the aforementioned three parties, three products containing low-molecular-weight heparins were

excluded. Neither guidelines nor generic versions for the lipid complex form of amphotericin B or ferumoxides in the US were publicly available; therefore, these products were not included in the present study. Furthermore, neither guidelines nor generic versions were publicly available for the emulsion form of cyclosporine on the websites of the EMA or HMA. Thus, this product was also excluded, either. A total of 16 products (Table 1) were investigated in the present study.

3.2. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) injections

The traditional formulation of paclitaxel utilizes a derivative of castor oil to overcome the limited water solubility of paclitaxel, which necessitates steroid or antihistamine prophylaxis for hypersensitivity reactions. The novel formulation with nanoparticle albumin-bound paclitaxel (Abraxane) was approved in 2005 and 2008 by the FDA and the EMA, respectively [14,16]. This formulation not only eliminates the use of the toxic solvent but also has higher response rates and improved tolerability in patients with advanced metastatic breast cancer and advanced non-small cell lung cancer. Upon injection, the particles would dissolve into soluble albumin-paclitaxel complexes, and paclitaxel may bind to albumin or other molecules or exist in free forms [22]. Although there are no generic versions approved in the US, a draft product-specific guidance published by the USFDA [12] states that two studies including one *in vivo*, single-dose, two-way crossover study evaluating the area under the concentration–time curve (AUC) and maximum concentration (C_{max}) for unbound and total paclitaxel and one *in vitro* particle size distribution study are required for the demonstration of bioequivalence (BE). The test product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) and the sameness should be demonstrated with comprehensive *in vitro* characterization such as the characterization for particles, release properties, and the status of albumin. Three batches of both the test and reference products should be used with at least one test product manufactured by the commercial scale process. The pivotal BE study should also be conducted using the test product manufactured on the proposed commercial scale.

In the EU, a generic version (Pazenir) was approved in 2019 via Article 10(1) of Directive 2001/83/EC. According to the assessment report [16], the investigation of pharmaceutical comparability, including physicochemical characterization, *in vitro* dissociation, protein characterization, and the sameness and nature of bonding between paclitaxel and human serum albumin, was conducted. Upon the request by the EMA concerning the differences, extensive additional data demonstrated that the differences were not significant in comparison with the batch-to-batch variability. Further studies, such as integrity studies conducted for albumin and additional dissociation studies, were also performed for clarification. Considering that the nanoparticles would rapidly dissociate upon *in vivo* dilution and bind to endogenous albumin, in addition to the sameness demonstrated, the biowaiver request for not performing BE studies was justified. The non-clinical overview was primarily based on a scientific literature review. Although non-clinical studies, such as comparative pharmacokinetic studies and studies demonstrating the similarity of anti-tumor effects, were submitted, methodological weakness was identified. Overall BE was mainly based on *in vitro* comparative characterization. Product-specific guidelines are currently not available in the EU for *nab*-paclitaxel.

3.3. Liposomal injections

With many desirable properties, such as the ability to improve toxicity and distribution profiles, biocompatibility, and biodegradability, liposomes have become widely used vehicles for drug delivery [23]. However, only a handful of generic liposomal products are available due to the inherent complexity of the manufacture of liposome-based drug products. Among the eight liposomal products investigated in the present study, only two of them have generic products [14]. In the US, the first generic version of the liposomal product of doxorubicin hydrochloride was not available until 2013 after the shortage of the innovator product beginning in 2011 [24]. The current version of the draft guidance on doxorubicin hydrochloride (injectable, liposomal) revised in 2018 was first recommended in 2010 [12]. The test product should be Q1 and Q2 the same as the RLD except for differences in buffers, preservatives, and antioxidants demonstrated to have no impact on the safety/efficacy profile. Moreover, the generic version should be manufactured by an active liposome loading process with an ammonium sulfate gradient. Two BE studies, including one *in vivo* study with a single-dose, two-way crossover design assessing AUC and C_{max} for both free doxorubicin and liposome encapsulated doxorubicin and one *in vitro* study on liposome size distribution, are required. Pharmaceutical comparability information based on extensive physicochemical characterization studies, such as *in vitro*

Table 1. Products investigated in the present study.

Active substance	Trade name in the US [14]	Availability of generic versions in the US [14]	Availability of guidance documents published by the FDA [12,25]	Trade name of the product approved through the CP, DCP, or MRP in the EU [16–20]	Availability of generic versions approved through the CP, DCP, or MRP in the EU [16–20]	Availability of guidance documents published by the EMA [15]
nab-Paclitaxel	Abraxane	No	Yes	Abraxane (CP)	Yes	No
Amphotericin B (liposomal)	Ambisome	Yes	Yes	-[c]	No	Yes
Daunorubicin citrate (liposomal)	DaunoXome (discontinued)	No	Yes	DaunoXome (DCP/MRP)	No	Yes
Cytarabine (liposomal)	DepoCyt (discontinued)	No	No (product-specific); yes (general)	DepoCyte (CP) (withdrawn)	No	Yes
Morphine sulfate (liposomal)	DepoDur (discontinued)	No	No (product-specific); yes (general)	-[c]	No	Yes
Doxorubicin hydrochloride (liposomal)	Doxil	Yes	Yes	Caelyx pegylated liposomal (CP); Myocet liposomal (CP)	No	Yes
Bupivacaine (liposomal)	Exparel	No	Yes	Exparel liposomal (CP)	No	Yes
Vincristine sulfate (liposomal)	Marqibo (discontinued)	No	No (product-specific); yes (general)	-[c]	No	Yes
Irinotecan hydrochloride (liposomal)	Onivyde	No	Yes	Onivyde pegylated liposomal (CP)	No	Yes
Glatiramer acetate (injection)	Copaxone	Yes	Yes	Copaxone (DCP/MRP)	Yes	No
Iron dextran (injection)	Dexferrum (discontinued);[a,b] INFeD[a,b]	No	Yes	Cosmofer (DCP/MRP)	Yes	Yes
Ferumoxytol (injection)	Feraheme	Yes	Yes	Rienso (CP) (withdrawn)	No	Yes
Sodium ferric gluconate complex (injection)	Ferrlecit[a]	Yes	Yes	-[c]	No	Yes
Ferric carboxymaltose (injection)	Injectafer	No	Yes	Ferinject (DCP/MRP)	No	Yes
Ferric oxyhydroxide (iron sucrose) (injection)	Venofer[b]	No	Yes	Venofer (DCP/MRP)	Yes	Yes
Sevelamer carbonate[d]	Renvela	Yes	Yes	Renvela (CP)	Yes	No

Abbreviation: CP, centralized procedure; DCP, decentralized procedure; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; MRP, mutual recognition procedure; US, United States.

[a] The active substance is also called ferric oxyhydroxide.

[b] The trade name of other products (discontinued) listed in Drugs@FDA database but not included in reference [3] are iron dextran and Proferdex. The active substance is ferric oxyhydroxide.

[c] Not listed in the websites of the EMA and the Heads of Medicines Agencies (HMA).

[d] Although the product recognized as NBCDs by the three parties mentioned in the present study refers to Renvela which contains sevelamer carbonate and is available as oral tablet and powder for oral suspension dosage forms, generic products for both hydrochloride and carbonate forms are discussed in the present study.

leakage under multiple conditions and the characterization of the liposome, should be performed on at least three batches of both the test and reference products. In addition, at least one test product should be produced by the commercial scale process and be used in the *in vivo* BE study. Comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products should be conducted. According to the two publicly available review reports for the first and second generic versions approved by the FDA in 2013 and 2017, respectively [14], the product-specific guidance document was referenced in the second generic version. The study conducted for the second generic version was more similar to the current requirements in comparison to that of the first version. There is one generic version for the liposomal amphotericin B product. However, the review report is not publicly available. In addition to doxorubicin hydrochloride, product-specific guidance documents for developing generic versions of liposomal products containing amphotericin B, daunorubicin citrate, bupivacaine, or irinotecan hydrochloride are available [12]. Except for bupivacaine, for which only one pharmacokinetic BE study is recommended for the demonstration of BE, the requirements are similar to those stated for doxorubicin hydrochloride. According to the FDA, when a product-specific guidance document is not available, applicants should refer to another general guidance document for liposome drug products [25].

In the reflection paper for follow-on liposomal products published by the EMA [26], pharmaceutical comparability was also based on comprehensive characterization. For comparative pharmacokinetic studies, a validated bioanalytical method should be applied to quantify total, encapsulated and unencapsulated drug substances. Conventional pharmacokinetic metrics such as AUC and C_{max} are not considered sufficient for indicating the rate of release at the target sites, thereby highlighting the need for the evaluation of additional pharmacokinetic parameters, such as distribution and elimination, in addition to the rate and extent of release. For example, according to the product-specific guidance documents for liposomal amphotericin B and pegylated liposomal doxorubicin hydrochloride [27,28], the main pharmacokinetic variables consist of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, partial AUCs. Moreover, although the considerations are on a case-by-case basis, it is highly likely that non-clinical studies using *in vivo* models are needed. Moreover, whether additional clinical efficacy trials are needed would depend on the results of the aforementioned quality, non-clinical, and pharmacokinetic studies. No follow-on products for the liposomal products investigated in the present study were approved by the EMA or through the DCP/MRP.

3.4. Glatiramer acetate injections

Glatiramer acetate is a mixture of synthetic polypeptides containing L-alanine, L-lysine, L-glutamic acid, and L-tyrosine, with average molar ratios of 0.427, 0.338, 0.141, and 0.095, respectively [9,12]. The average molecular weight of the polypeptides lies within the range of 5000–9000 Da [14]. The complexity is mostly attributed to the complicated nature of the heterogeneous mixture of incompletely characterized synthetic polypeptides [3,9,12]. Although the mechanism of glatiramer acetate is not fully elucidated, it is thought to have an immunomodulatory effect indicated for treating patients with relapsing forms of multiple sclerosis [14].

Despite the inherent difficulty in demonstrating of pharmaceutical equivalence and BE with regards to generic versions, two follow-on products with two strengths for each product were approved by the FDA via the 505(j) pathway (Table S1 (https://www.jfda-online.com/cgi/editor.cgi?article=3441&window=additional_files&context=journal)). Merely a single review report for the generic version is currently available on the Drugs@FDA website. This review report for the first generic version approved in 2015 reveals the same principles in the assessment, as stated in the product-specific guidance document published in 2016 and revised in 2018 [12]. The guidance document states that a proposed generic product needs to demonstrate the sameness of the active pharmaceutical ingredient (API). The demonstration should include the following four aspects: (1) equivalence of the fundamental reaction scheme; (2) equivalence of physicochemical properties, including compositions; (3) equivalence of structural signatures for polymerization and depolymerization; and (4) equivalence of biological assay results. The side-by-side comparison should be performed with three batches of the API of the proposed product and three batches of the API from the RLD. In addition, the RLD product is for parenteral use. If the API sameness is shown and the proposed product is Q1 and Q2 the same in terms of active and inactive ingredients as the RLD product, the *in vivo* BE study may be waived.

On the other hand, in the EU, the follow-on products approved through the DCP/MRP obtained marketing authorization as "hybrid applications" via Article 10(3) except for those applied by the innovator company as "informed consent applications" via Article 10(c) (Table S2 (https://www.jfda-

online.com/cgi/editor.cgi?article=3441&window=additional_files&context=journal)) [17–20]. Although the product-specific guidance document for glatiramer is not available, the PARs [17–20] revealed that non-clinical studies and clinical studies were performed in addition to assessment for quality comparison. Extensive physicochemical and biological characterizations were conducted on multiple commercial scale batches of the drug substance. Non-clinical studies involved the use of an experimental autoimmune encephalitis (EAE) mouse model, rats, and the cell-based assay demonstrating gene expression data. A multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted to compare the efficacy, safety, and tolerability of the follow-on products and the reference product. Bridging studies and the rationale were provided for products with different unit doses.

3.5. Iron carbohydrate complexes

Products in this category include parenteral products containing iron dextran, ferumoxytol, sodium ferric gluconate complex, ferric carboxymaltose, or iron sucrose indicated for treatment of patients with iron deficiency (Table S3 and Table S4 (https://www.jfda-online.com/cgi/editor.cgi?article=3441&window=additional_files&context=journal)) [14,29]. In the US, another name of the active substance for products containing iron dextran, iron sucrose, or sodium ferric gluconate complex is ferric oxyhydroxide [14]. For iron dextran, no generic versions were approved in the US [14]. In the EU, the follow-on version approved through DCP/MRP with the legal basis mentioned on the HMA website was via Article 10(a) as a well-established use application [17–20]. No generic versions for products containing ferric carboxymaltose were approved by the FDA, EMA, or through the DCP/MRP [14,16–20]. For iron sucrose, the follow-on version, approved through DCP/MRP with the legal basis mentioned on the HMA website, was via Article 10(1) (&10(2)) as generic products in the EU [17–20]. No generic products are available in the US [14]. The generic versions of the product containing ferumoxytol or sodium ferric gluconate complex were approved after more than 11 or 12 years, respectively, via the 505(j) pathway [14]. In the EU, the first product containing ferumoxytol was withdrawn by the company in 2015 [16]. There is no product containing ferumoxytol or sodium ferric gluconate complex approved by the EMA or through the DCP/MRP [16–20].

Both the EMA and FDA published reflection papers [29] or product-specific guidance documents [12] for iron carbohydrate complexes (Table 2). Similar to the requirements for liposomal generic products, the FDA requires two studies, including one *in vivo* study and one *in vitro* study based on particle size distribution for the demonstration of BE. Moreover, quality comparability should be demonstrated using at least three batches of both test and reference products while the test product should be Q1 and Q2 the same as the RLD. In contrast, in addition to pharmaceutical comparability and BE studies, non-clinical studies focused on bio-distribution are required in the EU. Based on the concept of a "weight of evidence approach" for assessing data from quality, non-clinical, and human pharmacokinetic studies, findings of minor differences between two products would render the additional requirement of a therapeutic equivalence study necessary in order to address the concerns.

3.6. Sevelamer oral dosage forms

Sevelamer, a phosphate binder used for patients with hyperphosphatemia, is a polymeric drug substance intended for oral administration [12]. Without the possible effects of decreasing serum bicarbonate concentrations caused by sevelamer hydrochloride, sevelamer carbonate may be more suitable for patients at risk of metabolic acidosis [30]. Although the product recognized as an NBCD by the aforementioned three parties refers to Renvela which contains sevelamer carbonate and is available as oral tablet and powder for oral suspension dosage forms, a list of generic products for both hydrochloride and carbonate forms is displayed in Table S5 and Table S6 (https://www.jfda-online.com/cgi/editor.cgi?article=3441&window=additional_files&context=journal). In the US, the application procedures were based on the 505(j) pathway [14]. In the EU, most follow-on applications were approved through Article 10(3) procedure except for the Informed Consent marketing authorization applications, as well as duplicate applications with the reference made to the documentation approved for the reference product [16–20].

While the specific guidance document for sevelamer is not available in the EU, product-specific guidance documents are published by the FDA for generic drug development [12]. Emphasis is placed on the demonstration of API sameness through various characterization approaches, such as degree of crosslinking, degree of protonation, total

Table 2. Comparison of requirements for the application of follow-on versions of iron carbohydrate complex drugs between the European Medicines Agency (EMA) and the Food and Drug Administration (FDA).

Drug name (active substance)/ Product category	FDA [12]					EMA [29]
	Iron dextran; injectable; injection	Ferumoxytol; injectable; injection	Sodium ferric gluconate complex; injectable; injection	Ferric carboxymaltose; injectable; intravenous	Ferric oxyhydroxide; injectable; intravenous (previously titled "draft guidance for iron sucrose")	Intravenous iron-based nano-colloidal products
Version (date) of the guideline document	2016/10	2012/12	2013/6	2016/4	2021/9	2015/3
Quality aspect	The test product should be qualitatively (Q1) and quantitatively (Q2) the same as the RLD. Sameness in physicochemical properties needs to be established.					The qualitative and quantitative composition of the developed product should be identical or closely match the reference product. Pharmaceutical comparability between test and reference products should be established. Several different batches of the reference medicinal product should be used and the relative age of the different batches of reference products should also be considered.
Non-clinical aspect	Not mentioned					Non-clinical studies should be undertaken with test and reference products that have been characterized appropriately. A main distribution study including one or two genders with one to two dose levels and single administration showing comparability between test and reference products may be sufficient. Appropriate safety endpoints included in the design of the bio-distribution study may be sufficient if there are specific safety concerns.

In vivo study for the demonstration of bioequivalence	Single-dose, randomized, parallel, fasting				Single-dose, randomized; parallel or crossover design; a replicate crossover study may be an appropriate alternative to the parallel or nonreplicated crossover study.	Single-dose parallel or crossover design
Subjects	Male or female patients with iron deficiency anemia who are indicated for their initial treatment with parenteral iron dextran (who have not received parenteral iron supplementation in the past)	Healthy males and non-pregnant females, general population	Healthy males and females, general population	Adult patients with iron deficiency anemia, for whom oral supplementation alone was not adequate or is not appropriate, and/or patients with non-dialysis dependent chronic renal disease	Healthy males and females	Not mentioned
Analytes to measure	Total iron in serum; transferrin-bound iron in serum	Ferumoxytol-associated iron in plasma or serum; transferrin-bound iron in serum	Total iron in serum; transferrin-bound iron in serum		Option 1: Iron in the form of colloidal ferric oxyhydroxide in serum when a direct measurement of the colloidal form is achievable; option 2 (option 1 not possible): Measure each of the following: 1) Total iron in serum 2) Transferrin-bound iron in serum	Primary variables: AUCt and C_{max} of total- and transferrin-bound iron; baseline correction is recommended; other supportive endpoints
Basis for bioequivalence	Maximum value of the difference in concentration between total iron and transferrin-bound iron over all time points measured; difference in area under curve (AUC) between total iron and transferrin-bound iron	Ferumoxytol-associated iron in plasma or serum	Maximum value of the difference in concentration between total iron and transferrin-bound iron over all time points measured; difference in AUC between total iron and transferrin-bound iron	Total iron	Option 1: Iron in ferric oxyhydroxide colloid in serum; option 2: Maximum value of the difference in concentration between Total iron and transferrin-bound iron over all time points measured; and difference in AUC between total iron and transferrin-bound iron	If a replicate design is applied then acceptance ranges for C_{max} can be extended as described in the relevant guideline for bioequivalence. Otherwise the 90% confidence interval of the baseline corrected values should be in 80−125% range. The sampling period should be sufficiently long to demonstrate that the iron levels return to the previous baseline level.
In vitro testing for the demonstration of bioequivalence	Particle size distribution					Note: Particle size distribution is included as one of the parameters used for the demonstration of pharmaceutical comparabili

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Table 2. (continued)

Drug name (active substance)/ Product category	FDA [12]					EMA [29]
	Iron dextran; injectable; injection	Ferumoxytol; injectable; injection	Sodium ferric gluconate complex; injectable; injection	Ferric carboxymaltose; injectable; intravenous	Ferric oxyhydroxide; injectable; intravenous (previously titled "draft guidance for iron sucrose")	Intravenous iron-based nano-colloidal products
Samples	At least three batches of both test and reference listed drug (RLD) products; the three batches of the test product should be manufactured using three different lots of the drug substance. At least one of the three batches of the test product should be produced by the commercial scale process and used in the *in vivo* bioequivalence study.	At least three batches of both test and reference products			At least three batches of both test and reference products; at least one test batch should be produced by the commercial scale process.	Please refer to the quality aspect.
Parameters to measure	Harmonic intensity-weighted average particle diameter and polydispersity index (PDI)	D_{10}, D_{50}, D_{90}		Z-average size and PDI	Z-average size and PDI or D_{50} and SPAN as appropriate	Not mentioned
Basis for bioequivalence	Harmonic intensity-weighted average particle diameter and PDI using the population bioequivalence statistical approach	D_{50} and SPAN [i.e. $(D_{90}$-$D_{10})/D_{50}$] or PDI using the population bioequivalence statistical approach		Z-average size and PDI using the population bioequivalence statistical approach	Z-average and PDI or D_{50} and SPAN using the population bioequivalence statistical approach	Not mentioned
Efficacy and safety considerations/ studies	Not mentioned					Risk management plan should be developed. If the results of any of these studies, such as quality, non-clinical, and human pharmacokinetic studies, show minor differences between the two products, a therapeutic equivalence study might be necessary to address their impact on efficacy and safety.

titratable amine, particle size, elemental analysis, and swelling index. Moreover, recommended BE studies are demonstrated which consist of two *in vitro* studies evaluating the binding characteristics.

On the other hand, review reports are not publicly available on the FDA website, while some of the PARs could be retrieved for the follow-on versions approved in the EU [16–20]. According to the PAR, various methods were used for characterization, including nuclear magnetic resonance spectroscopy (NMR). Since sevelamer is not systemically absorbed, conventional BE studies were replaced by *in vitro* studies similar to those requested by the FDA. In addition, a pharmacodynamics (PD) study in patients was performed to evaluate the comparability between the follow-on versions and the reference product regarding safety and tolerability, based on adverse events and compliance, while the requirement for PD studies is not stated in the FDA draft guidance documents.

4. Discussion

Recognizing the unique complexity of NBCDs, the EU and the FDA incorporated additional requirements into their regulatory frameworks for the follow-on versions of NBCDs. However, the specific requirements may differ between the EU and the FDA, as seen from the NBCDs investigated in the present article. The requirements primarily differ regarding the necessity of non-clinical or clinical requirements. For example, for generic products for *nab*-paclitaxel, BE studies could be waived if the sameness is properly demonstrated through comprehensive *in vitro* physicochemical characterization and literature review for non-clinical aspects in the EU [16]. However, *in vivo* and *in vitro* BE studies are required in addition to pharmaceutical comparability studies in the US [12]. On the other hand, if the proposed product is Q1 and Q2 the same as the RLD product, the *in vivo* BE study may be waived by the FDA if the API sameness for glatiramer acetate is shown [12]. In the EU, non-clinical studies and clinical studies were submitted despite the fact that data demonstrating the API sameness were provided [17–20].

Klein et al. [31] proposed a determination approach for submitting a 505(j) or 505(b)(2) application based on the complexity of the API. "A 505(b)(2) application is an NDA (new drug application) submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use [32]." A 505(b)(2) application is considered similar to the hybrid application approved via Article 10(3) in the EU for which "the results of appropriate pre-clinical tests and clinical trials will be necessary where the strict definition of a 'generic medicinal product' is not met; where the bioavailability studies cannot be used to demonstrate BE; where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product [31,33]." If a complete characterization of the API is not possible, Klein et al. [31] suggested that the 505(b)(2) approval pathway should be utilized.

In view of the concept proposed by Klein et al. [31], the 505(b)(2) approval pathway would be more likely to be applied in the applications for follow-on versions of glatiramer acetate, iron carbohydrate complex, and sevelamer among the product categories investigated in the present study. Currently available generic versions in the US were approved via the 505(j) approval pathway [14]. As mentioned earlier, clinical studies were not required for generic applications of glatiramer acetate and sevelamer in the US, while the demonstration of API sameness was heavily stressed [12]. In contrast, in addition to the physicochemical characterizations, clinical studies were submitted for the hybrid applications of the follow-on products of glatiramer acetate and sevelamer in the EU [17–20]. For iron carbohydrate complex, *in vivo* bioequivalence studies and the sameness in physicochemical properties such as particle size distribution are essential requirements as described by the FDA [12]. In the EU, the reflection paper published by the EMA [29] exhibited the data requirements of non-clinical studies in addition to comparability in physicochemical properties and BE studies. Moreover, if there are remaining concerns, a clinical trial that lasts a duration of at least 3 months is recommended to address them.

In response to the need for harmonization between the stringent regulatory authorities for facilitation of developing NBCDs, a pilot program was jointly established by the EMA and FDA to provide parallel scientific advice to applicants of marketing authorization applications for hybrid products and abbreviated new drug applications for complex generic drug products. This pilot program starting from 2021 enables the early exchange of views between the two agencies and applicants and

may thus facilitate the inter-agency harmonization of regulatory requirements [34].

As seen from the aforementioned comparison, the overall concepts for regulating NBCDs were found to be similar to those for biosimilars based on a stepwise approach and a totality-of-the-evidence approach to address the inherent complexities of the products [35,36]. In the EU, guidelines describing overall regulatory considerations for similar biological medicinal products were published; these guidelines were accompanied by various product-specific biosimilar guidelines. For liposome drug products, a guidance document focused on liposome drug products was published by the FDA [25]. Moreover, product-specific guidance documents for generic drug development for a specific product, such as specific guidance on amphotericin B (liposomal injection), would further provide detailed requirements based on the fundamental concepts [12]. A similar approach is applied in the EU for liposomal products [15,26]. It is suggested that an approach consisting of an overall regulatory consideration for a specific type of NBCDs, accompanied by product-specific guidance documents for generic drug development, could be applied for all NBCDs since this is considered an effective method of communication between regulatory authorities and the stakeholders.

5. Conclusions

To develop generic products of inherently complex NBCDs, the importance of the comprehensive characterization for demonstrating pharmaceutical comparability between the generic products and the reference products is stressed by all the regulatory authorities in the EU and the US. However, detailed requirements, especially in terms of non-clinical and clinical aspects and the approval pathways, may differ. The combination of an overall guideline with a product-specific guidance document is considered effective in conveying regulatory considerations. Moreover, it is anticipated that through the pilot program established by the EMA and FDA, harmonization will be achieved, and this could largely mitigate the uncertainties in the drug development process and facilitate the development of the follow-on NBCD products.

Conflicts of interest

All authors declare no competing interests.

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