Equivalence of complex drug products: advances in and challenges for current regulatory frameworks

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Biotechnology and nanotechnology provide a growing number of innovator-driven complex drug products and their copy versions. Biologics exemplify one category of complex drugs, but there are also nonbiological complex drug products, including many nanomedicines, such as iron–carbohydrate complexes, drug-carrying liposomes or emulsions, and glatiramoids. In this white paper, which stems from a 1-day conference at the New York Academy of Sciences, we discuss regulatory frameworks in use worldwide (e.g., the U.S. Food and Drug Administration, the European Medicines Agency, the World Health Organization) to approve these complex drug products and their follow-on versions. One of the key questions remains how to assess equivalence of these complex products. We identify a number of points for which consensus was found among the stakeholders who were present: scientists from innovator and generic/follow-on companies, academia, and regulatory bodies from different parts of the world. A number of topics requiring follow-up were identified: (1) assessment of critical attributes to establish equivalence for follow-on versions, (2) the need to publish scientific findings in the public domain to further progress in the field, (3) the necessity to develop worldwide consensus regarding nomenclature and labeling of these complex products, and (4) regulatory actions when substandard complex drug products are identified.

Keywords: complex drug; biosimilar; pharmaceutical; nonbiological complex drugs (NBCDs); regulatory science; EMA; FDA; therapeutic equivalency; generics

Introduction: a complex landscape

The rise of biotechnology and nanotechnology has accelerated the development of complex drug products and their copy versions, and this growth is expected to increase significantly. 1 While regulatory guidance for authorization of generic versions of small molecule drugs is well established, guidance for complex drug products is still evolving. On November 9, 2016, experts from various backgrounds and parts of the world gathered at the New York Academy of Sciences to discuss the current regulatory frameworks, share experiences, and identify open issues. The outcome of these discussions and the identified outstanding challenges are reported here.

The complex drug landscape is visualized in Figure 1, which classifies products based on the challenge to assess pharmaceutical equivalence (PE) and bioequivalence (BE) of two drug products (i.e., the reference product and its generic version). According to this classification, complex drug products can be divided into two categories: (1) products with complex active ingredients and/or complex formulations for which both PE and BE are difficult—if
Figure 1. The complex drug landscape. Drug products are positioned on the basis of the challenge to assess pharmaceutical equivalence (PE) and bioequivalence (BE) of two drug products (i.e., the reference product and its generic version). Conventional low-molecular-weight drugs that can be fully characterized are shown in orange; demonstration of PE and BE is relatively simple. Biologics are shown in green; demonstration of PE and BE is slightly more difficult. Complex drugs are shown in blue (NBCDs) or white (other complex drugs). For the majority of NBCDs, both PE and BE are difficult to demonstrate, owing to the inability to synthesize homomolecular material, an unknown mode of action, and/or the difficulty to fully characterize the products. Albumin-bound nanoparticles and low-molecular-weight heparins are blue with a green outline (classification of these drugs varies across the globe).

not impossible—to demonstrate and (2) products with complex routes of delivery, dosage forms, or complex drug–device combinations, where (only) BE or PE is difficult to establish. The first category includes the majority of nonbiological complex drugs (NBCDs). Together with biologics and their similars, NBCDs will be the main topic discussed herein.

Biologics (known as biologicals in Europe and some other parts of the world) are products used for the prevention or treatment of diseases. They are generally derived from living material, such as cells or tissues, or produced using cellular organisms. Analogous to generic versions of small molecule drugs, copy versions of biologics that have successfully undergone a rigorous comparability program or more active substances made by or derived from a biological source. Some of them may be already present in the human body and examples include proteins such as insulin, growth hormone, and erythropoietins. The active substances of biological medicines are larger and more complex than those of nonbiological medicines. Only living organisms are able to reproduce such complexity. Their complexity as well as the way they are produced may result in a degree of variability in molecules of the same active substance, particularly in different batches of the medicine.” Finally, the World Health Organization (WHO) refers to vaccines and biotherapeutic products; the latter are products of biotechnology prepared using genetically engineered bacteria, yeast, fungi, cells, or even whole animals and plants.
are referred to as “biosimilars;” they are highly similar to another biologic drug in terms of quality, biological activity, safety, and efficacy, and many have already been approved by regulatory authorities.

NBCDs are fully synthetic materials: they are medicinal products but not biological medicines, 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 physicochemical analytical means. Like biologics, the composition, quality, and in vivo performance of NBCDs are highly dependent on the manufacturing processes of the active ingredient, as well as (in most cases) the formulation. Although the term NBCDs is not officially recognized by the European Medicines Agency (EMA) or the U.S. Food and Drug Administration (FDA), it is gaining traction in the scientific community. Copy versions have been referred to as “follow-on products” (e.g., by the EMA; the FDA includes them in the category of “complex generics”). Here, we first discuss the regulatory frameworks currently in place to evaluate equivalence of biosimilars and NBCD follow-ons, followed by the corresponding quality, safety, and efficacy considerations. We also address the need for regulatory alignment and outline the importance of defining those product characteristics that ensure safety and efficacy in humans (critical quality attributes). We conclude with a section on pharmacovigilance and a discussion of the points of consensus and remaining unresolved challenges.

Regulatory practice

The United States of America

The FDA regulates drugs on the basis of two different statutes: the Food, Drug & Cosmetics Act for low-molecular-weight drugs and generics and the Public Health Service Act for biologics and biosimilars (Fig. 2A). The FDA has generated guidance documents for the development of biosimilars in the United States, and, as of the end of 2016, four biosimilar products were approved for the U.S. market.

The FDA did not adopt the term “NBCD” but uses the term “complex product” instead, which generally includes products with complex active ingredients, complex formulations, complex routes of delivery, complex dosage forms, complex drug–device combination products, or other products where complexity or uncertainty concerning the approval pathway—or a possible alternative approach—would benefit from early scientific engagement. These complex products, not being of biological origin, automatically fall under the Food, Drug & Cosmetics Act. According to this act, novel products are evaluated through the new drug application (NDA) regulatory pathway, while generics or copies are authorized through the abbreviated new drug application (ANDA) regulatory pathway.

A side-by-side comparison of the NDA and ANDA pathways shows that animal studies, clinical studies, and bioavailability studies required by the NDA pathway are replaced by BE testing in the ANDA pathway. Generic products receive marketing authorization once therapeutic equivalence (TE) to the originator product is established on the basis of demonstration of PE and BE. The vast majority of generics are homomolecular, low-molecular-weight drugs that can be fully characterized. Consequently, it is relatively straightforward to demonstrate TE for such drugs. For complex products for which the ANDA pathway applies, however, there are scientific challenges associated with the demonstration of PE and BE, including the inability to synthesize homomolecular material, an unknown mode of action, and/or the difficulty to fully characterize the products. This requires a stepwise comparison of the reference drug and the complex drug generic, and the FDA generally adopts a weight-of-evidence approach.

The amount of evidence that is required for the authorization of a certain complex drug product is evaluated by the FDA through a case-by-case approach. In support of this methodology, the FDA encourages research via the Generic Drug User Free Amendments (GDUFA) regulatory science funding. Enoxaparin sodium (low-molecular-weight heparin (LMWH) and glatiramer acetate (GA) are two complex drugs that were approved by the FDA under the ANDA pathway. When looking, for example, at the draft guidance for enoxaparin sodium, an LMWH, and GA, four common themes can be identified (Table 1). Per the FDA, equivalence across these four themes will ensure safety and efficacy in humans without the need for additional clinical trials. Interestingly, the fourth theme, confirmatory (biological) assays, shows an important difference in the approach to equivalence assessment.
between enoxaparin sodium and GA copies: while the FDA requires demonstration of statistical equivalence of pharmacodynamic parameters in humans for enoxaparin sodium, the experimental autoimmune encephalomyelitis (EAE) mouse model is recommended for GA; no test in humans is requested.

**Europe**

The EU law distinguishes full dossiers and so-called “abridged applications” regulated under Article 8 and Article 10 (Fig. 2B) of Directive 2001/83/EC,\(^\text{12}\) as amended. Article 10 has three possibilities for abridged applications: 10(1) for generic applications, 10(3) for hybrid applications, and 10(4) for biosimilar applications. Authorization through 10(1) requires the originator-reference product and the generic drug to be the “same,” while 10(4), which applies only to biological substances, allows for small differences between the reference product and the biosimilar if those differences are not meaningful in terms of quality, safety, or efficacy.\(^\text{13}\) Of note, abridged applications can be accepted for consideration under the Centralized Procedure (through the EMA) or national procedures, including the Decentralized Procedure and the Mutual Recognition Procedure, depending on the nature of the product and the authorization procedure of the originator.\(^\text{14,15}\)

Up to November 2016, 23 biosimilar products have been authorized in the EU (14 distinct substances developed as biosimilars to eight reference products) through the 10(4) pathway. Clinical use of biosimilars by the medical community varies per product and country; it ranges from 0% to 100% replacement of the originator product by the biosimilar. Typically, prescription of a biosimilar is less controversial when starting a new biologic therapy, but there are still questions in the medical community regarding interchangeability and

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**Figure 2.** Schematic representation of the (A) FDA and (B) EMA approval pathways.
substitution, which is regulated at the national level. An interesting example in this respect is the NOR-SWITCH study on Celltrion’s infliximab biosimilar Remsima, which was designed to reassure physicians that patients on stable treatment with Remicade (the originator product) may be successfully switched to a biosimilar version of this drug. The results of the 2-year phase IV study, funded by the Norwegian Medicines Agency, showed that approximately half of the patients were switched to Remsima, and that efficacy and safety were comparable for this group and for those who remained on the originator product.\textsuperscript{16,17}

According to a recent publication by Ehmann and Pita,\textsuperscript{4} NBCD follow-on products should either fall under the 10(1) or the 10(3) pathway, depending on the extent of data needed to support BE. They argue that the 10(1) pathway will suffice if BE can be demonstrated by appropriate bioavailability studies. If BE cannot be demonstrated through bioavailability studies, the results of preclinical tests or clinical tests should be provided as per the hybrid 10(3) pathway to demonstrate that the efficacy and safety of the follow-on are sufficiently similar to the efficacy and safety of the reference product, assuming that the (physico)chemical equivalence of the two active substances has been established.

The extent of \textit{in vivo} studies that may be necessary to demonstrate BE is considered on a case-by-case basis. Like the FDA, the EMA considers the “totality of evidence” when assessing the benefit–risk ratio of a NBCD follow-on product undergoing a marketing authorization review.\textsuperscript{4} In order to define appropriate quality standards, the European Directorate for the Quality of Medicines & Healthcare (EDQM) has established a working party on nonbiological complexes to elaborate and revise monographs on such products on request by National Regulatory Authorities to the European Pharmacopoeia Commission.\textsuperscript{18}

**Safety, efficacy, and quality considerations for complex drug follow-on products**

Several products depicted in Figure 1 illustrate the challenges associated with establishing PE and BE for complex drug products. An interesting case involves cyclosporine ophthalmic emulsions (marketed as Restasis by Allergan) used to increase tear production in patients suffering from chronic eye disease. These emulsions contain an oil phase, an aqueous phase, and interfaces populated by surfactants and other stabilizing polymers; their characteristics fully depend on robust manufacturing processes. In 2013, the FDA published a draft guidance on cyclosporine, requesting Q1 (qualitative) and Q2 (quantitative), as well as some simple physicochemical parameter testing to demonstrate equivalence between an originator and a follow-on product. In response to the guidance document, Allergan showed, in some \textit{in vivo} studies, that emulsions could be developed that passed the criteria of the original guidance but that behaved differently when additional physicochemical parameters (not included in the original guidance document) were tested.\textsuperscript{19} In 2016, the FDA revised the draft guidance and further specified which product properties need to be characterized.\textsuperscript{20}

Another case is Copaxone (whose active ingredient is GA), an immunomodulatory drug used to treat relapsing forms of multiple sclerosis. GA is a heterogeneous mixture of potentially millions of distinct polypeptides, each containing up to
300 amino acids, with higher-order (secondary) structural elements. The exact (physico)chemical structures cannot be fully characterized. Copaxone, the originator product, is marketed by Teva Pharmaceuticals. Recently, the FDA approved Glatopa, a generic version of Copaxone developed by Momenta Pharmaceuticals. Decades of research and clinical use have shown that Copaxone is safe and effective, while the active moiety or moieties, as well as the exact mechanism of action, remain to be identified. The discussion regarding the regulatory requirements for generic/follow-on versions of Copaxone led to many publications with clearly different positions taken by the originator, follow-on manufacturer, researchers, and regulatory agencies in the United States and Europe. As input for the scientific discussions, both the originator and follow-on manufacturer published—besides biological and physicochemical analyses—gene expression profiles to substantiate their arguments regarding similarity or lack thereof. The FDA decided to approve Glatopa using four criteria deemed by the FDA to be sufficient to establish TE without requesting a clinical study (Table 1). The discussion on the final text of the FDA draft guidance document is ongoing.

In Europe, in contrast with the FDA approach, a follow-on version of Copaxone (manufactured by Synthion) has been approved through the decentralized authorization procedure, in accordance with the requirements of Article 10(3). Interestingly, although GA is not a biological medicinal product as such, Synthion followed a strategy similar to the dossier requirements of biosimilar applications and has provided a full Chemistry, Manufacturing, and Control (CMC) package, nonclinical studies, and the results of a comparative abridged clinical trial in subjects with relapsing–remitting multiple sclerosis. The Public Assessment Report states that, during the application, an interested party argued that the appropriate legal pathway would be Article 8(3) instead of 10(3) (Fig. 2B), because GA comprises a polypeptide mixture of which the specific sequences cannot be deciphered with current technologies as the active moiety (or moieties) are unidentifiable. It was argued that, as a consequence, it cannot be established that the active substances of Copaxone and the follow-on product are the same, which is a requirement for extrapolation of (non)clinical data under the abridged procedures. However, the regulatory authorities concluded that, although a generic application under Article 10(1) would not be acceptable, Article 10(3) is an appropriate legal basis for GA follow-ons. Of note, the U.S. Pharmacopoeia has recently established an expert panel tasked with the development of a monograph for GA; the EDQM is also currently considering doing so.

A third class of complex drugs, for which introducing follow-on versions is challenging, are the iron–carbohydrate complexes, prescribed worldwide for patients with iron deficiency or iron-deficiency anemia. They are nanometer-range particles consisting of a polynuclear Fe(III)-oxyhydroxide core surrounded by stabilizing carbohydrate structures. They interact with cells of the innate immune system for uptake and release of iron into the physiological iron metabolic pathways. In the past decade, various iron–sucrose similar (ISS) preparations have been authorized in Asian and European countries (through the decentralized or mutual recognition procedure) based on claimed TE to the originator (Venofer). However, clinical investigations and animal studies have since shown nonequivalence in efficacy and safety of these ISSs. In the United States, ISS products are not marketed. However, the FDA has approved a generic version of sodium ferric gluconate in sucrose injection (2011).

The examples presented above underline the challenges associated with regulatory approval of NBCD follow-on products. Many innovative and follow-on (similar) complex drug products are currently in development and will be submitted for approval in the next decade. It is obvious that, as a science-driven community of experts, we need to critically evaluate whether our regulatory framework is fit for its purpose.

The need for regulatory alignment

Efforts to align regulatory processes for complex drug follow-ons can decrease the costs of development and unnecessary repetition of clinical trials and lead to improved access to high-quality, affordable products for the global community. Globally, the WHO has taken the lead, and guidelines on evaluation of similar biotherapeutic products were published in 2009. These guidelines require a stepwise approach in the development process moving from characterization and quality comparisons of CMC aspects, via nonclinical studies, to clinical studies including a head-to-head
comparison of the originator and the biosimilar product. The WHO has not (yet) taken up the challenge to develop a global regulatory framework for NBCD follow-on products.

An illustrative case of different decisions taken for the same NBCD product is the evaluation of follow-on versions of Doxil/Caelyx (doxorubicin HCl liposome injection). Doxil and Caelyx are identical products but are marketed under different names by Johnson & Johnson in the United States and Europe, respectively. Owing to a shortage of Doxil, the FDA decided in February 2012 to temporarily allow the import of Sun Pharma's Lipodox, which had not been approved in the United States. In February 2013, the FDA granted approval to another doxorubicin HCl liposome injection product by Sun Pharma, which was made the reference listed drug. Once sufficient supplies of this product are available, the FDA expects to stop the temporary import of the unauthorized Lipodox. In Europe, the EMA assessed and rejected Sun's doxorubicin HCl liposome injection under Article 10(3) (through the centralized procedure) as a follow-on version of Caelyx. Consequently, industries seeking to develop follow-on versions of Doxil/Caelyx are now required to undertake two separate comparative BE trials, using Sun's doxorubicin HCl liposome injection in the United States and Caelyx in Europe. In addition, the FDA and the EMA request different batteries of studies to demonstrate BE.

Regulatory differences between the FDA and the EMA still exist for LMWHs, though a convergence in requirements recently occurred. These drug products are considered biologicals in Europe, since they originate from a biological source, and, consequently, follow-on versions are evaluated under Article 10(4) for biosimilars. On the basis of the rapid advances in analytical sciences and the recent experience with applications for biosimilar enoxaparin in the EU, the original product-specific guideline was recently revised substantially, and a clinical efficacy and safety trial is no longer considered mandatory; assessment of PD equivalence could suffice. In the United States, follow-on versions of LMWHs are considered generics and may be evaluated through the ANDA pathway; consequently, the FDA only recommends a comparative PD trial, but the texts of the EMA guideline and FDA guidance still differ. Such regulatory differences complicate requests for approval, and regulatory alignment will benefit all stakeholders.

Defining the critical attributes

In addition to regulatory guidance alignment, it is of critical importance to define and assess the critical attributes—those product characteristics that essentially ensure similar product efficacy and safety in humans.

To understand which product characteristics make up this set of critical attributes, physicochemical characterization, as well as the availability of appropriate and validated in vitro and in vivo models, is needed. Orthogonal testing (i.e., using different techniques to interrogate various physicochemical properties of a complex drug providing different measures of its characteristics) is the leading strategy. In some cases, defining the critical attributes is not possible with the current state of knowledge. However, novel techniques for evaluating complex drug similarity are becoming available at a rapid pace. For example, advanced methods recently developed by the Nanotechnology Characterization Laboratory may accelerate the understanding of which parameters are part of the critical attributes and thereby potentially speed up development of follow-on versions of nanoparticle-based products.

Looking beyond physicochemical characterization, nanomedicine pharmacokinetics pose yet another challenge for assessing BE. The dissociation kinetics of a drug from its carrier in vivo is an aspect that can critically influence the clinical performance of a product. Therefore, it is important to characterize the nonencapsulated (free) and encapsulated drug fractions. Indeed, the FDA and the EMA both request the assessment of free and liposome-associated drug when monitoring the pharmacokinetic profile of liposomal doxorubicin products.

For another liposomal drug product, the liposome-encapsulated cytarabine:daunorubicin (at a 5:1 molar ratio) drug product Vyxeos, critical attributes and associated manufacturing controls were identified early in development by in vitro and in vivo testing. In addition to analysis of physicochemical properties of the carrier and the encapsulated drugs, a biophysical characterization profile was established. Because of careful design and control of the critical attributes, Vyxeos exhibited predictable pharmacokinetics in the clinic.
based on the outcome of preclinical models. This complex drug product is currently in the process of obtaining regulatory approval.

**Pharmacovigilance**

Another important point to consider is the use of biologics and NBCD products in practice. Lively discussions are still ongoing on how to deal with pharmacovigilance of biosimilars or NBCD products currently available in clinical practice.\(^{46,47}\) Analyses have been performed in Europe and in the United States on reporting of adverse events, concluding that current pharmacovigilance frameworks do not allow for proper assignment of adverse effects to specific products (originator or generic/follow-on).\(^{33}\) Especially when there is no preapproval clinical data available, it may take years before one can perform a comprehensive analysis on the TE of the products. This also speaks to another challenge that is especially relevant for medicines with immunogenic potential: do medical practitioners and other health care professionals appreciate the complexity of the products? For biologics, this may be the case, considering the (heated) discussions and position papers released by professional medical bodies. This may not be the case for NBCD products. Early analyses in Europe show that many healthcare professionals are unaware of the intricacies of the structures of NBCD products and their clinical consequences.\(^{48}\) This lack of awareness may lead to an inappropriate substitution practice with products that are not therapeutically equivalent, further complicating safe and effective therapy, though thorough and comprehensive review by regulatory authorities may mitigate those concerns.

**Conclusions and unresolved challenges**

As a global scientific community, we generally recognize the challenges in developing and regulating approval of biosimilars and NBCD follow-on versions and bringing them to patients. The meeting at the New York Academy of Sciences on November 9, 2016 revealed important advances: all stakeholders agreed that complex drugs and their follow-ons should be evaluated with great care and that it is an absolute necessity to define the critical attributes in order to ensure safety and efficacy. Although progress has been made in defining common ground, it is important to continue the discussions, especially since increasing numbers of complex products are under development,\(^{1}\) and the accessibility to generic, biosimilar, and/or follow-on versions has shown to play an important role in lowering the overall expenditure in health care.\(^{49}\) In order to guarantee the provision of high-quality, safe, and effective biosimilar and NBCD follow-on products to patients in a timely fashion, there are a number of open issues that we, as a scientific community, have to address. We list the outstanding challenges here and hope that they may lead to actions to resolve them.

**Critical attributes for assessment of therapeutic equivalence of complex drug follow-on versions**

What are the critical attributes that are responsible for clinical performance of biologics and NBCD products? Are clinical trials required if the critical attributes are unknown? Is a global approach feasible (draft the same guidance documents throughout the world with the WHO in the driver seat)?

**How do we provide the science base for assessing critical attributes?**

This report brings together several concerns regarding the science base of the current decision-making processes. Scientists in academia, industry (both the innovators and the generic/follow-on companies), and regulatory bodies should be encouraged to perform research on outstanding questions and to publish their finding in the public domain. It is crucial to strengthen our knowledge base. The GDUFA Regulatory Science Research Program is an example of an FDA-driven initiative in that direction.

**Nomenclature and labeling**

Differences in terminology still exist; they even grow. For example, the terms “complex drug generic” and “biosimilar” are used for LMWH follow-on products by the FDA and EMA, respectively, because they are considered chemical drugs under one jurisdiction (FDA) and biologicals/biotherapeutics under another (EMA). A second example is the difference in the definition of the term “biologic(al)” by different organizations (the WHO, FDA, and EMA).\(^a\) Moreover, there is no worldwide consensus regarding the labeling of biologics and biosimilars: while the voluntary WHO biologic qualifier concept\(^{50}\) and the FDA name guidance proposals follow the same logic, the EMA adopted a different strategy.
Another unresolved issue is the meaning of the terms “interchangeability,” “substitution,” and “switching” in relation to the prescription and dispensing of biosimilars and NBCD products. The interpretation depends on the jurisdiction. Some bar interchanging, substitution, and switching altogether, others assume that approvability is synonymous with switching, and others pursue various middle-ground options on a case-by-case basis.

Substandard follow-on products
The number of identified substandard but approved follow-on complex drug products is growing within Europe (NBCD products) and outside Europe (NBCD products and biologics). This calls for action: should literature reports of substandard complex drug products (from both originator and follow-on manufactures) be investigated as part of regulatory agency and sponsor pharmacovigilance?

Final comments
The lively discussions on equivalence of complex drug products during international meetings and in scientific publications indicate that the outstanding challenges addressed above continue to be a topic of debate. Although this community consists of stakeholders with often different, either complementary or conflicting interests, the most important stakeholder—the patient—should always be our top priority. It is in our hands to bring high-quality, safe, effective, and affordable medicines to patients in a timely and efficient manner. A critical assessment of how we currently work with in the existing frameworks and whether these provide us with the highest chances of bringing those medicines to patients requires this community to critically reflect on its activities. Science-based discussions, joint definition of the next steps, and reflection on our activities will tell us whether we are moving in the right direction and whether our regulatory frameworks reflect the best science, are fit for purpose, and are ready for the future. Initiatives for NBCD products similar to what the WHO has done for similar biotherapeutics and the recently requested study by the U.S. Governmental Accountability Office may aid our efforts in resolving outstanding issues.

Acknowledgments
S.N. thanks Chetan Pujara for contributing knowledge on ocular emulsions. The opinions expressed in this article are those of the authors and not of any regulatory, industry, or medical organization they may be affiliated with, including the EMA and the FDA.

Competing interests
D.J.A.C. is a member of the steering committee of the Non-Biological Complex Drugs Working Group, an initiative hosted by Lygature. B.F. and S.M. are employees of Vifor Pharmaceuticals, Ltd. G.B. received funding for a research project from Vifor Pharmaceuticals, Ltd. and has consulted for Teva Pharmaceuticals. S.N. is an employee of Allergan Plc. V.W. is an employee of Teva Pharmaceuticals. J.S.B.d.V. and L.H. are employed by Lygature, an independent Netherlands-based not-for-profit organization facilitating the NBCD Working Group. The NBCD Working Group consists of experts from industry, academia, and knowledge institutes and is currently supported by Allergan Plc, Vifor Pharma, and Teva Pharmaceuticals.

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