

Non-biological complex drugs (NBCDs) and their follow-on versions: time for an editorial section

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This paper discusses the group of non-biological complex drug (NBCD) products and presents the reasons why NBCDs should be assigned a special position in our arsenal of medicines as well as why from now on a special section will be devoted to report on these NBCD products in the *GaBI Journal*.

Keywords: Glatiramoids, iron-carbohydrate complexes, liposomes, nanomedicines, Non-Biological Complex Drug (NBCD) products, therapeutic equivalence

Introduction

The concept of non-biological complex drug (NBCD) products has been presented and discussed on several occasions in the *GaBI Journal* [1-4]. The growing interest in this topic in academic, industrial and regulatory circles led to the establishment of an Editorial Section on Non-Biological Complex Drugs in both the *GaBI Journal* and *GaBI Online* starting in the third quarter of 2015.

In 2011, the first publication on NBCDs appeared [5] as a result of a workshop held in Leiden, The Netherlands, in 2009. For the first time this class of drug products was identified and recognized. These products are more complex than small, low molecular drugs and as complex or even more complex than biologicals; sharing many of the characteristics of the latter category but not being derived from living sources. As a consequence, the authors argued that for the equivalence testing of NBCD follow-on products a regulatory pathway should be developed that was similar to the pathways developed by the European Medicines Agency (EMA) and later the US Food and Drug Administration (FDA) for approving

biosimilars. This proposal was backed up by evidence provided by a (still growing) number of published studies on NBCD follow-on versions that were authorized using a 'standard' but inadequate generic assessment protocol.

A working group hosted by the Dutch Top Institute (TI) Pharma in Leiden was set up to raise awareness of the challenges NBCD products present worldwide, to stimulate the publication of scientific reports and discussions and to provide a rigorous, science-based, regulatory policy for NBCD products [6]. These efforts led to a number of publications and a book exclusively dedicated to the NBCD concept and its regulation. These publications provide a definition for NBCD products, discuss different classes of NBCDs, propose an overarching regulatory philosophy for evaluating NBCD follow-on versions and, finally, outline what issues are still unresolved [7-9].

This paper to the *GaBI Journal* further explains:

- Definition: how NBCD products are defined

- Present product 'families' and beyond: which NBCD product families are identified today and how this group may expand in the coming years
- The regulatory landscape: which regulatory frameworks are in place through EMA and FDA
- Performance of NBCD products and follow-on versions: evidence in the public domain, i.e. what information is accessible in the public domain regarding the performance of NBCD products and their follow-on versions, including some reflections on the nanoparticulate nature of many NBCDs
- The future: *Quo Vadis?*

Definition

A definition of NBCD products that was published earlier by the NBCD working group reads: 'A Non-Biological Complex Drug is 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 state-of-the-art (physico)chemical analytical means and where the clinical meaning of the observed differences is not known. The composition, quality and *in vivo* performance of NBCDs are highly dependent on manufacturing processes of both the active ingredient as well as in most cases the formulation' [7].

Present product 'families' and beyond

At present the following NBCD product groups or 'families' have been identified and discussed in the literature: liposomes, polymeric micelles, glatiramoids, iron-carbohydrate complexes, albumin-anticancer drug nanoparticles and nanocrystals. The rapidly growing group of nanomedicines will add many NBCDs to this list [9-10]. Interestingly, there are also medicinal products such as the low molecular weight heparins (LMWHs) showing similar complexity but falling under different regulatory policies, i.e. by EMA LMWHs are seen as biologicals and by FDA as non-biologicals.

Over the last few years a number of studies on these NBCD product families have been published. This list is growing and expanding beyond only parenteral drugs. Recently, the present science base,

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including the: (1) chemistry and structure; (2) manufacturing; (3) (physico)chemical characterization; (4) pharmacology; and (5) regulatory status, of these product groups was reviewed in a book [9]. The availability of these data in the public domain should contribute to science-based discussions and could serve as a model to be followed for consideration of other NBCD product families. In addition, questions regarding interchangeability and substitutability of NBCD follow-on versions have important implications for the handling of such medicinal products by healthcare professionals. Requests are being made by these healthcare professionals for education on the topic of NBCDs and for further, tailor-made, reliable information for patients.

Other candidate NBCD product families that are waiting to be identified include emulsions (parenteral or ocular), dry powder inhalers and oral bioactive polymers such as complex phosphate binders.

The regulatory landscape

In earlier publications in *GaBI Online* the differences between the characteristics of small, low molecular weight molecules and biologicals were listed, see Table 1 [11]. If the items in the ‘biological drugs’ column (*in italics*) that relate to the biological source of the product and immunogenicity are removed, what remains demonstrates that there is a striking resemblance between the characteristics of biologicals and NBCD products.

Because of this similarity in product characteristics, the NBCD Working Group has proposed on several occasions that regulators should follow the same regulatory pathway for NBCD follow-on products as for biosimilars. This proposal is schematically shown in Figure 1 where ‘Totality of evidence’ is the key phrase when assessing therapeutic equivalence of NBCD innovator and follow-on products.

Neither FDA nor EMA uses special NBCD regulatory schemes. These agencies use existing pathways for the introduction of innovative and follow-on NBCD products. FDA uses the 505(b)(1)/505(b)(2) and 505(j) pathways for innovator products and follow-on versions, respectively. However, both FDA and EMA are paying increasing attention to regulatory issues related to NBCD families [12-13].

Generally speaking, there are two clearly distinct regulatory documents for these NBCD product families. On the one hand, FDA and/or EMA published ‘draft guidance’ and/or ‘reflection papers’ on *new* products such as liposomes [14], polymeric micelles [15], and surface coatings [16]. On the other hand, both agencies issued documents on the development of *follow-on* versions of NBCD products such as EMA documents on iron-based nano-colloidal products [17-19] and on existing products [20], and FDA on iron complexes [21], ciclosporin emulsions [22] and on liposome follow-on products [23-24]. Interestingly, FDA has awarded

funding to characterize and clinically compare originator and follow-on versions after approving these products [25–26]. It is clear that the present arsenal of regulatory documents from these agencies will be expanded in the years to come. Hopefully, it is not too late to reach global agreement through the World Health Organization (WHO) or perhaps the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) initiatives. On the pharmacopoeial side, interest is growing in dealing with NBCD families. For example, a European Directorate for the Quality of Medicines and HealthCare (EDQM) working group is developing a monograph on ‘iron sucrose concentrated solution’ as an example for non-biological complexes and the United States Pharmacopeia (USP) is currently evaluating similar actions [27]. The British Pharmacopoeia (BP) has published a new monograph on iron sucrose injections, which is basically in line with the USP existing monograph.

One interesting feature of the European legal landscape is that certain NBCD product families are not approved through the centralized procedure (EMA). Instead, approval follows either the purely national procedures or the mutual recognition procedure under the aegis of national competent authorities. This is true for iron sucrose products and for oral bioactive polymer phosphate binders [28]. Considering the complexity of these

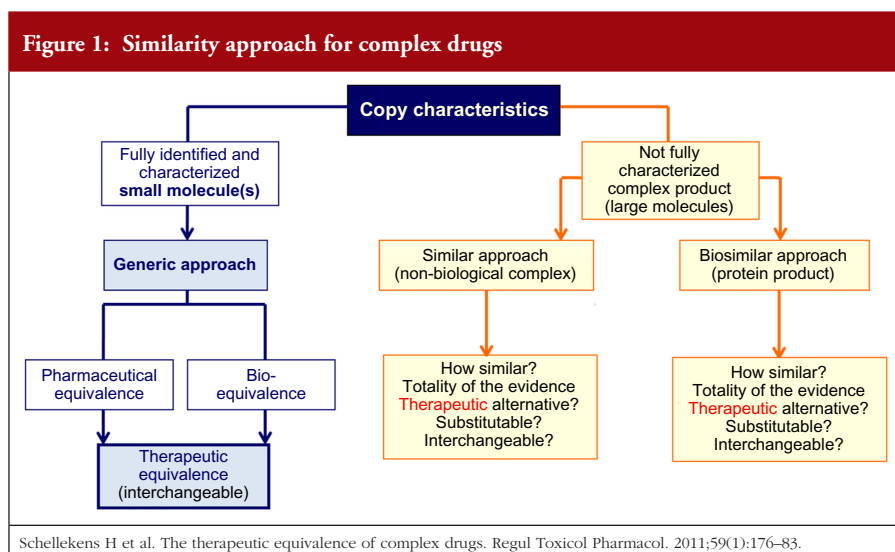
products and the problems encountered in certain countries with generic versions of NBCD products (see below), approval through the centralized procedure and the CHMP team would be preferred.

Performance of NBCD products and follow-on versions: evidence in the public domain

For all NBCD product families where follow-on versions are on the market, a growing number of studies have become available in the public domain demonstrating examples of follow-on products that were approved by (national) competent authorities that differed structurally and/or in clinical practice from the originator

Table 1: Characteristics of small molecule drugs compared to biologicals		
	Small molecule drugs	Biological drugs
Size	– Small (single molecule) – Low molecular weight	– Large (mixture of related molecules) – High molecular weight
Structure	Simple, well-defined, independent of manufacturing process	Complex (heterogeneous), defined by the exact manufacturing process
Modification	Well-defined	Many options
Manufacturing	– Produced by chemical synthesis – Predictable chemical process – Identical copy can be made	– <i>Produced in living cell culture</i> – Difficult to control from starting material to final API/MP – Impossible to ensure identical copy version
Characterization	Easy to characterize completely	Cannot be characterized completely regarding their molecular composition and their heterogeneity
Stability	Stable	Unstable, sensitive to external conditions
Immunogenicity	Mostly non-immunogenic	<i>Immunogenic</i>

API: active pharmaceutical ingredient; MP: medicinal product.
Adapted with permission from GaBI Online [11].



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Competing interest: All authors are members of the steering committee of the Non-Biological Complex Drug (NBCD) Working Group, hosted at the Dutch Top Institute Pharma (TI Pharma), Leiden, The Netherlands (<http://www.tipharma.com/NBCD>).

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products [9]. Often these differences were clinically relevant. Examples include publications by Rottembourg et al. [29]; Martin-Malo et al. [30]; Stein et al. [31]; Lee et al. [32] and Agüera et al. [33] for iron sucrose similars; and Weinstein et al. [34] and Towfic et al. [35] for glatiramer acetate follow-on products. These (clinical) examples raise questions to the regulatory science community in the countries mentioned in these publications about how appropriate the current systems are in ensuring equivalence in NBCD product quality, efficacy and safety. Is the current approach rigorous enough?

These examples provide lessons that should be communicated throughout the scientific community as well as to medical/pharmaceutical practitioners. Moreover, in the years to come, study of these examples can also help competent authorities to establish appropriate, science-based approval procedures for these complex drug products.

The future: Quo Vadis?

Expanding: The number of NBCD product families will continue to grow. It is time to pay attention to these (new) families and discuss their specific characteristics and their implications for the regulatory process at an early stage. Much information is often already available but there is a need to go through the archives and analyse these data so that scientific deficiencies are brought to the forefront.

Outstanding issues: for a list of outstanding issues concerning NBCD products one can refer to the list drawn up for biologicals.

For example, labelling, comparability and attribute drift, NBCD-questionables (cf. bio-questionables [36]), extrapolation [37], interchangeability, substitution, and last but not least: a single global approach (WHO in the lead?) [38].

Facts please: For a fact-based debate on NBCD products we need to stimulate publications in the public domain. This will strengthen the science base for decision-making. Transparency of the regulatory process is another essential element for such a discussion. We hope that all parties (academic, industry and regulatory) involved in this debate will continue, and even step up their efforts to provide this science base.

Goal: We feel that the *GaBI Journal* and the *GaBI Online* platform offer excellent opportunities to stimulate awareness around the critical issues related to both new, innovative NBCD products and the introduction of follow-on versions. The growing science base for NBCD product legislation, e.g. in Europe and the US, and hopefully in other countries in the future, needs a non-biased publication outlet. With the GaBI publication platform we have the ambition to become the central and preferred publication hotspot for this complex topic.

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