EDITORIAL

Non-Biological Complex Drugs

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Complex molecules – current developments

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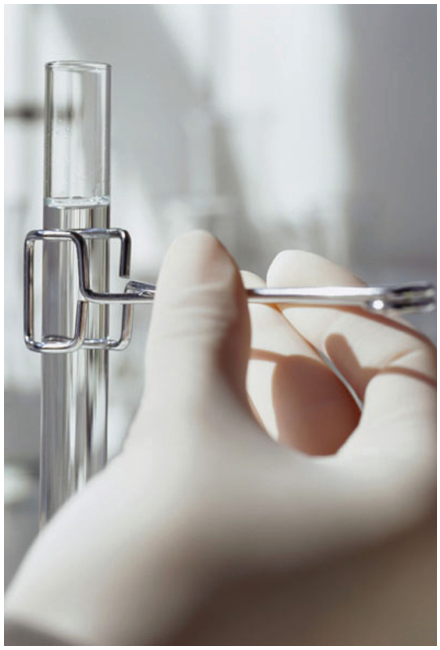

The pharmacological activity and toxicity of non-biological complex drugs (NBCDs) depends on their complex structure and composition. The regulatory approach leading to the registration of such drugs and their follow-on products, deemed 'nanosimilars', must be based on emerging scientific knowledge of NBCD properties determining their *in vivo* fate.

Keywords: Nanomedicines, nanosimilars, non-biological complex drugs, regulatory approach

The pharmacologic activity of a small molecular weight drug largely depends on its absorption, distribution, metabolism, elimination and toxicity (ADME-T) profile. While such a profile, especially with regard to metabolism and toxicity may be rather 'complex', the physicochemical properties of such drugs can be sufficiently measured and thus the drug fully described, even in the case of mixtures of (optical) isomers. At the other end of structural complexity, therapeutic proteins, such as cytokines and antibodies have entered the market. These drugs typically represent mixtures of various molecular entities of highly organized structures that cannot be completely characterized. This micro-heterogenicity of an otherwise completely human sequence is known to induce interactions with the immune system resulting in the creation of binding and/or neutralizing antibodies that hamper or suppress pharmacological activity.

Regulatory strategies exist for the registration of both drug species based on the most recent scientific knowledge and analytical capacity. While for copies of small molecular weight drugs, due to their well-describable structures, a rather straightforward 'generic' regulatory pathway is in place, follow-on products of therapeutic proteins need a more complex approach. In general, the properties of therapeutic protein products are determined by the parameters of their biotechnological manufacturing process – 'the process is the product'. Because a therapeutic protein produced by two, even slightly different processes, cannot be identical, follow-on products are defined by their similarity to the originator product and are thus called 'biosimilars'. The regulatory process for biosimilars is based on the complexity of protein drugs, demanding studies to show sufficient similarity of the follow-on product to the originator drug.

In addition to these two drug classes, a third has been described recently and coined 'non-biological complex drugs' (NBCDs), i.e. drugs showing inherent complexity that determines their pharmacologic activity and ADME-T profile, but being of non-biological, i.e. synthetic, origin. As a consequence, like therapeutic proteins, NBCDs include complex mixtures of macromolecules and even small molecules that cannot be fully characterized [1]. As the pharmacological activity of NBCDs is governed by the complexity of their structures, the determination of their physico-chemical properties such as size and size distribution, surface charge, and simple measurements of serum concentrations after injection are considered not to be sufficient to prove similarity. As an example, the active ingredients in Copaxone, a glatiramoid approved for the treatment of relapsing-remitting multiple sclerosis (RRMS), are a complex mixture of polypeptides. This mixture of a huge, perhaps incalculable, number of active amino acid sequences, render Copaxone extremely difficult to characterize and the product as such impossible to copy. In addition, the exact mode of action of this complex mixture remains largely unknown.

In addition to mixtures of large molecular entities such as glatiramoids and low molecular weight heparins (LMWH), the term 'NBCDs' also include 'nanomedicines' such as, liposomal doxorubicin (Doxil), nanoparticulate drugs like Abraxane, and iron-carbohydrate complexes, e.g. Venofer. Follow-on versions of some of these products have already been introduced into the market or are entering the development pipelines, partially as intended copies of existing products. Considering the complexity of such products as described above, there is a need to define a regulatory approach that assures quality and safety of this class of drugs as well as their intended copies. A sufficient approach currently does not exist [2].

Interchangeability/substitution of NBCDs also remains a challenge. Therefore, a

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novel, multi-pronged scientific approach to characterize NBCDs is needed. Determination of bioequivalence of two NBCD products using not a generic, but rather a 'nanosimilar' regulatory approach comparable to the biosimilar pathway for biological drugs, is advised [3]. Beyond registration, clinicians must be trained in the specific aspects of treatment opportunities and restrictions offered by NBCDs. Last but not least, to determine whether these products are really interchangeable patients should also be involved in pharmacovigilance, by constant monitoring of both side effects caused by treatment with NBCDs as well as measurement of disease progression and treatment effects [4].

Acknowledging the importance of establishing an effective 'nanosimilar' regulatory strategy for NBCDs and their intended copies, some activities were recently initiated. A draft of a reflection paper on 'data requirements for nano-sized colloidal intravenous iron-based preparations' has been published by the European Medicines Agency (EMA) [5] for public comment. The US Food and Drug Administration (FDA) is sponsoring a three-year project to examine the therapeutic equivalence between an intended copy (Nulecit) and the original iron-gluconate product, Ferlecit [6]. As another example, the European Directorate for the Quality of Medicines (EDQM), following an initiative by SwissMedic, has installed a working party on non-biological complexes charged with the task of developing a *European Pharmacopoeia* monograph for iron-sucrose complexes [7].

This series of manuscripts is intended to describe and discuss recent developments in the field of NBCDs from various perspectives. It includes a commentary by Moghimi and Farhangrazi [8] discussing the characterization of NBCDs using the specific example of liposomal doxorubicin (Doxil) and its generic, Lipodox. The story of liposomal doxorubicin is an interesting example of a science-based regulatory process. Coming off patent protection in 2009, an exclusivity extension for Doxil until May 2014 was granted by FDA. However, because of a shortage of Doxil, caused by a reduction of manufacturing capabilities that began in 2011, FDA approved a 'nanosimilar', Lipodox, and published non-binding recommendations for the biophysical characterization of 'generic injectable PEGylated liposomal doxorubicin formulations'. The deposition of NBCDs in the body, like liposomes, is highly dependent on the recognition by the immune system and activation of opsonization with protein components in the blood. Because this interaction takes place at the surface of particulate NBCDs, changing the surface parameters such as charge, density of PEGylation, etc., can lead to an alteration in immune recognition, activation and thus the disposition of such drugs. In their contribution, Moghimi and Farhangrazi describe how, in their opinion, scientific knowledge of immune recognition and activation by NBCDs must guide the required regulatory pathway for approval of 'nanosimilars'.

Aspects of the clinical development, immunogenicity and interchangeability of follow-on NBCDs in comparison to the originator products are also discussed in a review by JM Nichols [9]. The review focuses especially on liposomal drugs, iron-carbohydrate complexes and glatiromoids, and discusses considerations relevant to the approval of follow-on NBCDs. The clinical repercussions of switching NBCD products is described in a case study included in a research article by Rottembourg, Emery and Moglia [10]. The series concludes with an updated overview of NBCDs currently on the market or in development deemed 'nanomedicines' by Borchard and di Francesco.

I would like to personally thank the editorial team of *GaBI Journal* for giving us the opportunity to present manuscripts devoted to this exciting field under the 'Non-Biological Complex Drugs' editorial series, and all authors for their highly valued contributions. We are hoping to be able to continue to the current discussions on the science of this field and to help deal with the gap in the regulatory approach for NBCDs.

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