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The Non-Biologic-Complex-Drug Concept

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Abstract

When the patent of a small molecule drug expires, generics may be introduced. They are considered therapeutically equivalent once pharmaceutical equivalence (i.e.,, identical active substances) and bioequivalence (i.e., comparable pharmacokinetics) have been established in cross-over volunteer study. However this generic paradigm cannot be applied to complex drugs as biologics. For copies of biologics EMA, and FDA, have introduced a new regulatory biosimilar pathway which mandate clinical trials to show therapeutic equivalence. However for some complex drugs, such as iron-carbohydrate drugs, liposomal drugs, glatiramoids (named Non Biologic Complex Drugs [NBCD]), regulatory guidance is still mostly lacking. In this paper we will discuss therapeutic experiences with these different classes of complex drugs and their specificity, to provide scientific arguments for consideration for a new regulatory framework.

Keywords

Generic; Biosimilars; Therapeutic Equivalence; Iron-carbohydrate complexes

Introduction

The concept of Non-Biologic-Complex-Drug (NBCD) was introduced as the result of a workshop in Leiden (Netherlands) in 2009 [1]. For the first time, this class of drug products was identified and recognized: they are more complex than small, low molecular drugs and as complex as or even more complex than biologicals, sharing many of the characteristics of the latter category but not being derived from living sources [2,3]. More recently the NBCD concept was extended to nanomedicines, which are highly complex drugs and are the result of difficult to control manufacturing processes [4,5]. They are numerous evidences that for the equivalence testing of NBCD follow-on products, a regulatory pathway should be developed similar to the pathways developed for biosimilars by EMA and later by FDA. Numerous publications, studies, workshop demonstrated that NBCD follow-on versions authorized are inappropriate through the standard generic protocol [6-8]. This publication provides a definition for NBCDs products, discuss different classes of NBCDs, propose a regulatory philosophy for NBCD follow-on versions and outline the relationship between NBCD and nanomedicines.

Definition of NBCD

When the patent of a classical small molecule drug expires, generics may be marketed if their therapeutic equivalence to the original drug has been established [9,10]. Conventional generics for an orally administered drug are considered to be therapeutically equivalent to a reference once pharmaceutical equivalence (i.e., identical active substances) and bioequivalence (i.e., comparable pharmacokinetics essentially on healthy volunteers) have been established in a cross over study and do not require formal clinical efficacy and safety studies. The therapeutic equivalence allows then the therapeutically interchangeability [11]. The acceptance intervals to show that bioequivalence for the logarithm transformed AUC and Cmax ratios lie within an acceptance range of 0.80-1.25 for the 90% confidence intervals. In some cases the acceptance interval need to be tightened and in other cases a wider acceptance may be acceptable. The NBCD landscape is visualized in Figure 1 which classified products based on the challenge to assess Pharmaceutical Equivalence (PE) and BioEquivalence (BE) of different products.

The classical generic approach based on showing pharmaceutical equivalence and bioequivalence has been the basis of the introduction of many safe and effective alternatives to innovative medicines. However, this approach has been far only applied to products, which can be fully characterized. Changes in the composition and morphology of an NBCD can substantially influence the quality, biological properties and therapeutic profile of the medicinal product and result from minute variations in the manufacturing process [12]. However, not all structural changes and mechanisms that affect the therapeutic profile are fully understood. Notably, the complexity of NBCD prevents establishing full proof of pharmaceutical equivalence by state-of-art analytical means, which comprises one of

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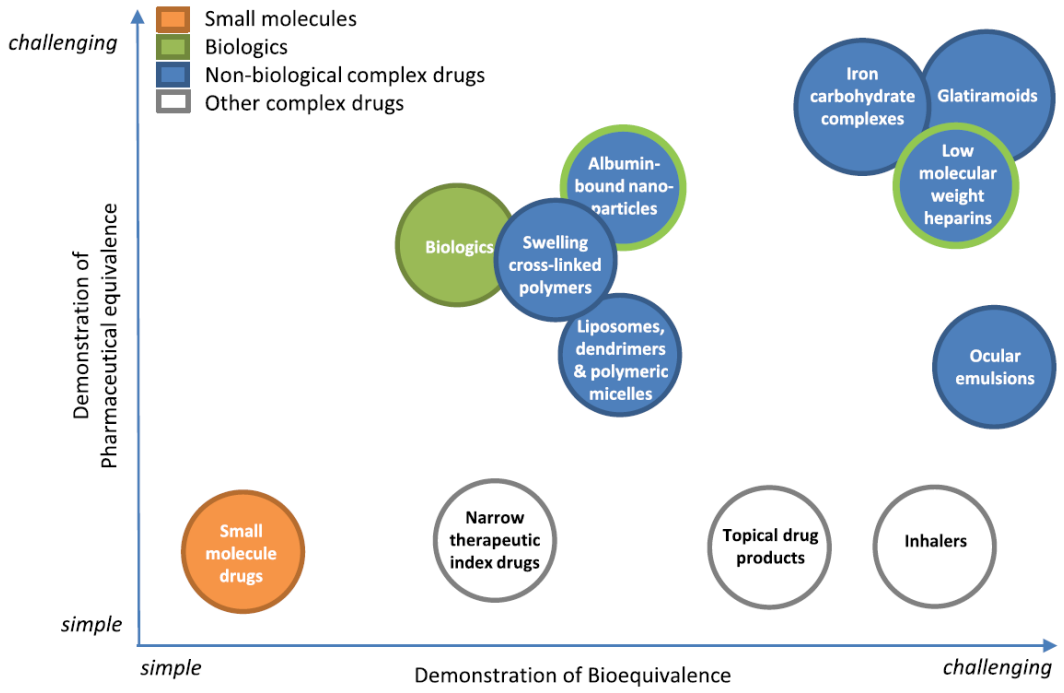

Figure 1: The Non Biological Complex Drug landscape. Conventional low-molecular-weight drugs that can be fully characterized are shown in orange. Biologics (biosimilars) are shown in green. Complex drugs are shown in blue (NBCDs) or white (other complex drugs). For the majority of NBCDs both PE and BE 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 in blue with a green outline (classification of these drugs varies across the globe). Derived with permission from Hussaarts L, et al. [33]

the two pillars in the evaluation of a generic medicinal product. In contrast to the mainly direct and systemic drug-target interaction of small molecules with defined receptors in a concentration-dependent manner, most NBCDs comprise nanoparticles from which the active ingredient can negatively affect the safety and efficacy of an NBCD or its follow-on product. The example of products for intravenous iron therapy is developed further. Hence, the biological activity of an NBCD is not necessarily correlated to its serum pharmacokinetics (central compartment), the generic pathway is the second pillar to show bioequivalence.

The NBCD products and their follow-on versions

For all NBCD product families, where follow-on versions are available, a growing number of studies become available, demonstrating that follow-on products that were approved by competent authorities differed structurally and/ or in clinical practice from the originator products [13].

The Iron carbohydrate complexes: An iron-sugar nanoparticle consists of a polynuclear iron (III) hydroxide core surrounded by sugar molecules. Apart from the size, the reduction potential of the iron (III/II) and the strength of the interaction between the iron core and the surrounding sugar are closely dependant to the product's quality, safety, efficacy and immunogenicity profile. The totality of the physicochemical properties of iron nanoparticle products defines the bio-interference including their ability to interact with physiological acceptors (transferrin, ferritin, enzymes, specific cells like monocytes, etc.). The iron nanoparticles are defined by proprietary manufacturing processes, which complicates the development of comparable or even interchangeable follow-on products [12]. The pharmacokinetic parameters including the dissociation of the complex in plasma and the bio-distribution of the product into different tissues as well as the kinetics of the release of the active ingredient (iron) and the uptake into the physiological iron metabolism pathways may be profoundly different between products. Differences in efficacy and safety between originator iron sucrose and formerly authorized similar preparations have been published [14-17]. These data raise concerns about interchangeability of such products based on both efficacy and safety. Patients treated in a recent study with an iron sucrose similar product required on average 34% more iron compared to patients treated with the originator product [14]. Given the most common use of chronic Intra Venous (IV) iron treatment for anemia in haemodialysis patients and knowing that the excretion of iron in man is limited and not well regulated, concern must be raised regarding what potential harmful effects this excess iron may cause [18].

Both the FDA and EMA acknowledge that nanoparticle (colloidal) iron (sucrose) preparations cannot be authorized by the so far, well-established (classical) generic approval paradigm for small molecules, which is based on the sameness of the product shown by physicochemical full characterization and a bioequivalence in healthy volunteers. But the situation is changing: both EMA and FDA have issued 'reflection papers' and 'draft guidance' documents respectively, regarding data requirements [19-20]. Since a meeting in 2012 with FDA there is no follow-on iron sucrose authorized on the US market. Recently the FDA contracted out a prospective randomized, 2-way cross-over study on the comparison of the iron-gluconate innovator product and the follow-on version, previously authorized [21].

The liposomal drugs: Liposomes are vesicles with (phospho) lipid bilayer membranes that can carry drugs. The safety and efficacy of these liposomal drugs depend on their lipid composition, size,

charge, the rigidity of the bilayer and their production process [22]. Clinical work on new liposomal formulations of a variety of drugs is thriving and as of the end of 2012, over 550 clinical trials are registered using the search term 'liposomes' under www.clinicaltrials.gov.

The discussion on the regulatory aspects of the introduction of follow-on versions of liposome products focuses on those containing doxorubicin (Doxil®/Caelix®). Recently, the innovator published findings showing that doxorubicin liposomes with a different lipid composition differed in their antitumor activity in animals although they had similar pharmacokinetic (PK) profiles [23]. A plea was made for clinical studies to show therapeutic equivalence between original and follow-on versions of liposomal drugs [24].

The FDA published a draft guidance paper on follow-on versions of doxorubicin hydrochloride liposomes [25]. The applicant of a follow-on version needs to show that the physicochemical characteristics of the follow-on version are equivalent to the originator's product. In addition, *in vitro* studies are needed measuring particle size distribution and doxorubicin release characteristics in different media and a clinical bioequivalence study measuring both free and encapsulated doxorubicin. Clinical efficacy and safety studies are not necessary. In 2013, the FDA approved the first follow-on liposome containing doxorubicin. So far, no follow-on versions of liposomal formulations have been approved by the EMA.

The Glatiramoids: Glatiramoids comprise a family of synthetic copolymer mixtures comprising the four amino acids, L-glutamic acid, L- alanine, L-lysine and L-tyrosine, in a defined molar ratio. The prototype is glatiramer acetate (Copaxone®), a mixture of hundreds of thousands polypeptide sequences with immune-modulating activity authorized for the treatment of multiple sclerosis. The composition of glatiramer acetate is highly dependent on the manufacturing process. Minor changes in this process can produce altered entities which are likely to significantly affect the safety and efficacy of the product [26]. In addition to its inherent compositional complexity, glatiramer acetate comprises a nano-sized polypeptide mixture with molecules and molecular structures ranging from 1.5 to 550 nm in size; some of them to be deemed proteins because of their size [27]. Due to these sizes, Copaxone® is considered to be a colloidal solution. Its biological activities are related to cytokine induction and its immunogenicity that is a key parameter of the quality, safety and efficacy of the drug and very sensitive to any modification of chemical and physical characteristics. 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 Moneta Pharmaceuticals and the EMA does recently the same. For decades, the use of Copaxone® is safe and effective, while the active moiety or moieties, as well as the exact mechanism of action, remain to be identified. The FDA decided to approve Glatopa using the criteria deemed by the FDA to be sufficient to establish therapeutic equivalence without requesting a clinical study. In Europe, in contrast with the FDA approach, a follow-on version of Copaxone® (manufactured by Synthon) has been approved through the decentralized authorization procedure in accordance with the requirement of Article 10(3) [19]. Interestingly, although this product is not a biological medicinal product as such, Synthon followed a strategy similar to the dossier requirements of biosimilar applications and has provided a full chemistry, manufacturing and control package, non clinical studies and the result of a comparative abridged clinical trial in subjects with relapsing-remitting multiple sclerosis.

Nanosimilars and follow-on nanosized therapeutics: Other drug products will be recognized as NBCD in addition to the products discussed in the section above, it is the nanomedicines. Nanomedicines have been successfully used as medicinal products in clinical routine over the last several decades, frequently without taking into account either their specific nanoparticular structure or the resulting complexity of their mechanical, chemical and pharmacological properties [28]. Examples include polymer-drug conjugates, polymeric nanoparticles, polymeric micelles, iron oxide particles and innovative biological complex therapeutics like monoclonal antibodies. It is also expected that these will include older products that are in fact colloidal nanoparticle systems and will be reclassified as nanoparticles and NBCD or Nanosimilars. There is a lack of knowledge on which parameters are critical for the evaluation of nanomedicines during early development. For instance, nab-paclitaxel (Abraxane®, Celgene Corporation, NJ, USA) a nanoparticle, albumin-bound anticancer drug is the first approved protein-based nanoparticle medicinal product as Nanosimilars. The manufacturing processes, the use of proteins from different sources, result in variations quality, purity and difficulties in scale-up production. The performed tests with intended copies suggest fundamental differences in manufacturing and resulting product composition: these differences may potentially lead to undesirable effects and safety concerns [29]. Biologics of very high molecular weight, such as antibody-drug conjugates may also be considered as nanomedicines [30].

Acknowledging the complexity of biologics such as therapeutic proteins and the impossibility to exactly reproduce biological products, a specific biosimilar regulatory approach for follow-on versions was elaborated and established by EMA [1]. Up until now, 17 biosimilar products received marketing authorization by EMA [31]. The FDA developed a regulatory approach for such products, but accepted the similarity instead of the sameness approach [32]. In analogy to the biosimilar concept for therapeutic follow-on products, the term 'Nanosimilar' has been coined in the context of NBCDs follow-on versions [28]. The mostly unknown existence and nature of clinically meaningful components in nanomedicines or NBCDs result from the manufacturing process. It makes it so difficult or even impossible to appropriately characterize such products physico-chemically and has a special importance for the regulatory evaluation in follow-on versions. Therefore, nonclinical and clinical evaluations are needed to characterize such product and to obtain the totality of evidence to achieve comparability [33].

Conclusion

NBCDs and related nanomedicines regulatory awareness is documented by a series of reflection papers and industry guidance's released from important authorities on evaluation of follow-on versions of established NBCDs like the nanocolloidal IV iron carbohydrates or liposomes. Non equivalence of NBCD follow-on versions, authorized by the classical generic paradigm, which is not valid for these highly complex synthetic nanoparticle drugs, has triggered these considerations [3]. Therefore a similar instead of a sameness approach is necessary [12], a defined and accepted nomenclature is lacking but is mandatory for harmonized regulations. Whereas for NBCDs a defined similar approach is almost lacking, support and experience from the biosimilars approach could be used to progress although these Nanosimilars are synthetic and therefore not biological.

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