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Commentary

The similarity question for biologicals and non-biological complex drugs ☆

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ABSTRACT

For small – low molecular weight – molecule medicines a robust regulatory system has evolved over the years. This system guarantees high and constant quality of our (generic) medicines. Pharmaceutical equivalence and bioequivalence assessment are the pillars under that system. But there are complex medicines where the question of equivalence is more challenging to answer. For biologicals the paradigm of similarity rather than equality (the emergence of 'biosimilars') was developed in the past decade. This has been a program where an evolutionary, science based approach has been chosen by the frontrunner regulatory body, the EMA, with a 'learn and confirm' character.

In addition, there is another group of complex drugs, the *non-biological* complex drugs, NBCDs, where the generic paradigm can be challenged as well. The NBCDs are defined as: 1. consisting of a complex multitude of closely related structures; 2. the entire multitude is the active pharmaceutical ingredient; 3. the properties cannot be fully characterized by physicochemical analysis and 4. the consistent, tightly controlled manufacturing process is fundamental to reproduce the product. NBCDs encompass product families such as the glatiramoids, liposomes, iron–carbohydrate colloids and many candidates of the group of the upcoming nanoparticulate systems. Following the main principles of regulatory pathways for biologicals (with appropriate product-by-product adjustments), instead of that for small molecules, would be the more logical strategy for these NBCDs.

The status and outstanding regulatory issues for biosimilars and NBCD-similars/follow on versions were discussed at a conference in Budapest, Hungary (October 2014) and this commentary touches upon the issues brought up in the presentations, deliberations and conclusions.

1. Introduction

This conference was organized in Budapest (October 2014) by the department of Pharmaceutics of Semmelweis University with other Hungarian science organizations and under the auspices of the American Association of Pharmaceutical Scientists (AAPS), the International Pharmaceutical Federation (FIP) and the European Federation of Pharmaceutical Sciences (EUFEPS). It brought academic, industrial (both the innovator and follow-on companies) and regulatory experts together to discuss the topic: 'complex drug products and similarity', a topic that is at present high on the agenda of the regulators and health care policy decision makers.

2. Small molecule medicines: a mature system for approval of generic/follow-on versions

Over the years the regulatory policies for the development of generic versions of small molecule medicines have evolved and a

☆ Reflections based on the presentations and panel discussions during the International Symposium on the Scientific and Regulatory Advances in Complex Drugs, Budapest, Hungary, October 27–28 2014.

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solid regulatory framework has been established using the concept of pharmaceutical equivalence and bioequivalence (left side of Fig. 1). This paradigm is based on the assumption that the molecular structure of the bioactive molecule is known and can be exactly reproduced and fully characterized. Typically, it is one well-defined molecule, the active pharmaceutical ingredient, embedded in an appropriate formulation. Mixtures (e.g. enantiomers of chiral molecules) may occur, but their exact composition should be known and be constant. Regulatory experts from all over the globe (e.g. from FDA, EMA, WHO) have developed their guidance documents to assure equality in terms of quality, efficacy and safety between the innovator's and various generic versions of these medicines. The different guidance documents have a common philosophy. But, even with their common science base, there are differences in position, e.g. regarding the rules for biowaiver policies. In general, no preclinical and clinical trials to compare the performance of the generic drug with the innovator product are requested. However, for some small molecule formulations and specific devices authorities are cautious to rely on the pharmaceutical quality/bioequivalence protocols alone. In this context narrow therapeutic index drugs, controlled release and modified release formulations, skin patches, inhalers and multi-ingredient products are mentioned (Dunne et al., 2013). Thus, there is a worldwide clear, common denominator for the regulatory process to give a market authorization to generic small molecule preparations. But, in spite of extensive efforts e.g. through the ICH, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, no real, total global consensus has been reached yet. However, work is in progress (cf. the EUFEPS Global Bioequivalence Harmonization Initiative, March 2015).

3. Complex drugs: a regulatory framework under development

Next to these small molecule medicines, complex drugs have been developed and the regulatory challenges that come with evaluating these complex drugs were the major discussion points for this conference. While *equal or identical* are the key terms for small molecule medicines, *similar* is the key word for complex drugs. And the question is: how similar is similar?

In the regulatory world, there is a dichotomy between two groups of complex drugs. Those complex drugs that are produced through living organisms (biologicals) and the *non-biological* complex drugs (NBCDs): complex drugs that are *not* produced through living organisms, but through a fully synthetic process. In particular, the advent of follow-on versions of biologicals has drawn a lot of attention to the class of complex medicines and the inherent regulatory challenges. The lectures and discussions during the conference formed the basis of the following text on the history and current developments of this fast growing area in the world of medicines. A general discussion on comparability/similarity of *biologicals* will be followed by a list of 'outstanding issues' that are still to be resolved: bioquestionables, comparability and product attribute drift, interchangeability and substitution, extrapolation and naming. This will be followed by a description of the status of the legislation and practical experience with *non-biological* complex drugs (NBCDs) and attention will be paid to the similarities and differences between the existing regulatory frameworks for follow-on versions of biologicals and NBCDs.

4. Biologicals and follow-on versions

In the Budapest conference the issues around the follow-on versions of biologicals were first discussed as the regulatory framework has been more extensively debated in the literature than the NBCD-regulations. Drs. Greiner, Crommelin and Declerck addressed different aspects of the legislature and regulatory rulings regarding the comparability of biologicals and their follow-on versions. As these speakers pointed out, over the last decade a lot of progress has been made to develop such a regulatory framework but there are quite a few outstanding issues that will be part of the text below.

4.1. The EMA as frontrunner

The EMA has taken the lead in building a regulatory structure for biologicals starting as early as 2001 with Directive 2001/83/EC (EMA, 2001) where the term biological is defined: 'A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source

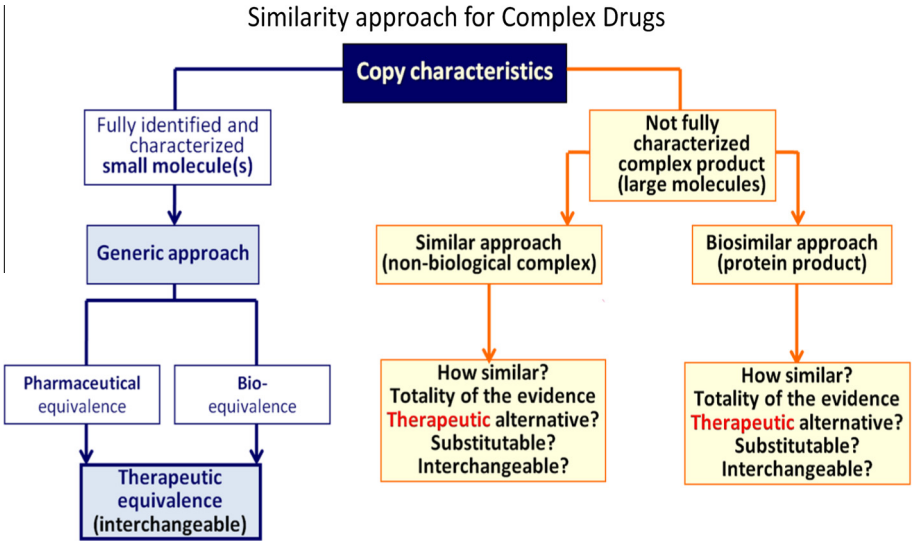

Fig. 1. Adapted from Schellekens et al., 2011: Similarity approach for complex drugs. The term ' Totality of (the) evidence' has been defined as: A scientific principle that, in the context of biosimilars, establishes biosimilarity by using an extensive set of decisive methods sensitive enough to detect relevant differences, if present. These methods involve a large battery of state-of-the-art physicochemical, analytical, and functional methods and clinical studies (from Weise et al., 2014).