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Commentary

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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.

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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

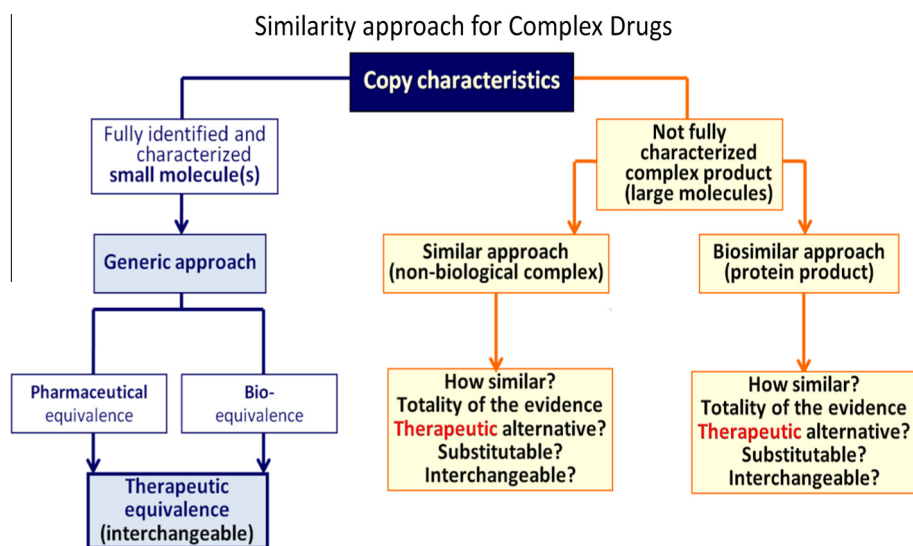


Fig. 1. Adapted from Schellekens et al., 2011: Similarity approach for complex drugs. The term 'Totality of (the) evidence' has been defined as: A scientific principle that, in the context of biosimilars, establishes biosimilarity by using an extensive set of decisive methods sensitive enough to detect 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).

and that needs for its characterization and the determination of its quality a combination of physico-chemical–biological testing, together with the production process and its control'. And then the basis for the development of guiding documents for follow-on biologicals/biosimilars was formulated: 'Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided... ' (directive 2004/27/ec article 10 4; 31 March (EMA, 2004)). The central procedure through the EMA is the legal route to obtain market approval for a biological or biosimilar medicinal product.

The EMA uses the term biosimilar for EMA approved biologicals. This term was defined by Crommelin et al. (2014) as: 'A similar biological medicinal product (also known as biosimilar) is a biological product authorized by an abbreviated regulatory pathway requiring similarity to an already licensed biological product (the reference product) in physicochemical, in vitro and in vivo biological characteristics, and clinical data showing similarity in efficacy, safety, and immunogenicity'. The use of this term (biosimilar) is restricted to products that underwent a rigorous test program e.g. based on the EMA guidelines for biosimilars (Weise et al., 2011). These guidelines are divided in three sections: 'overarching biosimilar guidelines', 'product specific guidelines' and 'other guidelines relevant for biosimilars' (EMA, 2015). These documents are regularly updated and expanded.

The EMA has been in the lead in defining the guidelines for biosimilars and 21 biosimilars were approved in the EU (per 10/2014). Countries as Japan (5 biosimilars), Canada (3 s entry biologicals) and Australia (8 biosimilars) followed the principles of the EMA framework. The EMA rejected a number of applications or applicants withdrew their application. The applications for interferon-beta and interferon-alfa (BioPartners) were rejected and Marvel LifeSciences Ltd (India) withdrew its application for insulin follow-on products. More details about the approved and rejected/withdrawn applications can be found in the epar's (European Public Assessment Reports) published by the EMA and in Heinemann and Hompesch (2011).

4.2. Similarity between the regulatory views worldwide?

And other initiatives? In 2009, the WHO published guidelines to evaluate "similar biotherapeutic products" (SBP). This publication was e.g. the basis for the Korean legislation (Wang and Chow, 2012) and countries in Latin America (Desanvicente-Celis et al., 2013). And in the USA a framework for biosimilars (indeed using the same term) is being set up by the FDA and the first 'tentative' approval have been announced (for filgrastim) (FDA, 2015a). Unfortunately, the EMA and FDA systematics are different and there is definitely a need for harmonization. But, both agencies recommend two important ways to proceed: use a 'stepwise approach' and 'totality of evidence' as guiding principles to obtain market approval for biosimilars. That means that (on a case-by-case basis) the results obtained in comparing product quality, outcome of safety and efficacy experiments are being evaluated and being used for further planning of necessary/required experiments (cf. Fig. 2).

4.3. Bioquestionables

The term bioquestionables is defined as: A copy version of a therapeutic protein, which has not been developed and assessed in line with the scientific principles of a comparative development program against a reference product showing similarity in quality, safety and efficacy. In certain countries the quality of the approval process for follow-on biologicals has been questioned. E.g. 12 copies of erythropoietin ('bioquestionables') approved through a classical generic regulatory pathway in Thailand were compared and significant variation in physico-chemical and chemical characteristics was found (Halim et al., 2014). The authors state that 'This comparison study supports a link between the quality attributes of copy rHPO products and their immunogenicity'. Immune reactions against epo lead to pure red cell aplasia, PRCA, a serious, life threatening disease.

4.4. Comparability and product attribute drift

The quality of a biological product depends on a robust, well controlled manufacturing process including the downstream processing and filling and finishing steps. But these processes may

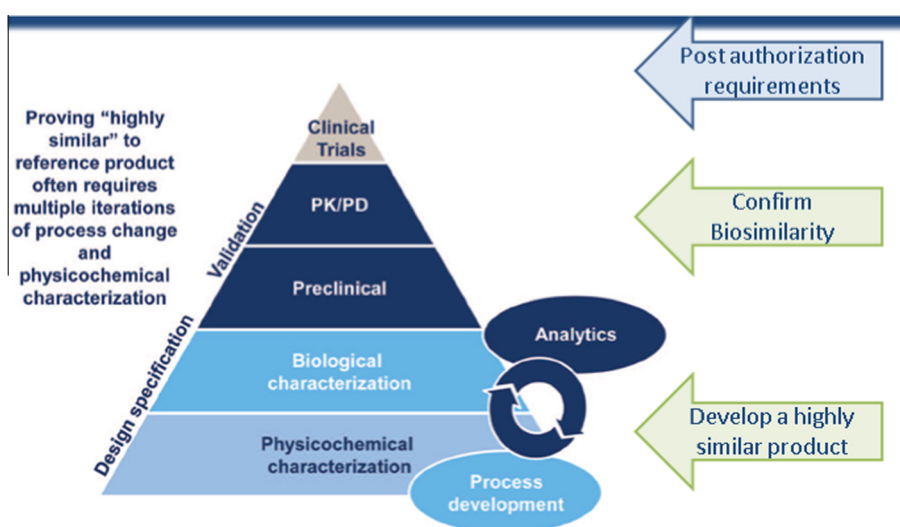


Fig. 2. 'Biosimilar development process. The development of a biosimilar relies on creation of a design space based on analysis of the reference product and then iterative development of a biosimilar to fit the chosen specifications. There is no access to, nor need for, originator data at any point in this process. The early process development is essential, and later development cannot compensate for this initial generation of a "highly similar" candidate product. As the complexity of the reference product increases, the initial development becomes more challenging, and the likelihood that multiple iterations will be needed increases (adapted from McCamish and Woollett, 2011)'.

change and such changes have to be reported to the regulatory authorities. E.g., for Rebif™ more than 35 changes were reported to the EMA since its launch. Among those: changes in the host cells, active molecule, specifications and formulation (cf. EMA, 2014). The innovator is requested to show ‘comparability’ between the product attributes before and after a change. Assessment of comparability can be based on a combination of analytical testing, biological assays, and in some cases non-clinical and clinical data. Schiestl et al. (2011) showed physico-chemical differences in three innovator products after manufacturing process changes with no changes in the product label. This drift in innovator product attributes may have interesting consequences. The innovator and a new biosimilar product show similar, but not equal characteristics. If the innovator manufacturing process, or *mutatis mutandis*, the biosimilar manufacturing process changes, then the two product characteristics may drift so far apart that similarity cannot be preserved: divergence over time occurs. The implications of this drift have not been discussed in depth in the existing literature.

Our analytical capabilities to characterize pharmaceutical proteins are growing at a rapid pace (Berkowitz et al., 2012; Beck et al., 2015). In the conference Dr. Sandra showcased the enormous resolution of today’s mass spectrometry (MS)/chromatography combinations when characterizing pharmaceutical protein formulations and the increasing power of MS to identify the structure and quantity of the different components. These are very powerful tools, indeed, not only to identify structural differences between the innovator and biosimilar product, but also to monitor batch to batch quality in detail. And then the question should be asked: if differences are detected in comparability studies between innovator/innovator, innovator/biosimilar, or biosimilar/biosimilar products: what does that do to their clinical performance? Are (pre)clinical tests necessary to show similarity in clinical outcome? Subsequently, drs. Ferrari and Bansal worked out a number of practical cases where state of the art equipment for protein analysis was used to characterize proteins and they identified and discussed outstanding issues e.g. ‘carry over’, sensitivity and linearity of response.

4.5. Interchangeability and substitution

The following definition of interchangeability is proposed: ‘Interchangeability can be at the population level meaning both products can be used for treatment for the same condition in the same population. Interchangeability at the individual level means that for an individual patient, the products can be alternated or switched. Interchangeability at the individual level is a condition for substitution’ (Crommelin et al., 2014). And ‘Substitution is a policy to allow replacement at the individual level of a medicinal product for a similar/bioequivalent product’ (Crommelin et al., 2014). Clarity about this issue is of key importance to the pharmacist when dispensing a prescribed medicinal product. When the EMA recommends market approval for a biosimilar, this doesn’t mean that the product is automatically interchangeable and can be substituted throughout the EU. To decide on interchangeability between an innovator’s product and a biosimilar is a competence of each individual state in the EU and is beyond the authority of the EMA. And the state policies differ markedly per country and are subject to change over time (Niederwieser and Schmitz, 2011). The European map shows all kind of options varying from ‘substitution under certain conditions’ in France (GaBi, 2014) to ‘no substitution allowed for biologicals’. In the US the decision on substitution is a state responsibility and different states have passed legislation. Here again, differences in state legislation over the country seem to appear and the discussion is still ongoing (GaBi, 2015).

4.6. Extrapolation

Recently, the issue of ‘extrapolation of indication’ has been subject of an intense debate and at the conference different aspects were discussed by the speakers. First a definition: ‘extrapolation is the possibility to use the clinical data showing safety and efficacy in one indication (reference indication) to claim safety and efficacy in other indications’ (Crommelin et al., 2014). This discussion was in particular fuelled by the differences in opinion between the EMA and Health Canada regarding the extrapolation of indications for the biosimilar version of infliximab, approved both in Europe and Canada, but where the Canadian authority rejected the proposal to extrapolate the indication to intestinal bowel disease, and the EMA did approve the extrapolation. Weise et al. (2014) provide insight in the philosophies behind these decisions and list the arguments. But, here again, this is another example where a globally harmonized decision would have been the preferred outcome.

4.7. Naming

The naming of biosimilars (next to their brand name) causes an intense debate. Worldwide different approaches are being followed, often with the WHO-INN as source of inspiration. This leads to confusion and might cause medication errors. E.g., an epoetin alfa in the EU is registered as epoetin lambda in Australia. High time for a global initiative with WHO in the lead. In July 2014 the WHO published a draft document where – on a voluntary basis – the different biosimilars would be named with the INN name, followed by a WHO assigned ‘biological qualifier’ (BQ). The discussion is still ongoing (after an October 2014 WHO consultation meeting) and no final WHO document has seen the light yet.

5. Concluding remarks re biological complex drugs

A lot has been achieved regarding the pathways to provide the patient with safe, efficacious and high quality biologicals, be it innovator products or their biosimilar(s). Today the EMA has most experience with designing and evaluating the regulatory path. It is an evolutionary process: learning and confirming. WHO followed suit and FDA is in the process of setting up its own system, similar but not identical to the EMA path. Thus there is – and will be – no worldwide accepted science based regulatory system for biologicals in place.

6. NBCDs: non-biological complex drugs

During the first day of the conference, six lectures and a panel discussion were dedicated to NBCDs, i.e. by drs. De Vlioger, Mühlebach, Weinstein, Gaspar, McNeil and Zoubek. Dr. De Vlioger introduced the goals and activities of the NBCDs working group (TI Pharma, 2015) and defined the term NBCD. He listed the following key attributes for a NBCD:

1. it consists of a multitude of closely related structures,
2. the entire complex is the active pharmaceutical ingredient,
3. the properties cannot be fully characterized by physicochemical analysis,
4. the well-controlled, robust manufacturing process is fundamental to reproduce the product.

NBCDs are a ‘mixed bag’ of medicinal products; they cover a number of ‘medicine-families’ such as the glatiramoids for subcutaneous injections, iron-carbohydrate-complexes for i.v. administration, liposomes, polymeric micelles, swelling polymers (oral administration), albumin-cytostatic complexes and other

nanomedicines. Sometimes low molecular weight heparins (FDA), dry powder inhalers, ocular/intravenous emulsions and dermal patches are seen as NBCDs as well. More detailed information about NBCDs can be found in the book published in the spring of 2015: 'Non-biological complex drugs; the science and the regulatory landscape' (Crommelin and de Vlieger, 2015). Drs. Mühlebach and Weinstein discussed specific NBCD families, see below, while Dr. McNeil demonstrated how within the Nanotechnology Characterization Lab, NCI–NCL, techniques are developed to physico-chemically characterize nanomedicines and to monitor their behavior in vivo. Finally, Dr. Gaspar gave an overview of the regulatory status of the approval process of innovator and follow-on liposome products and other nanoparticulate medicines.

6.1. The legal landscape

In the past the complications with the approval of NBCD innovator products have been recognized by the EMA and regulatory routines for such medicinal products have been developed over the years. Dr. Pita from EMA gives his (personal) views on the position of NBCDs in the regulatory framework of the EMA in a recent publication (Pita, 2015). The advent of follow-on versions of these NBCDs asked for specific rulings for approval with the requested extra information provided on a case-by-case basis. The EMA has not formally classified certain product families (cf. above) as NBCDs. But, nanomedicines are often mentioned in the context of NBCDs. The EMA tends to refer to the biosimilar framework when issues regarding similar-NBCDs (follow-on versions of NBCDs) are discussed. A concrete difference with biosimilars in the European legislation is that clear similar-NBCD applications are not necessarily following the central procedure and may receive marketing approval through the decentralized route. That happened in the past (e.g. in France 5 brands of iron-sucrose are marketed) and recently, an iron-sucrose product was approved for the Swedish market through the national procedure and considered 'as similar to the innovator product' (PAR, 2012). No clinical data were requested by the Swedish authorities. In the PAR (public assessment report) reference is made to the EMA Reflection paper (see below).

For the FDA NBCDs are not formerly recognized. Complex drugs follow the 505(b)(1) or 505(b)(2) route for NDA and the 505(j) route for ANDA. For both routes (NDA/ANDA) additional information compared to the standard small molecule package may be requested. That is decided on a case-by-case basis. However, for certain NBCD product families such as liposomes, different iron carbohydrates (iron sucrose, iron gluconate, ferumoxytol) and cyclosporine ophthalmic emulsions, draft guidance documents have been issued, which were open for discussion while drafted. This helps in establishing science based regulatory procedures for NBCD families.

Information on NBCD regulations in other countries of the world has not been collected and analyzed yet. It suffices to state, that there is a need to obtain such an overview as there may be NBCD-questionables (cf. bio-questionables) on the market. In the following sections on NBCD product families some examples of NBCD-questionables will be presented. Are they the tip of the iceberg?

7. NBCD product families

7.1. Liposomes

Liposomes may be seen as frontrunners for the now upcoming nanomedicines family (e.g. polymeric micelles and colloidal gold

dispersions) and much of the experience obtained with liposome registration may – in adjusted form – be applied to submissions for other nanomedicine systems. Dr. McNeil explained that the NCL is working on the development of analytical techniques and procedures to characterize liposomes/nanomedicines and to measure relevant aspects of their performance in vitro and in vivo (Table 1), often to be part of the data package to support submission to the regulator.

The first guidance paper published for liposomes appeared in 2002 (FDA CDER, 2002). This document dealt with the 'liposome drug products: chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation' and explicitly did not provide information on clinical efficacy and safety studies and nonclinical pharmacology and/or toxicology studies. The 505 (b)(1) or (b)(2) pathways are available. Later another guidance document was drafted (FDA CDER, 2014), which specifically focused on the development of follow-on versions of doxorubicin liposomes through the 505(j) pathway. Here again, this document does not provide information regarding clinical efficacy and safety studies. In the EU innovative and follow-on liposome products follow the centralized procedure. For innovator liposome products no specific guidance documents are available. For follow-on versions of doxorubicin liposomes a 'reflection paper' was issued in 2009/2013 (EMA, 2013). From this reflection paper on can read that proper handling of issues like "sameness" of the follow-on product and reference product, a 'stepwise development approach' and 'totality of evidence' is important and key to successfully submit the dossier and receive approval.

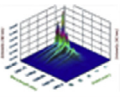


In the EU and USA 11 innovator liposome products have been registered (Crommelin et al., 2015). In the USA one follow-up product is approved in a two step process (Lipodox[®] as follow-on version of Doxil[®]). Interestingly, the dossier of Lipodox was rejected by the EMA (EMA, 2011). Here no bioequivalence for free doxorubicin could be established for Lipodox and Caelyx[®], which is (just) the European brand name of Doxil: produced by the same manufacturer in the USA. Thus, two different decisions were taken for the same follow-on product. In other parts of the world like India, Taiwan, Argentina and China follow-on versions of doxorubicin and amphotericin liposomes are on the market. But little information can be found on the registration criteria for these liposome products. So far, WHO has not come out with regulations, but the model of the World Health Organization (WHO) prequalification system could be considered.

In short, both in the EU and USA material has been published to guide both innovator and follow-on liposome product manufacturers to submit a dossier.

7.2. Glatiramoids

The glatiramoid class of drugs was presented by Dr. Weinstein. She focused on quality attributes of glatiramoids. Glatiramoids are non-biological complex drugs (NBCDs) comprising of a highly complex mixture of copolymers based on four amino acids (Ala, Tyr, Lys and Glu) of varying sequences and sizes obtained by a process of polymerization followed by partial hydrolysis. The first and most thoroughly studied glatiramoid, glatiramer acetate (Copaxone[®], Teva Pharmaceutical Industries, Ltd.) was approved for treatment of relapsing–remitting multiple sclerosis, an autoimmune disorder. Copaxone[®] is an extremely complex mixture of these four amino acid copolymers. Its components are neither fully identifiable nor quantifiable even by the most modern analytical techniques. The mechanism of action and the active components responsible for its clinical effect are still uncertain in spite of extensive research and a multitude of publications in peer-reviewed journals. Therefore, the entirety of the Copaxone[®] constituents is considered to be the API. The composition of Copaxone[®] is

Table 1
NCL assay cascade.

|  Physicochemical Characterization |  In Vitro Characterization |  In Vivo Characterization |
|---|--|--|
| <p>Size/Size Distribution</p> <ul style="list-style-type: none"> • Dynamic Light Scattering (DLS) • Electron microscopy (TEM, SEM, crvo) • Atomic Force Microscopy (AFM) • Field Flow Fractionation (FFF), SEC-MALLS <p>Composition</p> <ul style="list-style-type: none"> • TEM with EDS • Inductively coupled plasma-mass spec. (ICP-MS) • Spectroscopy (NMR, CD, Fluorescence, IR, UV-vis) <p>Purity</p> <ul style="list-style-type: none"> • Chromatography • Capillary Electrophoresis <p>Surface Chemistry</p> <ul style="list-style-type: none"> • Biacore • Zeta Potential <p>Stability</p> <ul style="list-style-type: none"> • Stability can be measured with any number of instruments with respect to time, temperature, pH, etc. | <p>Sterility</p> <ul style="list-style-type: none"> • Bacterial/vital/mycoplasma • EndotoxinCell uptake/distribution • Cell binding/internalization • Targeting <p>Hematology</p> <ul style="list-style-type: none"> • Hemolysis • Platelet aggregation • Coagulation • Complement activation • Plasma protein binding <p>Immune cell function</p> <ul style="list-style-type: none"> • Cytokine induction • Chemotaxis • Phagocytosis • Leukocyte Proliferation • Leukocyte Procoagulant activity <p>Toxicity</p> <ul style="list-style-type: none"> • Oxidative stress • Cytotoxicity • Autophagy | <p>Initial disposition study</p> <ul style="list-style-type: none"> • Tissue distribution • Clearance • Half-life <p>Immunotoxicity</p> <ul style="list-style-type: none"> • Local lymph node proliferation assay • T-cell dependent antibody response • Rabbit pyrogen test <p>Single and repeat dose toxicity</p> <ul style="list-style-type: none"> • Blood chemistry • Hematology • Histopathology (42 tissues) • Gross pathology <p>Efficacy</p> <ul style="list-style-type: none"> • Therapeutic • Imaging <p>Pharmacology</p> <ul style="list-style-type: none"> • Clinical Tx cycle • NP quantitation methods • PK parameters |

inexorably linked to its robust and tightly-controlled manufacturing process. Being a synthetic mixture of a variety of structurally related components, Copaxone® fulfills all criteria of a NBCD (see above).

Throughout the world, however outside the EU and the USA, purported follow-on versions of Copaxone® are available, e.g. Glatimer®, Escadra®, and Probioglat®. Publications (cf. Weinstein et al., 2015) compare the quality of these follow-on products with regard to physicochemical composition. Various techniques, including HPLC (high performance liquid chromatography), IEF (iso-electric focusing), CE (capillary electrophoresis), AFM (atomic force microscopy), DLS (dynamic light scattering) and two-dimensional IMMS (ion mobility mass spectrometry) show substantial differences between Copaxone® and the follow-on products, whereas Copaxone® batches fall within its inherent microheterogeneity range. The biological impact of Copaxone® versus the follow-on versions, was shown to be different as well, e.g. in transcriptional profiles (Towfic et al., 2014). There are also indications of ADR (adverse drug reactions) increase when Probioglat was used instead of Copaxone® in Mexico (Citizens Petition, 2014). Are these purported follow-on versions indeed similar to Copaxone®? These publications suggest that the answer is: No.

7.3. Iron carbohydrate complexes

The last NBCD product family to be discussed in this commentary is the family of the intravenously administered iron-carbohydrate colloids (Dr. Mühlebach). Iron-carbohydrate colloids are

- (1) non-biological complex drugs,
- (2) carbohydrate coated polynuclear iron(III)-oxo-hydroxide cores with a still unknown structure,

- (3) nanosized dispersions,
- (4) pro-drugs: highly reactive active Fe³⁺ to be released in a controlled manner upon administration,
- (5) the result of laborious, tightly controlled manufacturing processes.

In the body iron transport/storage is mediated through different specific proteins like transferrin and ferritin. The released iron is transported, distributed, and stored in reservoirs in the MPS/RES (mononuclear phagocyte system/reticulo-endothelial system). This distribution pattern is linked to their nanoparticulate properties which are dependent on their specific manufacturing process. If iron delivery is not targeted in the same way to defined structures, cells and pools, the iron product will show clinically meaningful differences. A changed product availability and disposition may cause iron overload or undesired storage (e.g. hemosiderosis) affecting efficacy and safety. Oxidative stress may occur when the biological acceptor proteins like transferrin are saturated. Labile iron, non-transferrin bound iron, consist of highly reactive species and may induce oxidative and/or nitrosative stress contributing to inflammation and apoptosis. This was shown by Toblli et al., 2012 and Toblli et al., 2015 in non-clinical investigations in non-anemic rats when comparing the originator iron sucrose and follow on products.

Iron carbohydrate complexes are made out of different mono- or polymeric “sugars” like sucrose, gluconate, dextran, carboxymaltose, isomaltoside or polyglucosorbitorol stabilizing the polynuclear oxyhydroxy core and affecting the kinetics and (dose) tolerance of the product. All these innovator's colloidal products are registered in the EU. Interestingly, some follow-on versions have been authorized via the generic regulatory pathway (national route/decentralized procedure) without considering the

consequences of their complex, colloidal/nanoparticulate structure. A number of studies appeared lately where the in vivo performance of follow-on versions (iron sucrose similars) of the iron-sucrose innovator product (iron sucrose innovator) was compared in clinical settings (Rottembourg et al., 2011; Martin-Malo et al., 2012; Stein et al., 2012; Lee et al., 2013). In clinical studies differences were found with an increase in ADR/reduction in efficacy in the case of the follow-on product. One may wonder on the basis of what documentation these follow-on versions were registered.

Is the situation changing? Recently, both EMA (EMA, 2011, 2013a) and FDA (FDA, 2013) have issued 'reflection papers' and 'draft guidance' documents, respectively, regarding data requirements. It is hard to understand with all the clinical relevant differences available and also with a referral procedure for all i.v. iron products in place (EMA, 2013b), that still market authorization of an iron carbohydrate follow-on version is granted by the bibliographic pathway in the EU. That happened in Sweden with new approvals of iron carbohydrate products (dextran derivatives) in their life cycle development (Cosmofer® and MonoFer®) and as consequence for Diafer®. The inappropriateness of approval via the bibliographic documentation route (article 10a of Directive 2001/83/EC 10a) for such colloidal NBCDs follow-ons was pointed out by Dr. Zoubek, an experienced regulatory consultant. Recently, the FDA contracted out a study on the comparison of the iron-gluconate innovator product and the follow-on version (FDA, 2015b). It calls for "a prospective, randomized, 2-way cross-over study to compare plasma NTBI (non-transferrin bound iron) levels in hemodialysis patients treated with the follow-on and reference drug" to evaluate the products, and, in addition, the FDA evaluation tools and – to gain more insight into pros and cons – a direct head to head evaluation for therapeutic and safety equivalence of such products.

8. Concluding remarks re non-biological complex drugs

When one compares the situation between biologicals and non-biological complex drugs one should recognize that there are, in principle, important commonalities between these two groups of medicines. Both are complex, difficult to characterize and the production process is key to obtain reproducible product attributes and subsequent the desired/defined in vivo performance. For innovator NBCD products, as for biologicals, this means that ample attention must be paid to these key aspects before the clinical test phase can be entered which is also mirrored by the stepwise approach indicated in the guidance and reflection papers of the FDA and EMA.

It is clear, that in particular in the EU the thinking and resulting paradigm shift regarding the handling of follow-on versions of biologicals compared to generic, small molecule compounds is way ahead of the situation around NBCDs. In Fig. 1 the NBCD route is drawn parallel to the biosimilar route with the same key word: 'totality of evidence', and one could add 'stepwise approach' to develop the product. In Europe the centralized procedure should be the mandatory route for submission of applications. But that has not been the real situation yet. Companies developing NBCD-follow-ons can still use the national or mutual recognition regulatory route and, as mentioned above, that may lead/led to the approval of 'NBCD-questionables'. Outside the US and Europe the situation may differ by country, but in general, there is little appreciation for the challenges the developers of a follow-on version of a NBCD face as illustrated by literature references in all three NBCD families discussed above. There are also national authorities, especially in some Asia Pac countries, that give market access to NBCD-similar/NBCD-questionables in the absence of the authorization of the innovator product.

Further, one can identify the same outstanding issues for NBCDs as for biosimilars: questions should be answered/actions undertaken, re: similarity between the regulatory views worldwide (role WHO?), re: comparability and product attribute drift, re NBCD-questionables, re extrapolation, re interchangeability and substitution, re naming.

There is a lot to be done!

9. Epilogue

This conference gave food for thought. The pharmaceutical science community should engage in answering the pending questions around complex drugs. We need even better tools in the analytical toolbox, better preclinical tests in vitro and in animals, but only if relevant, and last but not least to measure efficacy and safety in the clinic using the proper read-out parameters (new biomarkers?). And make sure this material is published both by the innovator and follow-on product manufacturers! The NBCD-working group, hosted at the Dutch Top Institute Pharma is stimulating dissemination of science based information and discussions on the regulatory aspects of NBCDs.

Finally, we should educate and train experts who understand and appreciate the complexity of this field. For biologicals there are ample teaching facilities/initiatives and relevant text books and dedicated journals. For NBCDs there is only a beginning (Crommelin and De Vlieger, 2015), but certain Journals like the Generics and Biosimilars Initiative (GaBi) are also starting to regularly publish material on NBCDs.

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