The therapeutic equivalence of complex drugs

Huub Schellekensa,b,* Ety Klinger,c,1 Stefan Mühlebachd,2 Jean-Francois Brin,e,3 Gert Stormf,g, Daan J.A. Crommelinf,g,h,i

a Department of Pharmaceutical Sciences, Utrecht University, P.O. Box 80.082, 3508 TB Utrecht, The Netherlands
b Department of Innovation Studies, Utrecht University, P.O. Box 80.082, 3508 TB Utrecht, The Netherlands
c Global Innovative R&D, Teva Pharmaceutical Industries, P.O. Box 8077, Netanya 42504, Israel
d Vifor Pharma Ltd., Flughofstrasse 61, P.O. Box CH-8152 Glattbrugg, Switzerland
e Pharmaceutical Customer Solutions, 46, Quai de la Rappée 75601, Sanofi-Aventis, Paris Cedex 12, France
f Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, UIPS, P.O. Box 80.082, TB Utrecht, The Netherlands
g Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands
h Dutch Top Institute Pharma, Galileiweg 8, 2333 BD Leiden, The Netherlands
i P.O. Box 142, 2300 AC Leiden, The Netherlands

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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 a cross-over volunteer study. However this generic paradigm cannot be applied to complex drugs as biologics and a number of other therapeutic modalities. For copies of biologics the European Medicine Agency and other regulatory agencies have introduced a new regulatory biosimilar pathway which mandates clinical trials to show therapeutic equivalence. However for other complex drugs such as the iron–carbohydrate drugs, low molecular weight heparins (LMWHs), liposomal drugs and the glatiramoids regulatory guidance is still mostly lacking. In this paper we will discuss (therapeutic) experience obtained so far with these different classes of ‘complex drugs’ and their specifics to provide scientific arguments and criteria for consideration for a regulatory framework for the market authorization for these type of drugs.

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1. Introduction

This paper is based on the presentations and discussion during the TI Pharma workshop on the therapeutic equivalence organized in Leiden, 7 October 2009. A follow-up workshop is organized during the EUFEPSS/AAPS meeting in New Orleans in 2010. The aim of the workshops and follow-up discussions with stakeholders including the manufacturers of original products as well as generics and biosimilars is a consensus paper about the scientific issues involved in showing therapeutic equivalence of complex drugs to support the development of harmonized regulatory pathways for generic/similar of these drugs.

This paper intends to give a global view about the difficulties involved in assessing the therapeutic equivalence of complex drugs by some examples and also outlines also a possible regulatory framework. The paper is not the consensus of the Leiden workshop but only reflects the opinion of the authors and want to contribute to the ongoing debate. The issues are highly controversial and are currently discussed at many levels, including most regulatory agencies. A number of guidelines are under development and official opinions have been made public, showing some fundamental differences between the approach by the FDA and the EMA.

2. The generic paradigm

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 (Al-Jazairi et al., 2008; Chen et al., 2001; Meredith, 1996). 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) have been established in a cross over volunteer study and do not require formal clinical efficacy and safety studies.

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 specific cases of a narrow therapeutic dose range the acceptance interval may need to be tightened. In rare cases a wider acceptance range may be acceptable if it is based on sound clinical justification and addressing in particular any safety or efficacy concerns for patients switched between formulations.

Based on criteria defined by the Biopharmaceutics Classification System, a waiver can be given for the bioequivalence study (PK) for oral formulations (Graffner, 2006; Faassen and Vromans, 2004). In these cases, in vivo PK studies are only needed when there is a risk for a possible difference in bioequivalence due to different formulations or excipients.

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 so far only been applied to products which can be fully characterized. For more complex molecules, which are difficult to characterize, such as proteins, low molecular weight heparins (LMWH), the glatiramoids, and the iron–carbohydrate drugs, the demonstration of bioequivalence requires an alternative approach.

3. Therapeutic proteins

Therapeutic proteins are the clinically most widely used class of drugs for which the classical generic paradigm cannot be used (Crommelin et al., 2005; Schellekens, 2005). The molecular mass of most of the therapeutic proteins varies from 5 to 150 kDa, which is 25–1000 times larger than the average small drug molecule. Nearly all therapeutic proteins are produced by living cells and these cells in general make mixtures of different proteins, e.g. by variation in the process of post-translation modification such as glycosylation.

Modified molecules lacking terminal amino acids by clipping or deamidation are also often found in therapeutic protein products. Modification as aggregation and oxidation may occur during storage which also can influence safety and clinical efficacy. In addition, protein products may contain process related impurities like host cell proteins which may add to the complexity of protein products.

There are many tools to analyze the structure and in vitro activity of therapeutic proteins (biologics). However because of their complexity there is no combination of techniques that can completely describe all structural features of a protein drug. The pharmacokinetic analysis of biologics requires a different type of analytical expertise and is often more demanding than the bioanalytical testing of standard generic drugs (Baumann, 2009). Currently, only limited data are available regarding the predictive value of PK studies for the clinical activity of biologics. The dose–response curve of biologics is often non-linear, bell shaped and/or protracted. Some of these products may be metabolized at the injection site or enter the lymph system directly from the injection site without entering the circulation. Also the presence of the endogenous homolog may alter the pharmacokinetic behavior of the exogenously administered biologic.

The most important difference between biologics and low molecular weight drugs is their immunogenicity (Baumann, 2009). Nearly all therapeutic proteins induce antibodies, irrespective of whether these proteins are (partly) non-human or completely human homologs. In many cases these antibodies have no biological or clinical consequences. However these antibodies may alter the PK of the proteins. Neutralizing antibodies may decrease efficacy or may induce severe side effects by neutralizing endogenous factors. So assaying for antibodies is an essential part of the PK evaluation.

Because with proteins it is impossible to show two products to be identical, the term ‘biosimilars‘ was introduced in the European Union, which in 2004 adopted legislation to establish a comprehensive regulatory pathway for bringing biosimilars to the market (Moors and Schellekens, 2010).

Therapeutic proteins may differ from each other in that the reference product is unique and each product is identical to the reference product. In contrast, biosimilars are defined as biological products which are similar, but not identical, to reference products. They are submitted for separate marketing approval following patent expiration. To be allowed on the market the biosimilar product should be shown to be similar to the reference product in terms of quality, safety, and efficacy. Based on advice by the EMA/CHMP, the European Commission has approved biosimilar versions of recombinant somatropin, recombinant human EPO (rHuEPO) and filgrastim (status July 2010) (Moors and Schellekens, 2010).

Comparative pharmacokinetic data are also expected in a biosimilar marketing application. According to the EMA/CHMP guidelines the 80–125% acceptance range for classical drugs does not apply to biosimilars and a range specific for the product should be predefined and justified. However, for many if not all biotechnology derived therapeutic proteins, this is either impossible or needs extensive clinical trials (Moors and Schellekens, 2010).

Such pathway still does not exist for complex drugs. A forum of experts from industry, academia and RA gathered together in Leiden to discuss the potential issues and hurdles associated with the approval of follow-on complex drugs and drafted some recommendations for specific products, e.g. LMW heparin, liposomal drugs, glatiramoids and iron–carbohydrate complexes (iron sucrose).

4. Low molecular weight heparins (LMWH)

The complexity of LMWHs is given from the starting material. UFH (unfractionated heparin) is an incompletely characterized heteropolymer of 48 theoretical disaccharide variants (building blocks), extracted and purified from animal mucosa. LMWHs are obtained through specific and proprietary depolymerization processes of UFH with each process resulting in a distinct end product. LMWHs are comprised of a mixture of thousands of oligosaccharides (complex sugars) also incompletely characterized and which may differ between copies.

Each product displays a large spectrum of anticoagulant and non-anticoagulant properties. Structure–activity relationships have not been fully established due to an inability to separate the entire oligosaccharide mixture into individual and fully characterized oligosaccharides.

In Europe, in June 2006, as per the CHMP Biosimilar Working Party (BWP) recommendation, the Coordination Group for Mutual recognition and Decentralized procedures–human (CMDh) identified Low Molecular Weight Heparins as biological medicinal products. The CHMP released a specific guideline in March 2009 addressing the non-clinical and clinical aspects of the development of similar biological medicinal products containing LMWHs (European Medicines Agency, 2009).

In contrast, the US FDA currently regulates LMWHs and other product classes such as insulins or human growth hormones as drugs and not as biologics, mainly for historical reasons. Nevertheless, the FDA has recognized that LMWHs are not fully characterized and that the classical criteria applied to standard generic drugs are inadequate for these products. Recently the FDA approved a generic LMWH and described the evaluation criteria
that were considered for this decision (US Food and Drug Administration). FDA has yet to rule on several other abridged applications for generic LMWHs pending since 2003.

The worldwide heparin demand for 2009 is estimated to be 800 million doses requiring 1.2 billion pig gut mucosa, a figure that approaches the total worldwide pig production. Therefore, the complete pharmaceutical control of the sourcing is mandatory as the bulk product stability and process performance requires a first heparin extraction step is done locally in large scale prearranged facilities. This was evident from the 2008 heparin contamination case from China raw material with OSCS (Over Sulfated Chondroitin Sulfate) resulting in a significant number of fatal cases and resolved by an updated pharmacopoeia monographs. LMWHs manufacturers must guarantee an exclusive use of controlled sources and quality assurance resulting in a full traceability from the slaughterhouse to the finished product.

There is currently no enabling technology to completely characterize LMWHs and to conduct a full pharmaceutical comparability (equivalence) exercise. Even if specific differences in the PK and PD profile between UFH and LMWH exist, no classical PK profile may be determined for LMWHs due to the multi-component composition (heterogeneity) and (a) PD (pharmacodynamics) biomarker(s) as surrogate(s) is needed. The inhibition of activated Stuart factor (anti-factor Xa activity) and the inhibition of thrombin activation reflect the main anticoagulant activities of LMWH, but these correlate poorly with clinical outcomes and are not predictive of the PK profile of each of the active ingredients present in the mixture.

As a first part of the therapeutic (and safety) comparability exercise in humans, CHMP Guidelines on biosimilar LMWHs recommend for PK/PD comparison a randomized single dose two way crossover study using SC (and depending on the case, IV) administration in healthy volunteers measuring a variety of biomarkers (anti-Xa, anti-IIa, TFPI, etc.). We recommend investigating both low and high dosages to reflect the approved use and to take into account the non-linearity of the dose–response curves. Patients with severe renal impairment should also be considered in this evaluation in order to detect possible differences not detected in healthy volunteers. An acceptable range for such a comparability exercise would be similar to that for bioequivalence (80–125% of the innovator product).

Heparin products, including LMWHs, can elicit immunogenicity reactions like the Heparin Induced Thrombocytopения (HIT). The incidence of developing HIT antibodies is estimated up to 8% of heparinized patients and less than 1% for those exposed to LMWH (Ranchini, 2005). Approximately 1–5% of patients on heparin will progress to develop HIT with thrombocytopения, at least one-third suffering from thrombosis (Ranchini, 2005). Considering the vast number of patients exposed to heparins, HIT is a common drug-induced immunologic response. CHMP recommends following the Immunogenicity Guidance (CHMP/14327/06) for LMWHs. In addition to that guidance, we recommend that the assays for HIT antibodies be carefully standardized based on serum from patients with HIT.

The criteria recently described by the FDA for approving a generic LMWH do not include a head-to-head clinical trial vs the reference product (US Food and Drug Administration). In contrast therapeutic equivalence (clinical efficacy) according to CHMP should be demonstrated through at least one adequately powered, randomized, double-blind, parallel group clinical trials. Because of the high prevalence of Venous Thrombo-Embolism (VTE), a trial should be preferably conducted in patients undergoing major (orthopedic) surgery and should follow a strict equivalence design. The CHMP request for such a trial on top of a thorough comparability exercise, probably results from the fact that LMWHs are not fully characterized and that their structure–effect relationship is not fully elucidated. The clinical trial is aimed at assessing the clinical relevance of the differences both detected and undetected during the comparability exercise. Following demonstration of therapeutic equivalence in one indication in surgical patients at high risk of VTE (Prevention of Venous Thrombo-Embolic, as described above), CHMP guidelines indicate that extrapolation to all other indications may be acceptable if appropriately justified. It must be stressed that LMWH for prevention of VTE, but also for treatment of venous and arterial thrombosis with different dose regimens and/or routes of administration due also to major differences in the pathophysiology of venous and arterial thrombosis. Venous thrombosis mainly related to clot formation, whereas platelet adhesion/aggregation and inflammatory response are critical to arterial thrombus formation (Buffon et al., 2002). Some heparins exhibit anti-inflammatory activity involving interactions with pathways independent of AT like P-selectin, proteins of the complement system, and the contact-kinin system (Hostettler et al., 2007; Ludwig et al., 2006). Recent discoveries suggest that some oligosaccharides considered as “passive” ingredients for VTE prevention because they do not contain the classical AT binding site, exhibit pro-fibrinolytic activity and therefore would become “active” ingredients in presence of an existing clot (VTE or Acute Coronary Syndrome treatment). Consequently, justification of any extrapolation between the clinical outcomes in VTE prevention and clot treatment, as well as between the venous and arterial settings remains a complex issue. Therefore, biosimilarity between two LMWHs should be probably established rather in separate studies for prevention of VTE and for treatment in an arterial indication.

LMWHs have its own active ingredient structure and demonstrate a unique clinical profile as a result of their manufacturing process. As a consequence regulatory bodies such as FDA, as well as medical societies consider LMWHs as non-interchangeable (Ryan et al., 1999: US Food and Drug Administration).

The FDA has determined that the recently approved generic LMWH can be substituted for its reference product (US Food and Drug Administration).

Within the different CHMP guidances there is no specific recommendation regarding substitution and interchangeability of biosimilar products. In a Q&A document issued by the EMA it is stated that “since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional” (European Medicines Agency, 2008). However ultimately substitution rules are under the direct supervision of the national Health Authorities of the member states. As of today 17 states implemented specific rules preventing automatic substitution.

5. Liposomal drugs

Liposomes have been discovered more than 40 years ago, and represent a successful example of a particulate drug delivery system and a lot of literature is available. A list of recommended literature is added in the list of references (Maurer et al., 2001; Gabizon et al., 2003; Zuidam et al., 2003; Gregoriadis, 2007; Drummond et al., 2008).

Liposomes are vesicles composed of one or more phospholipid bilayers surrounding an aqueous compartment and can be formed from a great variety of lipid constituents. They have been shown to be able to accommodate a broad spectrum of different drug molecules widely varying in their physico-chemical properties. Examples include marketed intravenous formulations of anthracyclines encapsulated in liposomes (e.g. Doxil® (Caelyx® in Europe), Myocet®, and Daunoxome®). The objective here is to alter the
pharmacokinetics, tissue distribution, and the bioavailability profile so as to achieve a positive impact on the drug pharmacodynamics, i.e. to obtain an increased therapeutic index resulting from improved efficacy and/or reduced side effects. As commercial preparations have been available for more than a decade, the development and approval of generic formulations and therefore the issue of bioequivalence is receiving increasing attention.

Drug molecules can interact with the hydrophilic head group exterior of the bilayers, the hydrocarbon tail interior of the bilayer, and/or be dissolved in the aqueous compartment(s). It should be realized that liposomal particles are by far not all alike. They differ because of the many possibilities to vary the composition and thereby the physicochemical characteristics such as size, charge, bilayer fluidity, number of bilayers, hydrophilicity of the external surface, and the attachment of hydrophilic polymers and/or targeting ligands to the external surface.

Following years of extensive studies, many aspects of liposomal preparations are increasingly understood. This understanding has been made possible by several developments, three in particular:

1. availability of high quality commercial lipid supplies,
2. availability of robust preparation techniques (also for large scale production),
3. numerous analytical methods for characterization of properties critical for a solid understanding of many structure–function relationships.

In contrast to other examples of ‘complex drugs’ discussed in this report, we propose that the classical bioequivalence approach (i.e. evaluation of pharmacokinetics as surrogate for pharmacodynamics) used for the approval of oral dosage forms may be applied for the approval of generic liposomal formulations (non-vaccine based), if properly adapted. The dominant factor determining efficacy and safety of the liposomal drug formulation is the rate and extent of drug release from the liposomal particles upon administration to the patient. While several reports have described approaches allowing the study of drug release from liposomes circulating in the bloodstream, the study of in vivo drug release kinetics in tissues is much more difficult to assess as adequate analytical tools are lacking. Therefore, the question whether the generic formulation has an equivalent drug release profile when compared to its reference product, should rather be approached at the level of equivalence of composition and physicochemical characteristics of the product. This is warranted as it is well established within the liposome field that the in vivo fate of drug-containing liposome particles, including the drug release kinetics, are governed by both composition and physicochemical characteristics of the liposomal particles.

Speakers from the United States Food and Drug Administration (US FDA) have expressed (e.g. speech by Gottlieb in 2006) that the assessment of the bioequivalence of a “generic” or “similar” liposome product for comparison with its reference product presents several difficult issues, as liposomes represent a relatively new, complex drug type. Previously, the US FDA provided a draft guidance document for development of liposomal therapeutic preparations in 2002, which recognizes that they pose “unique technical aspects of liposomal drug products”. More recently, the US FDA has issued a draft guidance for bioequivalence determination of liposomes containing doxorubicin hydrochloride (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf). A generic liposome product should have the same physicochemical characteristics as the reference product, as is true in general for any generic, and therefore the complex parameters established as critical for liposomal drugs need to be addressed. Nonetheless, most if not all key aspects for replication of an approved liposomal therapeutic are well understood, by virtue of the extensive collective experience that has been built up over the years within the industry and within academia. While all the aspects for preparing and adequately documenting replication of a liposomal drug bioequivalent to a reference product may be challenging, the necessary scientific foundation exists for this to be accomplished. Note that the preparation methods are not simple, neither are the needed characterization methods for release of raw materials, in process testing, and release of the product. The documentation required to support regulatory approval of a bioequivalent liposomal drug should be extensive and detailed enough to warrant the conclusion that the generic product can be viewed as effective and safe as the reference product. To this end, both pharmaceutical and bioavailability equivalence criteria should be met.

One can envisage two scenarios regarding the requirements to be set for the approval of generic liposome products:

1. If the manufacturer of the generic product has decided to follow a ‘sameness’ approach by preparing the generic such that it is pharmaceutically equivalent to the originator’s product in terms of chemical composition and physicochemical properties, including the use of the same raw materials from the same suppliers, etc. then this can be adequately confirmed with the technological/analytical tools nowadays available. In principle it would suffice for crediting bioequivalence in this case, if the clinical pharmacokinetic studies would also show equivalence within the acceptance margins.

2. However, if the manufacturer can not adopt the sameness approach and has to follow a ‘similar-but-not-the-same’ approach by lack of materials and/or information in the public domain, and has altered for example the excipients (e.g. by using another saturated phospholipid if the originator’s lipid material is not available), then additional non-clinical studies would also be required to provide additional certainty. Such studies would include the determination of pharmacokinetics, tissue distribution, and antitumor activity profiles of the generic product vs. the reference product in suitable animal models, prior to the start of clinical bioequivalence studies.

6. Complex iron–carbohydrate (“iron–sugar”) drugs

Venofer® (iron–sucrose [IS]) is the main representative of the iron-oxyhydroxide carbohydrate drugs, a class of colloidal IV iron preparations (Crichton et al., 2008). For the treatment of iron deficiency anemia associated with chronic kidney disease (dialysis and pre-dialysis), in pregnancy, through malabsorption, autologous blood donation and other conditions, mostly with high prevalence in the population.

The physico-chemical properties and thus the pharmacological activity of these high molecular polymer iron complexes are strongly dependent on the extensive, multi-step manufacturing process (Toblli et al., 2009a). There is a large number of parameters that can be varied during the manufacturing process that determine the nature of the resulting iron sucrose complex (e.g. starting materials, synthetic pathway, reaction time, reaction temperature, etc.). Depending on the manufacturing conditions a variety of different iron–sucrose complexes may be produced. Differences in the structure, the molecular weight distribution and the stability of the iron-oxyhydroxide core, of the iron–sucrose complex, and of other characteristics may result. Therefore, the ISS (iron–sucrose-similars) may ultimately have different efficacy and safety characteristics which in part may be due to the manufacturing process and the resulting different complex stabilities essential for iron release.
Iron complexes are capable of redox cycling, which results in the formation of highly reactive hydroxyl radicals interacting with molecules and biological structures (DNA, proteins, lipids, etc.) and ultimately leading to oxidative stress (Van Wyck, 2004). Oxidative stress represents an imbalance between production of ‘reactive oxygen’ and the capacity of the biological system to detoxify reactive intermediates and/or to readily repair the resulting damage.

The specific iron-ligand-interaction and complex structure defines the stability and the reduction potential of the iron(III) complex, which determines whether and to what extent redox cycling can take place under physiological conditions. Two non-clinical studies have shown that three different ISS had higher positive reduction potentials for conversion of Fe(III) to Fe(II) than Venofer® Toblli et al., 2009b; Bishu and Agarwal, 2006. This indicates that these ISS would more readily undergo redox cycling with increased oxidative stress under physiological conditions compared to the IS originator Venofer®.

The characteristics of these iron compounds used in intravenous preparations depends in particular on the interaction between the iron(III)-hydroxide core and the surrounding carbohydrates. Less stable compounds contain significant amounts of weakly bound iron that rapidly saturates transferrin and leads to the generation of redox-active non-transferrin bound iron (NTBI). Chandler et al., 2001. The incidence of adverse effects following intravenous iron administration has been shown to correlate with transferrin saturation and the amount of NTBI (Beshara et al., 1999). The results of the physico-chemical analysis in the two studies mentioned above, showed that not all the parameters measured for the tested ISS comply with those of Venofer®. Thus, the ISS are not identical and may have different complex stabilities lending further support to potential safety concerns.

Results of these non-clinical studies demonstrate that subtle structural modifications may affect the stability and reactivity of macromolecular iron-sucrose complexes with safety implications as a result. Even compliance with existing physico-chemical analysis (pharmacopoeia) do not allow to fully characterize an IS complex and to show pharmaceutical identity.

Very recent clinical data in so far stable hemodialysis patients showed a significant destabilization of hemoglobin and related parameters after the substitution of Venofer by an ISS needing significantly higher doses of ESA (+20%) and ISS (+30%) compared to the originator period to reach again the target hemoglobin levels (Rottembourg et al., 2010).

Therefore, if the comparability of the pharmaceutical quality of a copy is established then at least a comparison of safety studies in rodents following a properly designed protocol (dose, duration, frequency) would be required. Assuming these studies show lack of induction of oxidative stress which may be associated by subtle differences which escape the physical chemical characterization, the product may be accepted as therapeutic equivalent to the reference product. In order to show interchangeability clinical data have to be considered.

Should the similar product show physicochemical characterization differences compared to the reference product, then clinical data are needed, including ⁵⁹Fe incorporation into RBC as PD marker (Beshara et al., 2003).

7. Glatiramoids

The prototype glatiramoid is Copaxone® approved for the treatment of relapsing-remitting multiple sclerosis (RRMS); containing the active substance glatiramer acetate (GA), which is classified as a chemically synthesized active substance. GA is a complex heterogeneous mixture of polypeptides with immunomodulatory activity (Aharoni et al., 2000; Schrempf and Ziemmsen, 2007; Sarasella et al., 2008; Hestvik et al., 2008; Begum-Haque et al., 2008; Liu et al., 2007). Until recently GA was the only member of the glatiramoid class, a family of synthetic copolymer mixtures containing four amino acids l-glutamic acid, l-alanine, l-lysine, and l-tyrosine, in a defined range of molar ratio (Wolinsky, 2004).

GA and other glatiramoids contain an almost incalculably large number of amino acid sequences (×10³⁶ possible theoretical sequences exist in GA). The consistency of polypeptide sequences within GA is dependent on a well-controlled proprietary manufacturing process. No two glatiramoid mixtures prepared by different manufacturers can be shown to be “identical” and new glatiramoids must be considered distinct NCEs of the class. Based on extensive studies of the correlations between the chemical, immunological, and biological properties of Copaxone® a series of well-controlled manufacturing processes and rigorous testing procedures-developed specifically for GA analysis were designed and implemented to ensure the batch-to-batch consistency, safety and efficacy.

The actual active sequences or structures (epitopes), within the complex mixture of GA, that are responsible for the efficacy and safety of the product are unknown. It is currently impossible to isolate and identify the active amino acid sequences in GA, even using the most technologically sophisticated multidimensional separation techniques. Copaxone® is believed to act by modifying immune processes thought to be involved in the pathogenesis of multiple sclerosis (MS). The precise mechanism(s) of action of the active sequences in the GA mixture and their specific effects on the immune system are still not fully elucidated. However, it is well established that the clinical effects of GA are mediated by immune cells. The drug’s multi-epitopic nature may be the source of its widespread biological and clinical activity. The heterogeneous and complex character of GA may be essential attributes that are needed to address the extraordinary complexity of the immune system itself and the inherent diversity seen in the immune systems of MS patients with unique genetic backgrounds (Varkony et al., 2009; Dhib-Jalbut, 2003; Arnon and Aharoni, 2004).

Glatiramoid products present a much more complex picture than the scenario for most biological products. Minor differences in the manufacturing process can produce altered polypeptide sequences, which are likely to affect the safety and efficacy of the product. Minor changes introduced in the manufacturing process of GA result in a new glatiramoid product (denoted TV-5010 or protiramer) that cause significant toxic effects in animals, especially in long-term, repeat-dose studies (Wolinsky, 2004). Therefore, it is not possible to predict the toxicity of a glatiramoid from its structural characteristics or bridging, shorter-term (subacute or subchronic) toxicity studies.

Results from studies with TV-5010 also showed an altered immunogenicity profile and increased potency to that of GA (Wolinsky, 2004), suggesting that the structural differences may affect the immune response, and as a consequence a complete analysis of the immunogenicity profile of any glatiramoid should be examined as part of the non-clinical and clinical studies.

GA affects immune cells in an antigen-specific way; that is, GA administered subcutaneously daily over many years works as an antigen-based therapeutic vaccine (Varkony et al., 2009; Dhib-Jalbut, 2003). The currently available data suggest that a substantial fraction of the therapeutic GA dose is hydrolyzed locally at the site of injection. GA interacts with peripheral blood lymphocytes (PBLS) locally at the site of injection, and the immune response is secondarily manifested as a systemic distribution of activated GA-specific T cells. T cells produced in the periphery cross the blood–brain barrier, accumulate in the CNS and induce anti-inflammatory and neuroprotective effects (Nicola et al., 2009). Thus, systemic distribution of the drug is irrelevant to effects following SC administration and systemic concentrations of GA or its metabolites are not indicative of drug activity or exposure to the immune system.
When PK testing is not informative, surrogate measures, for example, the pharmacodynamic (PD) effects of the drug, may be sought to establish bioavailability or bioequivalence. There are consistent immunological PD effects associated with chronic administration of Copaxone®. All MS patients treated with Copaxone® develop anti-GA specific antibodies (Ziemssen et al., 2002). Additionally, Copaxone® polypeptides stimulate peripheral blood lymphocytes (‘‘PBLs’’) in MS patients. Upon repeated exposure to Copaxone®, the specific proliferative response of PBLs decrease and GA-specific T cells shift from a TH1 (pro-inflammatory) to a TH2 (anti-inflammatory) phenotype. These PD parameters are indicative of immunoavailability. However, no correlation or validation between these PD-markers and clinical efficacy has been established (Varkony et al., 2009; Brenner et al., 2001; Chen et al., 2001).

GA is not considered a biologic and therefore the EU biologics and biosimilar legislation and regulatory pathway is not applicable. For any glatiramoid similar a detailed physical and chemical, biological and immunological characterization is necessary to show similarity with Copaxone. Considering the experience with serious long term toxicity in animals with glatiramoids developed, any similar should undergo long term toxicity in two species. This is in contrast to what is expected for a biosimilar in the EMA regulatory pathway.

As discussed the outcomes of PK studies with Copaxone are not related to PD effects, excluding bioequivalence studies to show the clinical equivalence of a glatiramoid similar. To be able to use PD studies as alternative for a comparative clinical trial, PD markers for clinical efficacy for glatiramoids should be developed on the basis of the biological activities described for Copaxone which are related to clinical activity, e.g. immunogenicity, T cell proliferation, cytokine secretion or other immunological markers. Similarity should be based on at least two properly validated PD markers. Standardization and validation of the antibody assays and assays for the PD markers is essential to use the PD markers for regulatory purposes.

As long as validated PD markers for clinical efficacy are not available, clinical efficacy of glatiramoid similars should be established in a three arm clinical trial in relapsing-remitting multiple sclerosis (RRMS) patients. The clinical trial should include a placebo arm because of the variable clinical course of MS, a second entry glatiramoid arm and a third arm treated with the reference medicinal product (Chen et al., 2001).

Testing for antibodies to the glatiramoid biosimilar is needed to exclude unwanted immunogenicity associated with adverse events and/or neutralization of efficacy. Because RRMS is the most sensitive clinical condition, extrapolation to other indications may be considered acceptable.

8. A regulatory framework for complex products

The regulatory approach for the authorization of generic products is based on the principle that two small molecule drugs are considered therapeutically equivalent if their active substance is shown to be structurally identical and their PK characteristics are equivalent. In this report we have discussed whether this classical generic paradigm applies to complex drug classes of biologics, the LMWH, glatiramoids and iron–carbohydrate complexes.

For biologics the EMA has pioneered a comprehensive biosimilar regulatory pathway, the principles of which are being followed by an increasing number of regulatory bodies in the world including WHO. The principles of this regulatory approach include full documentation of the quality and the inclusion of preclinical and clinical data, the extent of which depend on the type of biologic. In addition an extensive comparison of biosimilar and reference product needs to be performed showing the products to be similar in quality, safety and efficacy with an emphasis on immunogenicity issues. Extrapolation of the efficacy data to other indication is possible according to the EMA regulations, if the mode of action in the indications is considered to be the same. For biosimilars also a post marketing risk management program is mandatory.

The EMA has defined biologics as products of living cells. So the biosimilar pathway regulates nearly all therapeutic proteins and includes the low molecular weight heparins which are considered drugs by the FDA. However for the reasons discussed, we consider the EMA position the right regulatory approach for LMWH.

Concerning the other classes of complex drugs, we have the iron–carbohydrate (iron–sucrose) and the glatiramoids as extremes of complexity. Liposomes contain well characterized active substances in a vesicular carrier system with a well characterized

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**Fig. 1.** Algorithm for authorizations of copies (therapeutic equivalence): comparability of complex products by the similar pathway.
chemical structure intended to target drug delivery. The classical generic approach covers these issues sufficiently.

The glatiramoids cannot be completely characterized, have a complex mode of action which is not completely understood and do not appear in the circulation and do not have validated PD markers for clinical efficacy. In additions these products are highly immunogenic and can exert toxic effects depending on the production process. For the glatiramoids therapeutic equivalence can only be shown by the biosimilar-like approach.

The iron–carbohydrate complexes are different to the glatiramoids. These complex products can be characterized but not to the extent, that small differences are reflected by the so far existing physical chemical characteristics (pharmacopoeia), so this characterization fails to predict important biological effects like the oxidative stress which results from free iron as a result of a too fast release of iron from the complex. To evaluate therapeutic equivalence of two iron–carbohydrate complexes, the safety of the products should be evaluated in both animal as well as clinical studies.

It is difficult to define a regulatory pathway which covers all possible complex products. However a case-by-case approach is also unsatisfactory from a regulatory point of view. In our view the generic approach should be limited to products which can be fully characterized and of which the physical–chemical characteristics predict the biological effects and PK data can be used as a surrogate for clinical efficacy.

For all other products the biosimilar-like approach should be applied (Fig. 1), which is mostly established for proteins, but not for non-protein large or multisource products. This approach could be modified depending on a number of factors:

- Validated PD markers, if available, may be used to assess clinical efficacy compared with the reference product.
- Indications may be extrapolated if the mode of action is identical.
- Animal models may be used for therapeutic equivalence studies if predictive for safety and/or efficacy.
- Clinical studies are necessary to show substitutability (interchangeable products).

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