

Regulatory Framework and Challenges for Approval of „Generic“ Non-biological Complex Drugs (NBCDs)

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List of Abbreviations

Ala	L-alanine
ANDA	Abbreviated new drug application
AUC	Area under the curve
AUC _t	Area under the plasma concentration-time curve from time zero to time t
BE	Bioequivalence
CDER	FDA's Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
C _{max}	Maximum (peak) plasma drug concentration
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
DCP	Decentralized procedure
EAE	Experimental autoimmune encephalomyelitis
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FDA	Food and Drug Administration
GA	Glatiramer acetate
Glu	L-glutamic acid
ISS	Iron sucrose similars
kDa	Kilodalton
LMWH	Low molecular weight heparins
Lys	L-lysine
MBP	Myelin basic protein
MRI	Magnetic resonance imaging
MRP	Mutual recognition procedure
MS	Multiple Sclerosis
NBCDs	Non-biological complex drugs
NDA	New drug application
NtA	Notice to Applicants
PD	Pharmacodynamic

PE	Pharmaceutical equivalence
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
RLD	Reference listed drug
Tyr	L-tyrosine
US	United States of America
USP	United States Pharmacopoeia

Abstract

In the recent years a new category of medicinal products, the so-called non-biological complex drugs (NBCDs) have received increasing attention. This diverse group contains medicinal products of chemical origin, which may be even more complex than biological products. Unlike for small-molecule generics and biosimilars, there is no dedicated regulatory pathway available for the approval of follow-on (“generic”) NBCDs. In the past, this caused controversial discussions on the required scientific data for applications and resulted in lengthy approval procedures.

In this thesis, the approval history of three examples of NBCD follow-on products for iron sucrose, glatiramer acetate and the low molecular heparin enoxaparin in Europe and the United States are compared. Since the approval of the first iron sucrose similars with questionable equivalence, much progress has been made. Within each jurisdiction, there seems to be consensus on the legal basis for the regulatory approval. Product-specific guidance documents for some follow-on NBCDs were developed, which help applicants to identify the expected data required for approval.

In Europe, NBCD follow-on products are usually approved under the Article 10(3) legal basis. As with biosimilars, NBCD comparability is assessed in a stepwise approach, starting with a comprehensive characterisation of the quality parameters, followed by non-clinical and clinical studies. The extent of the non-clinical and clinical studies depends on the weight of evidence obtained in the previous steps and therefore is determined on a case-by-case basis.

In the United States, the NBCD follow-on products are filed as abbreviated new drug applications (ANDAs). The U.S. FDA puts great emphasis on demonstration of active ingredient sameness and applies very stringent quality equivalence criteria, up to equivalent manufacturing procedures, to avoid the need for clinical efficacy studies. However, this approach may prevent the development of similar products with minor quality differences without clinical relevance.

Despite the different regulatory procedures and standards between Europe and the United States there seems to be a progress towards harmonized scientific requirements across jurisdictions. An overarching European guidance document, outlining the general principles for approval of NBCD-similars, could provide further guidance and help applicants in the development of these products.

1 Introduction

For many years, medicinal products derived from small, chemically manufactured active substances were the standard. Small molecule medicines still account for most medicinal products available today. Regulatory pathways for approval of small molecule medicines and their generic versions are well established across the globe.

In the recent years, new medicinal products derived from biological substances entered the market. These biological medicines (biologics), which are produced by or extracted from a biological source, often consist of large molecules with a complex structure, e.g. large recombinant proteins like monoclonal antibodies.

Besides these two established categories for medicinal products, the biologics and medicines derived from chemically well-defined small molecules, another group of complex drugs, the so-called non-biological complex drugs (NBCDs) came into the focus recently. NBCDs are not derived from biological sources, and therefore do not fulfil the definition of biologics. Instead, NBCDs are chemically synthesized. Like for biologics it is however not possible to fully characterize the complex structure.

Unlike for small-molecule generics and biosimilars, there is no dedicated regulatory pathway available for the approval of follow-on (“generic”) NBCDs. In the past, this was a cause for controversial discussions on the required scientific data, resulting in lengthy approval procedures.

The aim of this thesis is to review the approval procedures for follow-on NBCDs in Europe and in the US, to have a look at the developments in the recent years, and to see whether any additional measures could be taken to reduce the uncertainties on the approval path.

In the following sections, additional background information is provided and examples of NBCDs and their approval pathways in Europe and in the U.S. are reviewed.

2 Background Information

2.1 Non-biological complex drugs – a new category of medicinal products?

In 2009, an NBCD Working Group was founded in Amsterdam, with the aim to bring members of the pharmaceutical industry, international experts and academia together to initiate discussions among stakeholders and increase awareness for the NBCD topic (Lygature.org, 2018).

The terminology of NBCD was introduced first in 2011 to account for this group of products with a complex chemical structure such as iron-carbohydrate drugs, glatiramoids, liposomal drugs and low molecular weight heparins (LMWH) (Schellekens, et al., 2011). The following definition was proposed (Schellekens, et al., 2014):

“A non-biological complex drug is a medicinal product, not being a biological medicine, where the active substance is not a homo-molecular structure, but consists of different (closely related and often nanoparticulate) structures that cannot be isolated and fully quantitated, characterized and/or described by physicochemical analytical means. It is also unknown which structural elements might impact the therapeutic performance. The composition, quality and in vivo performance of NBCD are highly dependent on manufacturing processes of both the active ingredient as well as the formulation.”

It should be noted that “NBCD” is not a formally recognized category of drug products and the term is neither found in the European Union (EU) pharmaceutical legislation, nor in the United States (U.S.) Food and Drug Administration (FDA) guidance documents. The FDA rather uses the term of “complex drug products” and “complex generics” (Lionberger, 2013).

In this thesis, the term “follow-on NBCDs” is generally used for copy versions. Depending on jurisdiction and approval path also “generic NBCDs” and “NBCD-similars” may be used.

Table 1 below shows some of the characteristics of small molecule drugs, NBCDs and biologicals.

Table 1: Characteristics of small molecule drugs, NBCDs and biologicals

	Small molecule	NBCDs	Biological
Synthesis	Chemical synthesis	Chemical synthesis	Biological source
Molecular weight	Low molecular weight	High molecular weight	High molecular weight
Structure	Well defined	Complex, heterogenous	Complex, heterogenous
Manufacturing process	Mostly process-independent	Strongly process-dependent	Strongly process-dependent
Stability	Stable	Partly	Unstable, sensitive to external conditions
Immunogenicity	Mostly not	Partly	Yes
Mode of action	Known	Not fully clear	Not fully clear

Sources: (Declerck, 2012), (de Vlieger, et al., 2015)

NBCDs are not derived from living organism via biotechnology, therefore they do not meet the definition of biologicals, but as can be seen in Table 1, they share quite some characteristics with biological medicinal products (de Vlieger, et al., 2015):

- High molecular weight and complex structure – more complex than small molecules and sometimes even more complex than biologicals
- Product is strongly process-dependent – the process is the product
- Mode of action is not fully clear

Examples for nonbiological complex drugs include:

- Low molecular weight heparin, e.g. enoxaparin¹
- Glatiramoids
- Iron carbohydrate complexes
- Liposomal products

¹ EMA classifies LMWH as biologicals, whereas the U.S. FDA classifies them as NBCDs

Figure 1 gives an overview on the positioning of NBCDs in the landscape of medicinal products and the challenges to assess therapeutic equivalence between the reference product and the generic product. For small molecule drugs (shown in orange) the demonstration of bioequivalence (BE) and pharmaceutical equivalence (PE) is quite simple. For biologicals (shown in green) it is more difficult to demonstrate BE and especially PE. The graph shows also several other complex drugs, for which PE can be shown relatively easy, whereas demonstration of BE becomes more and more challenging. For most NBCDs (shown in blue) the demonstration of both PE and BE is very challenging. The classification of albumin-bound nanoparticles and LMWH differs according to jurisdiction with FDA classifying follow-on products of LMWH as complex generics while the EMA applies biosimilar rules (Hussaarts, et al., 2017) (FDA, 2016).

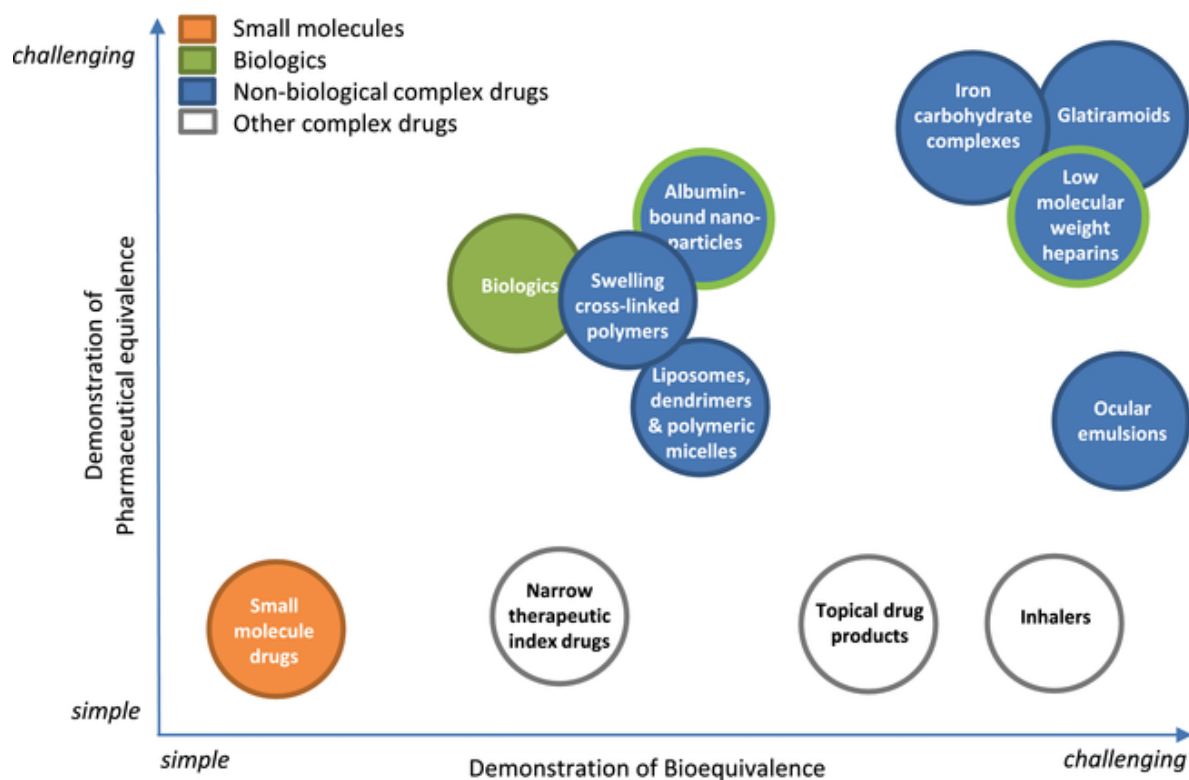


Figure 1: The complex drug landscape. From: (Hussaarts, et al., 2017)

With the first follow-on versions of NBCDs seeking approval, a discussion started on the appropriate regulatory approval path for these products. The options for abbreviated approval procedures are briefly reviewed in the following section.

2.2 Abbreviated approval pathways for follow-on products

2.2.1 Abbreviated procedures in Europe

Once the data protection of a medicinal product is expired, it is possible to apply for a marketing authorization of a follow-on product via an abbreviated procedure. Article 10 of Directive 2001/83/EC regulates the possibilities for generic, hybrid and biosimilar applications (Directive 2001/83/EC, 2012).

➤ **Article 10(1) applications - Generic medicinal products**

A generic medicinal product has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference product (pharmaceutical equivalence, PE). The applicant must provide full data on the pharmaceutical quality of the generic and demonstrate bioequivalence (BE) between reference and generic medicinal product, i.e. the same amount of the active substance is released at the same rate under similar conditions. It is not required to provide results from nonclinical and clinical testing. The generic pathway is typically followed for applications of generic small molecule medicinal products. With the demonstration of PE and BE, generic medicinal products are generally also considered interchangeable from a health care provider reimbursement perspective, although this aspect is not regulated by the pharmaceutical legislation.

➤ **Article 10(3) applications – Hybrid medicinal products**

The hybrid path must be followed when the definition of a generic product is not fully met, or when bioavailability studies cannot be used to demonstrate bioequivalence, or in case of slight changes to the active substance, to the indications, strengths, pharmaceutical form or route of administration. In this case the applications rely in part on the nonclinical and clinical data for the reference product, but in addition appropriate nonclinical tests and clinical trials with the new product will have to be conducted to establish the properties specifically related to the hybrid medicinal product (Vogel, 2012). This pathway is typically followed for medicinal products with established active substances which have been developed further to provide benefits for the patients, e.g. improved administration, supra-

bioavailability or additional indications. Such products are usually developed by originator companies for life-cycle management purposes, or also by generic companies as so-called “super generics” (Barei & Ross, 2015).

➤ **Article 10(4) applications – Biosimilar medicinal products**

A dedicated regulatory approval route for biosimilars was introduced in the EU in 2004 (Directive 2004/27/EC, 2004). This was deemed necessary because biosimilars cannot be regarded as generics of a biological reference product due to the inherent variability of these medicines from biological sources. Biosimilars are considered highly similar, but not identical to the reference product. The approval of biosimilars requires more studies than for generics to ensure those minor differences do not have a negative impact on the safety or efficacy. Data on the pharmaceutical quality of the biosimilar have to be provided and in addition it is required to compare the structure and biological activity of the biosimilar with the reference product. Since demonstration of bioequivalence is usually not possible for biosimilars, a comparison against the reference product regarding biological function, efficacy, safety and immunogenicity may be required, which means that for biosimilars usually a clinical trial to confirm biosimilarity is expected (EMA, 2017). The European Medicines Agency (EMA) constantly updates the science-based regulatory framework for approval of biosimilars with guidance documents such as overarching biosimilar guidelines and also product-specific biosimilar guidelines (Schiestl, Zabransky, & Sörgel, 2017).

2.2.2 Abbreviated procedures in the United States

➤ **Abbreviated New Drug Application (ANDA) - 505(j) pathway**

The ANDA pathway was established under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendment) as regulatory path for approval of generic drug products. The underlying idea of an ANDA approval is to ensure that a safe, effective and less costly alternative drug product with the same clinical effect and safety profile as the reference listed drug (RLD) is approved, meaning a therapeutically equivalent drug product with the underlying premise that the generic drug product and the RLD can be substituted for each other. The ANDA applicant does not have to provide results of nonclinical and clinical testing for the

generic drug product, but must submit sufficient information to demonstrate that its generic product has the same active ingredient(s), route of administration, dosage form, strength, previously approved conditions of use and generally the same labeling as the RLD. In addition, the applicant must also demonstrate that the generic drug product is bioequivalent to the RLD. The U.S. ANDA application corresponds to the European Article 10(1) generic application.

➤ **505(b)(2) pathway**

A 505(b)(2) application is a specific type of a new drug application (NDA), for which the applicant has to submit in parts full reports of investigations of safety and efficacy, but in parts relies also on literature and the FDA's finding of safety and effectiveness for an approved drug "*and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted*" (FDA, 1999). The 505(b)(2) pathway was added to the Hatch-Waxman Act and permits the FDA to approve applications based on data not developed by the applicant, but already assessed for a reference product. This kind of application is often used to support a modification of a previously approved drug, like a change in the recommended dose, new formulation, new route of administration or new combination and allows applicants to achieve approval in a shorter time and at less costs than for a full NDA. This path can be considered equivalent to the European "hybrid" path under Article 10(3), however with some differences as outlined below (FDA, 1999) (Vogel, 2012). Therefore, not all 505(b)(2) applications would be acceptable under the European Article 10(3) pathway and vice versa.

The 505(b)(2) path can be used for applications for certain new chemical entities or new molecular entities (for example pro-drugs or metabolites) or for changes to previously approved drugs and which rely on non-proprietary studies and literature for one or several reference products to support any part of the application. Applications under 505(b)(2) are eligible for patent and/or exclusivity protection, ranging from 0 to 7 years, depending on the type and extent of studies which had to be conducted by the applicant. European applications under Article 10(3) are mainly used for "pseudo-generics", for which bioequivalence to the reference product cannot be shown. Non-clinical and clinical studies must be tailored to address the differences from the reference product. These "hybrid" products are

legally allocated to the group of generics, and consequently are not eligible for data exclusivity and market protection.

For both 505(b)(2) and Article 10(3) hybrid applications it is only possible to rely on previous findings of safety and efficacy for the reference product to the same extent such reliance would be permitted for generic applications, i.e. only after expiry of any exclusivity protections.

➤ **Biosimilar application – 351(k) pathway**

The FDA also developed regulatory guidance for approval of biosimilars, however this framework came into force only several years later than in Europe. The statutory provisions are laid down in the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which defines the approval pathway for biosimilars, like the Hatch-Waxman Act does for small-molecule generics. The FDA defines biosimilarity or biosimilars as “*highly similar to the reference product notwithstanding minor differences in clinically inactive components*”, and that “*there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product*” (FDA, 2015). The FDA recommends that biosimilarity is demonstrated by a step-wise approach: at each step, the available information should be evaluated to assess the residual uncertainty about the biosimilarity, and then the next step to address that uncertainty has to be identified. The stepwise approach starts with an extensive analytical characterization, followed by animal studies and clinical studies. The FDA assesses biosimilars on a “totality-of-the-evidence” approach, which considers both the quantity and quality of the evidence to support effectiveness, i.e. comparison of structure, function, animal toxicity, human pharmacokinetics and pharmacodynamics, clinical immunogenicity and clinical safety and effectiveness between the biosimilar and the reference product. Of note, the FDA can determine that an element described above is not necessary in a 351(k) application, therefore the extent of the testing required to demonstrate biosimilarity is determined on a product-specific basis (Jeske, Walenga, Hoppensteadt, & Fareed, 2013) (FDA, 2015).

3 Problem Statement

With the first “generic” NBCDs seeking approval, it became apparent that the established regulatory framework for abbreviated procedures may not sufficiently address the requirements for these kinds of products. There appears to be a dilemma for regulators and scientists because none of the established regulatory paths, neither for generics nor for biosimilars seems to be appropriate.

Pharmaceutical companies developing originator products point out that a generic approach is not sufficient and claim that a similarity approach as for biosimilars with a therapeutic equivalence trial needs to be applied to ensure interchangeability. On the other hand, companies developing follow-on products want to bring affordable medicines on the market for the benefit of the patients and claim that unnecessary clinical trials should be avoided. The request for additional efficacy and safety studies could prevent the development of follow-on products.

Discussions started whether the current EU regulatory legislation and guidance is adequate and sufficient for the evaluation of follow-on NBCDs (Schellekens, et al., 2014) (Ehmann & Pita, 2016). There is no dedicated regulatory scheme available for approval of follow-on NBCDs and as chemical substances they can be approved either via the generic or the hybrid legal basis. Due to the complex structure of NBCDs some experts however request that a biosimilar approach should be applied (Crommelin, et al., 2015). The question arises whether the available regulatory paths are suitable for approval of follow-on NBCDs and can take the specific requirements for these products into account.

In addition, there seem to be different approaches between Europe and the U.S., which leads to the question whether different scientific standards are applied and whether the NBCD-similars approved in Europe and in the U.S. are equally safe and efficacious.

In the following sections, some examples of NBCDs and their approval pathways in Europe and in the U.S. are reviewed and discussed.

4 Case Studies - Approval of follow-on products of NBCDs

4.1 Iron sucrose similars

For many years, oral iron preparations were standard for the treatment of anaemia. Intravenous iron was only administered in case of malabsorption or intolerance against oral preparations, due to safety concerns associated with intravenous iron preparations, mainly acute hypersensitivity reactions and the risk of iron overload which can cause organ damage (CHMP, 2015). In the recent years however, iron preparations for intravenous application were re-discussed with regard to clinical relevance and product differences (Lipp, 2016). Oral iron treatment is associated with poor intestinal absorption and gastrointestinal side effects and requires long courses of treatment to replenish the iron stores and resolve anaemia. In a number of conditions, such as chronic kidney disease (CKD), irritable bowel disease (IBD) or for patients receiving erythropoiesis stimulating agents (ESA) for chemotherapy-induced anemia, intravenous iron offers advantages over oral treatment (Auerbach & Ballard, 2010).

Because free iron in plasma is highly toxic it is necessary to shield the iron in intravenous preparations. Intravenous iron preparations are complex molecules, consisting of trivalent iron in the core, which is stabilized by a carbohydrate complex. The iron-carbohydrate complex is necessary to ensure a controlled release of iron in the macrophages and to minimize the toxicity of free iron in the circulation, therefore stability of the complex is very important. The complexes have a molecular mass in the range of about 40 to 150 kilodalton (kDa) and have nano-sized colloidal structures. Intravenous iron preparations on the market contain the dextran-based complexes iron dextran and iron isomaltoside (IIM), and the dextran-free complexes ferric carboxymaltose (FMC), sodium ferric gluconate and iron sucrose (IS).

The main concern with intravenous iron preparations, e.g. iron dextran, is the risk of allergic reactions. The development of intravenous iron-based nano-colloidal products with sufficient stability of the complex to allow administration of larger iron amounts during fewer administrations on the one hand and a reduced risk of allergic reactions on the other hand was therefore an exciting and challenging area

of research in the last years (Lipp, 2016). Intravenous iron medicines were also in the focus of an Article 31 referral triggered by the French medicines agency. The Committee for Medicinal Products for Human Use (CHMP) review of intravenous iron-containing medicines was finalized 2013 with the conclusion “that the benefits of these medicines are greater than their risks, provided that adequate measures are taken to minimize the risk of allergic reactions” (EMA, 2013).

Most of the more recently developed intravenous iron medicines like ferric carboxymaltose (Ferrinject®) or iron isomaltoside (Monofer®) are still under data and patent protection. For iron sucrose, which has been marketed in Europe since 1975 however several follow-on products or so-called iron sucrose similars (ISS) gained approval.

Iron sucrose consists of a polynuclear iron(III)-hydroxide core which is superficially surrounded by a large number of non-covalently bound sucrose molecules. The complex has a molecular weight of approximately 43 kDa. The complex is sufficiently large to prohibit renal elimination and stable to ensure ionic iron is not released. The iron in the polynuclear cores is bound in a similar way as in the core of the physiological iron storage protein ferritin (Venofer® UK SmPC, 2016).

After intravenous administration, the complex is taken up by reticuloendothelial macrophages and dissociated into the sucrose and iron component. The sucrose component is eliminated via urinary excretion. The iron is transported as a complex with transferrin and available for the synthesis of haemoglobin, myoglobin and other iron-containing enzymes (Venofer® UK SmPC, 2016).

Details of the regulatory pathways to gain approval of follow-on products and regulatory development are discussed in the following sections.

4.1.1 European approval of iron sucrose similars

The European originator product Venofer® with the active ingredient iron sucrose (iron(III)-hydroxide sucrose complex) is marketed in European member states since 1975. One of the first follow-on products, IJzerhydroxide sacharose complex 20 mg/ml PCH, was approved in the Netherlands in 2009, under the Article 10(1) generic pathway (MEB Public Assessment Report, 2010).

The data package required for approval of this generic iron sucrose product was straightforward and restricted to information as expected for a small molecule generic product. The focus was on the quality aspects, while no non-clinical and clinical data were required. Bioequivalence studies were not deemed necessary because both the reference and the generic product are administered via the parenteral route (MEB Public Assessment Report, 2010).

Equivalence was based on the following comparative *in vitro* studies, based on the United States Pharmacopoeia (USP) monograph of the finished product (Iron Sucrose injection, USP):

- Sucrose content
- Fe³⁺ content
- Molecular weight distribution
- pH value
- Turbidity point

In addition, to account for the highly complex macromolecular structure the following additional evidence was provided:

- Photon Correlation Spectrometry (particle size)
- Atomic Force Microscopy (size and shape/morphology)
- Fourier Transformation Infrared Spectrometry (chemical structure)
- X-ray Diffraction analysis (chemical structure, polymorphic form)
- Reduction kinetics of the finished product

Since the approval of the first generics, several studies have however shown that the innovator Venofer and the follow-on products, the iron sucrose similars (ISS), cannot be considered as essential similar and therapeutic equivalent. A study in rats has shown differences with increased haemodynamic and oxidative stress markers for the ISS products, which could be explained by a reduced stability of the iron complex (Toblli, Cao, Oliveri, & Angerosa, 2009). An observational study investigated the impact of a switch from the originator iron sucrose to an ISS in haemodialysis patients and concluded that the switch was associated with a significant reduction in Hb level and a reduction of the transferrin saturation (TSAT)

value, indicating that a lower proportion of iron was available for erythropoiesis (Rottembourg, Kadri, Leonard, Dansaert, & Lafuma, 2011). Safety concerns were also addressed in case reports, raising doubts about the therapeutic equivalence of ISS preparations and originator iron sucrose (Stein, Dignass, & Chow, 2012). The differences between the originator iron sucrose and the ISS were confirmed in a prospective clinical trial in 342 patients on haemodialysis: the originator iron sucrose product required 34% less iron doses and 12.5% less erythropoiesis-stimulating agents compared to the generic product (Agüera, et al., 2015).

It was recognized by the EMA that the generic approval pathway with demonstration of identical physicochemical properties and equivalent plasma concentrations, and in case of solutions for intravenous use even a waiver for bioequivalence studies, is not a suitable approach for approving nanoparticle medicinal products. A first reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications was published in 2011, introducing the requirement to generate comparative data from non-clinical studies on the time-dependent iron content in the major target organs to support the similarity claim between generic and reference product (EMA, 2011). A bioequivalence study was however regarded of only limited value and not required at that time because such a study may not show in which extent the nanoparticles are taken up by different organs.

This reflection paper was further updated with the current “*Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product*” becoming effective in 2015, outlining a “weight of evidence approach” with the requirement for data from quality, non-clinical and now also human pharmacokinetic studies to account for the difficulties to fully characterize and define iron complex based particles (CHMP, 2015). Today’s expectations on the data requirements are outlined below:

Quality data

The quality data package which is expected today is far more extensive than what was seen for the initial generic applications. The current reflection paper gives an extensive list of quality parameters to be considered and highlights the importance

of a well-defined manufacturing process. A comprehensive side-by-side analysis of the test and the reference product of several different batches is required with focus on the following attributes considered as having a major impact on efficacy and safety:

- Stability of the iron-carbohydrate complex → looking at the fraction of labile iron to assess toxicity and pharmacokinetics
- Physicochemical properties of the carbohydrate matrix → looking at the potential for anaphylactic reactions, pharmacokinetics and degradation products
- Physicochemical properties of the iron and iron-carbohydrate complex → looking at the size and size distribution properties

Non-clinical data

It is expected to conduct distribution studies in a relevant animal model to evaluate distribution, metabolism and excretion of the nanoparticles and degradation products in at least the following three relevant compartments: Plasma, reticuloendothelial system (RES) (macrophages in spleen and liver) and pharmacological (bone marrow) and toxicological (kidney, hepatocytes, lung, heart) target tissues.

Clinical studies

Although the complex iron products are intended for intravenous use there is a requirement to compare the clinical pharmacokinetics of the test product and the innovator and assess the AUC_t and C_{max} of total- and transferrin-bound iron.

In case the data package consisting of quality comparison, non-clinical data and human pharmacokinetic (PK) study provides sufficient evidence of similarity no further studies are necessary. In case of minor differences shown in these studies a therapeutic equivalence study might be required. In case of major differences seen in these studies the products are not considered similar, and consequently results from further therapeutic equivalence studies would not be helpful.

In addition, a Risk Management Plan with additional risk minimization measures to address the safety concerns like hypersensitivity reactions and iron overload is required.

This reflection paper was developed and updated over a period of several years including consultation from stakeholders. The experiences made with ISS, and especially the differences seen between Venofer and ISS with regard to efficacy and safety profiles have alerted regulatory authorities and triggered an update of the guidance documents because it was clearly recognized that a simple generic approach is not suitable for this kind of complex drugs. The new findings were taken into account and critical parameters are defined to ensure similarity of the innovator and the follow-on product.

In addition, the European Pharmacopoeia (Ph. Eur.) Commission decided to add on its work program the elaboration of a monograph on iron sucrose concentrated solution. For this purpose, in 2011 the Ph. Eur. Commission approved the creation of the Non-Biological Complexes Working Party, with the aim to elaborate and revise monographs on non-biological complexes (e.g. nanoparticle solutions, such as Iron Sucrose Concentrated Solution) (EDQM, 2011).

Besides the initially via Article 10(1) approved ISS, no further follow-on products appear to be approved in Europe. Perhaps the increased expectations and requirements as laid down in the reflection paper have prevented generic companies from developing new iron based follow-on products.

4.1.2 U.S. approval of iron sucrose similars

The originator product Venofer was approved by the U.S. FDA in Nov 2000 (NDA 21-135) for the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. Interestingly, back in 2000, Venofer was classified by the Metal Complexes Working Group as “different formulation of the same active moiety of a drug that has been approved previously”, and not as new active ingredient. The similar drugs, the FDA’s Center for Drug Evaluation and Research (CDER) is referring to in their chemistry review are Iron Dextran (INFeD®) and Sodium Ferric Gluconate Complex (Ferrlecit®). The reason was that iron(III) is considered the active moiety for all three products and

the sugar component is considered as coordination complex to stabilize the iron core. All three products were seen as noncovalent derivatives or as different complexes of the same active moiety (CDER, 2000). The most recent intravenous iron product approved by the FDA in 2013, ferric carboxymaltose injection (Injectafer®) (NDA 203,565) was considered as NDA classification code type 2, new complex of iron, which shows that a more differentiated view on the carbohydrate component is applied in the meantime (CDER, 2013).

In contrast to the Ph. Eur., the U.S. Pharmacopoeia already contains a monograph for iron sucrose injection. Therefore, it could be assumed that products corresponding with the pharmacopoeial requirements are equally safe and effective. To date, there is no follow-on iron sucrose product approved in the U.S.. One bioequivalence (BE) study could be identified with the aim to assess the BE of the test product Hospira Iron Sucrose 20 mg/ml (Hospira, Inc.) to the reference product Venofer 20 mg/ml following intravenous administration to healthy subjects. The study was already completed in 2008, but apparently the results did not lead to an approval of an ISS.

The FDA issued a “Draft Guidance on Iron Sucrose” for approval of iron carbohydrate follow-on products, a relatively short document in which two studies to demonstrate bioequivalence are recommended (FDA, 2013).

- One clinical study (single-dose, randomized, parallel) to measure total iron and transferrin-bound iron in serum. Bioequivalence (90% CI) should be based on the maximum value of the difference in concentration and AUC difference between total iron and transferrin-bound iron.
- One *in vitro* study to measure the particle size distribution (D10, D50, D90). Bioequivalence should be based on D50 and SPAN (D90-D10)/D50.

Prerequisite for demonstration of bioequivalence is that the RLD and the follow-on product have the same qualitative and quantitative composition and that the sameness in the physicochemical properties of the two products has been established. The criteria to characterize the physicochemical properties are listed in the draft guidance document, but it should be noted that this list is not as

extensive as the quality parameter list in the EMA reflection paper. The following parameters have to be characterized:

- Iron core characterization (core size determination, iron oxide crystalline structure, iron environment)
- Composition of carbohydrate shell and surface properties
- Particle morphology
- Labile iron determination

4.1.3 Comparison European and U.S. approach

The experience with iron sucrose medicines approved via a simple generic pathway and the issues that have been observed when patients were switched from the originator product to a follow-on product resulted in the development of guidance documents for approval of ISS. It can be argued that the experiences with this new category of complex products alerted regulatory bodies and changed their view with regard to the appropriate data requirements and regulatory path for approval of follow-on products.

The European guidance document contains – in absence of a Ph. Eur. monograph for iron sucrose – an extensive list of quality parameters to be considered, reference to relevant pharmacopoeial monographs for routine tests and detailed information on the extensive comparability exercise to be conducted. There is also a requirement to conduct non-clinical distribution studies in an animal model to evaluate distribution, metabolism and excretion of the nanoparticles and degradation products in relevant compartments. The updated EU reflection paper requires now also a comparative pharmacokinetic study to be conducted, a requirement which may have been influenced from the FDA draft guidance. The EU reflection paper states that generally a therapeutic equivalence study is not necessary, provided that quality comparison, non-clinical data and the human PK study demonstrate similarity. This means however that in case of (minor) similarity differences a comparative pharmacodynamic (PD) study could become necessary.

In Europe, a ISS could nowadays only receive approval via the hybrid pathway, and with the data requirements as listed above and with the “weight of evidence” approach even a therapeutic equivalence study could be required. It also has to be

noted that several guidelines for biological and biotechnological products are referenced in the European reflection paper, which also shows that in Europe a biosimilar approach is applied.

The U.S. draft guidance document on iron sucrose gives by far less detailed guidance. The FDA appears to apply more a “true” generic approach, with no request for non-clinical studies and no reference to a therapeutic equivalence study. Despite the seemingly lower requirements there are no iron sucrose ANDAs approved to date.

4.2 Glatiramer acetate

Multiple Sclerosis

Glatiramer acetate is approved for the treatment of multiple sclerosis (MS), a chronic recurrent inflammatory disease affecting the central nervous system (CNS), characterized by degradation of the myelin protein sheath which protects the nerve cells in the brain and spinal cord. The pathogenesis of MS is not well understood, but it is believed that autoimmune mechanisms are involved in the pathogenesis of MS. It was found that myelin specific autoreactive T-cells interact with myelin degradation products such as myelin basic protein (MBP) in the CNS, which triggers inflammatory processes causing disease progression (Loma & Heyman, 2011).

Discovery and Mode of Action

Glatiramer acetate (GA) belongs to the class of glatiramoids. Glatiramoids are a family of heterogenous, synthetic copolymer mixtures consisting of the four amino acids L-glutamic acid (Glu), L-lysine (Lys), L-alanine (Ala) and L-tyrosine (Tyr) in a defined molar ratio. The amino acid copolymers were initially designed to mimic MBP, the major antigen in the autoimmune reaction. The idea was to initiate an immune response in animals to induce experimental autoimmune encephalomyelitis (EAE), as experimental animal model of MS. Surprisingly, the administration of GA did not induce EAE, but instead GA immunization was shown to be protective against EAE induction (Teitelbaum, Meshorer, Hirshfeld, Arnon, & Sela, 1971) (Connor, 2014). The mechanism of action from GA is complex and not fully understood, although numerous effects of GA on immune responses were

shown and new mechanisms are being identified. It is thought that GA acts by modifying immune processes which are responsible for the pathogenesis of MS (Copaxone U.S. prescribing information, 2018). Studies in animals and in MS patients suggest that GA can induce GA-specific suppressor T cells and activate them in the periphery (Copaxone UK SmPC, 2016).

Chemical nature

The peptide copolymer chains in in GA have an average length of approximately 60 amino acids, ranging from 20 to 200 amino acid residues and an average molecular weight of 5 to 9 kilodaltons. The four amino acids Glu, Ala, Tyr and Lys have an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively (Connor, 2014) (Copaxone U.S. prescribing information, 2018).

The synthesis of GA has been published in the literature and in patents (Teitelbaum, Meshorer, Hirshfeld, Arnon, & Sela, 1971) (United States Patent No. US 7,199,098, 2007) (FDA, 2016). Basically, the reaction consists of two steps: In a first step, the amino acid monomers are polymerized, leading to the intermediate copolymer, followed by a subsequent cleavage step into peptide polymer chains, the GA.

The reaction starts with a clearly defined molar fraction of each of the four amino acids. Because the amino acids are different in size and physicochemical properties and are available in different quantities in the reaction pool the polymerization reaction changes over time: the incorporation rate of the amino acids in the sequences and the composition of the peptide copolymers changes during the reaction, an effect which is called propagational shift.

As a result, the sequence of the amino acids in each copolymer is to a certain extent - however not completely - random. To ensure consistency of the polypeptide sequences in the mixture as far as possible it is necessary to have a starting material with defined physicochemical properties and a tightly controlled manufacturing process. A consistent propagational shift is considered important to achieve conservation of local sequences.

In the second step, called “partial depolymerization”, the polymer chains are cleaved into smaller polypeptide chains until the desired molecular weight

distribution is obtained. The molecular weight distribution depends on the cleavage time. This second step is a simple cleavage step without any re-arrangement of amino acid sequences.

The molecular formula for GA is described as follows (Copaxone DCP Public Assessment Report, 2017):

Poly [L-Glu¹³⁻¹⁵, L-Ala³⁹⁻⁴⁶, L-Tyr^{8,6-10}, L-Lys³⁰⁻³⁷]. n(CH₃CO₂H); n=15 to 24 units of acetic acid moieties per 100 amino acid residues

Due to the complexity and heterogeneity of GA the clinically active epitopes within the mixture cannot be identified or isolated. GA consists of thousands of different polypeptides within the mixture and each of them can potentially act as epitope and induce an immunological response. The efficacy, toxicity and immunogenicity of GA may be altered by even slight differences in the distribution of molecular masses or in the composition of antigenic polypeptide sequences (Varkony, et al., 2009) (Connor, 2014).

It should be noted that although GA has a protein-like structure it has to be distinguished from proteins because GA does not have a defined and specific amino acid sequence like proteins. Instead, FDA describes GA as “heterogenous mixture of copolymers” (FDA, 2015).

Regulatory situation

The originator GA is approved under the brand name Copaxone® from Teva for the treatment of relapsing forms of MS. Teva’s Copaxone 20 mg powder for solution received initial approval from the U.S Food&Drug Administration (U.S. FDA) in 1996. In Europe, a national license for Copaxone 20 mg powder for solution was first granted in the UK in August 2000, followed by line-extensions (new dosing regimen and strengths) and MRP approvals in most European Member States (Copaxone U.S. prescribing information, 2018) (Copaxone DCP Public Assessment Report, 2017). Copaxone is approved in both the U.S. and in Europe as chemical entity and not as biological drug product, therefore in both jurisdictions the generic approval pathway is principally available for follow-on GA products.

With Copaxone coming off-patent, generic companies were seeking approval for follow-on versions of GA, which was the starting point for controversial discussions, from a scientific, a clinical and a regulatory point of view. As can be shown below, scientist and regulators from the U.S. and Europe had divergent views.

4.2.1 U.S. approval of generic glatiramer acetate

The first “generic Copaxone” licence was granted by the U.S Food&Drug Administration (FDA) on 16th April 2015 to Sandoz for GA in a 20 mg/ml daily injection. The application was submitted and approved as ANDA according to section 505(j) of the Federal Food, Drug, and Cosmetic Act (U.S. Food&Drug Administration, 2015), which corresponds to the European Article 10(1) generic pathway. It took more than seven years from ANDA submission in December 2007 until the approval in 2015. The ANDA approval was the result of several years of debate, court litigation and consideration of eight citizens petitions submitted by Copaxone’s originator Teva to the FDA. To take the complexity of GA into account the FDA reviewed additional information and established a “*thorough scientific approach for demonstrating active ingredient sameness*” (FDA, 2015). This scientific approach is outlined in detail in a Citizen Petition Denial Letter from the CDER to Teva, which was issued at the same day of the ANDA approval (FDA, 2015). In this letter, the FDA describes in detail a) why it considers the ANDA regulatory path as appropriate and b) the criteria that need to be fulfilled to demonstrate active ingredient sameness.

As outlined in section 2.2.2 the ANDA approval is based on demonstration of active ingredient sameness and bioequivalence. Regarding active ingredient sameness, the FDA points out in the Citizen Petition Denial Letter that the type or amount of information to be provided and assessed to demonstrate that the active ingredient in the generic and the reference product is the same is not described in the statutory provisions, and that the FDA has “*broad discretion with respect to the information... [to] consider in making a finding on the “sameness” of an active ingredient.*” This flexible approach allows the FDA to “*consider an active ingredient [in a generic product] to be the same as that of the reference listed drug if it meets the same standards for identity*” (FDA, 2015).

In the case of GA the following two parameters were assessed during the ANDA review:

- Active ingredient sameness
- Bioequivalence

Regarding demonstration of bioequivalence, FDA considers that there is no need for *in vivo* bioequivalence studies if the generic product is a parenteral solution and contains the same active ingredient in the same concentration as the RLD and is administered via the same route of administration, i.e. is considered pharmaceutically equivalent. The focus of the assessment was therefore on demonstration of active ingredient sameness.

Active ingredient sameness

The chemical synthesis of GA yields a product with overall composition, certain physicochemical characteristics and short amino acid sequences being conserved, while the product also has inherent batch-to-batch variability, like the length of the polymer chains or entire amino acid sequences along the copolymer chains. The FDA considers both the conservation and the variations characteristics to establish the criteria for active ingredient sameness (FDA, 2015).

To assess active ingredient sameness, FDA expects “*the diversity (including the conserved aspects) of a generic GA to be shown to be equivalent to that of the active ingredient in Copaxone*”, i.e. the level of variability of Copaxone compared to generic GA is considered (FDA, 2015).

FDA has established the following four criteria to establish active ingredient sameness:

1. Equivalence of fundamental reaction scheme
2. Equivalence of physicochemical properties including composition
3. Equivalence of structural signatures for polymerization and depolymerization
4. Equivalence of biological assay results

FDA considers these four criteria as adequate when combined. The first three criteria are intended to provide increasing evidence of active ingredient sameness, while the fourth criterion provides confirmation.

The FDA recognizes the scientific and regulatory complex issues for the approval of ANDAs of GA and have subsequently published a Draft Guidance on Glatiramer Acetate Injection. The experiences made during the first generic GA ANDA approval process as described above and as discussed in detail in the Citizen Petition Denial Letter are essentially summarized in this Draft Guidance (FDA, 2016).

4.2.2 European approval of follow-on glatiramer acetate

In Europe, the first “generic” GA was approved in June 2016 in a decentralized procedure (DCP) (NL/H/3211/001/DC). The application was submitted and assessed as hybrid application based on article 10(3) of Directive 2001/83/EC. The correct legal basis was a matter of debate, because the applicant submitted initially under Art. 10(1), but was advised by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) that the legal basis 10(3) should be used because a PK study would not be sufficient (CMDh, 2015).

According to the Notice to Applicants (NtA), Volume 2A, Chapter 1, Section 5.3.2.1 additional information regarding derivatives of an authorized active substance must be provided to proof the safety and efficacy. If this additional information cannot rule out significant differences with regard to the safety and efficacy it is required to submit the application under Article 10(3) and include the results of non-clinical tests and clinical trials.

Unlike in the U.S. there is no product specific guidance document available in Europe. Information on the dossier expectation for a follow-on GA in Europe can be retrieved from Public Assessment Reports, e.g. from procedure NL/H/3211/001/DC (MEB Public Assessment Report, 2016). The main difference to the FDA approach was that according to the European view the active substance cannot be sufficiently characterized with available analytical tools, and it is not known which specific components are responsible for the therapeutic efficacy. This

lead to the assessment that it is not possible to demonstrate sameness, but only similarity.

Also, following subcutaneous administration, the product will be locally metabolized and degraded at the injection site, therefore it is not expected that pharmacokinetic and drug disposition data will generate new and relevant data. The aspect of active ingredient similarity, together with the understanding of the authorities, as also pointed out in scientific advice, that “simple pharmacokinetic studies would not be appropriate for bridging the current product to the innovator product Copaxone”, lead to the conclusion that only the hybrid approach was possible, which made additional non-clinical and clinical investigations necessary.

The European assessment of the first “generic Copaxone” was based on the following parameters:

- Quality aspects
- Non-clinical aspects
- Clinical aspects

Quality aspects

A rigorous determination of the manufacturing process is considered key to ensure consistency of the product. Similarity against the originator Copaxone is demonstrated by an extensive physicochemical and biological characterization program including isolation of nine different mass fractions which were further analyzed in chemical and biological tests. The results demonstrated strong similarities and overall equivalence between the generic product and Copaxone. However, the Member States pointed out that “there are inherent limitations for drawing a conclusion on similarity/comparability of highly heterogeneous mixtures such as glatiramer.” The comparative tests could only provide “fingerprints” and the question of impurities cannot be sufficiently addressed for this type of products. Altogether this lead to the conclusion that the similarity aspect needs to be further supported by non-clinical and clinical data.

Non-clinical aspects

The package included non-clinical pharmacology and toxicology assessment. Data from an EAE mouse model were assessed, although the assessors confirmed limited value of this model for comparison against Copaxone due to considerable inter- and intra-assay variability.

In addition, a cell-based potency assay in THP-1 cells demonstrated a similar response in human monocytes via production of the secreted form of interleukin-1 receptor antagonist (sIL-1RA). Also, at a level of gene expression in THP-1 cells there were no relevant differences between the follow-on product and Copaxone. The comparative toxicity studies in rats did not show differences compared to Copaxone.

Clinical aspects

The clinical assessment was partially based on scientific literature on the known active substance GA. In addition, a clinical study, the “Glatiramer Acetate Clinical Trial to Assess Equivalence with Copaxone (GATE)” study was performed by the applicant to compare the test product to the reference product Copaxone (Cohen, et al., 2015). The study included 794 patients, either treated with test GA (n=353), brand GA (n=357) or placebo (n=84) and consisted of a 9-month double-blind phase, followed by an open-label test GA treatment part to assess long-term efficacy, safety and tolerability of the test product. The primary endpoint was the total number of gadolinium-enhancing lesions as shown in magnetizing resonance imaging (MRI) during months 7, 8 and 9. The design of the study including the endpoints and equivalence margins for the primary endpoint was discussed during scientific advice (MEB Public Assessment Report, 2016). The aim of the study was not to assess efficacy per se, but to demonstrate equivalence between the test product and Copaxone. For this reason, MRI of disease lesions was considered an appropriate primary endpoint, rather than clinical outcomes like relapse rate or disability development, which would be required for pivotal studies. Although MRI measurements of disease lesions are expected to be more sensitive than clinical outcomes they are generally not a validated surrogate endpoint because of sometimes poor correlation between MRI lesion activity and clinical outcomes (Cohen, et al., 2015) (CHMP, 2015). They were considered acceptable in this case however because a meta-analysis demonstrated a correlation between MRI

lesions and relapse rates, and this was accepted as justification. This approach is also in line with the EMA guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2) which is valid for demonstrating clinical similarity of biosimilars, but also for generic applications. The approach for the study design and the efficacy endpoints of the GATE trial is also in line with the EMA guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMA/CHMP/BMWP/42832/2005 Rev. 1).

4.2.3 Comparison European and U.S. approach

For the approval of follow-on GA products, the FDA followed a generic approach and used the available scope and discretion they have in order to establish active ingredient sameness. Recognizing the complex scientific issues around the active ingredient, very stringent quality equivalence criteria were applied. The FDA focus is on the quality attributes and includes equivalence of the manufacturing process including critical process parameters.

The equivalence of the fundamental reaction scheme is the first key parameter which must be fulfilled. The FDA references here the initial publication from Teitelbaum and the U.S. patent which describes the synthesis of copolymer-1 (glatiramer acetate) (Teitelbaum, Meshorer, Hirshfeld, Arnon, & Sela, 1971) (United States Patent No. US 7,199,098, 2007). In the U.S., the applicant for a GA-similar is expected to use the same or equivalent key manufacturing steps. In Europe, the production process is also considered an important factor, however the focus here is much more on the tight control to ensure reproducibility, and there is no dedicated requirement for an equivalent manufacturing process used by the originator.

With regard to non-clinical data in both jurisdictions a biological assay is required, and in Europe in addition comparative toxicity studies are required.

The main difference is the European additional requirement for a comparative clinical study. With the U.S. generic approach, a clinical study per se is not required, and also was not requested in this case, e.g. to address bioequivalence, which could serve as surrogate parameter for efficacy and safety. It has to be noted that

it is also possible under ANDA applications that pharmacodynamic studies, well-controlled BE studies with clinical endpoints in patients or limited confirmatory testing may have to be conducted in case a simple PK study does not provide the required information (FDA, 2013). Interestingly, the pharmacokinetics aspect did not appear to play a role in the FDA assessment, i.e. the requirement for a bioequivalence study was waived in the first place because considered self-evident for a parenteral solution, while the pharmacokinetics aspect was part of the argumentation in Europe: the CMDh agreement that a PK study would not be sufficient lead to the conclusion that a generic approach is not feasible and a hybrid approach must be applied. The main differences between the U.S. and European requirements are summarized in **Table 2**.

The overall approach for demonstrating equivalence between the follow-on GA and Copaxone in the EU very much followed the principles laid down in the biosimilars guidelines, Guideline on similar biological medicinal products (CHMP/437/04 Rev. 1). The question arises whether a biosimilar approach is possible with a hybrid application. Article 10(3) of Directive 2001/83/EC requires that the results of appropriate non-clinical tests and clinical trials have to be provided under certain circumstances, e.g. if the strict definition of a generic product is not met or if bioequivalence cannot be demonstrated through bioavailability studies. The NtA, Volume 2A, Chapter 1, section 5.3.2.2 specifies that *“The extent of the additional studies required in the framework of an article 10(3) application depends on the changes introduced vis-à-vis the reference medicinal product (e.g. new strength, new route of administration, new therapeutic indication) and will be a matter of scientific assessment by the relevant competent authority.”*

This specification allows the relevant competent authority to apply a biosimilar approach also for hybrid applications for complex chemo-similars, because the content of the dossier is not determined by the regulatory basis, i.e. whether it is an Article 10(3) or Article 10(4) application, but is a matter of scientific assessment, related to the issues that need to be addressed for the specific active ingredient, regardless whether it is a chemical substance or a biological substance.

Annex II of the NtA, Volume 2A, Chapter 1 gives further guidance on the additional studies which may be required. For hybrid applications with derivatives of the active

ingredients (with the same therapeutic moiety) usually evidence has to be provided that there is no change in the pharmacokinetics of the moiety, pharmacodynamics and toxicity, i.e. demonstration that the safety and efficacy is not significantly changed. Complex chemo-similars can be considered derivatives of the active ingredients with the same therapeutic moiety. Especially for complex chemo-similars the demonstration that the safety and efficacy profile is not significantly changed can very well be achieved with a stepwise approach as applied for biosimilar applications. The first step is a comprehensive physicochemical characterization and focus on the manufacturing process. Once sufficient evidence of similarity is shown in this step the extent and nature of non-clinical and clinical studies needs to be defined. In the end, comparable clinical performance between the test and the reference product have to be shown and any relevant differences between the similar and the reference product have to be ruled out.

Table 2: Comparison U.S. and European approach for approval of GA follow-on products

	U.S. approach	European approach
Legal basis	ANDA, section 505(j)	Hybrid application, Article 10(3)
Justification	Active ingredient sameness : <ul style="list-style-type: none"> – FDA discretion to establish active ingredient sameness – Diversity of generic GA has shown to be equivalent to that of the reference product 	Active ingredient similarity : <ul style="list-style-type: none"> – Not possible to demonstrate active ingredient sameness, only similarity – PK not appropriate for bridging the current product to the innovator product
Quality data	Drug Substance requirements <ol style="list-style-type: none"> 1. Equivalence of fundamental reaction scheme 2. Equivalence of physicochemical properties including composition 3. Equivalence of structural signatures for polymerization and depolymerization 	Drug Substance requirements <ul style="list-style-type: none"> – Rigorous drug substance manufacturing process fixation to ensure compositional reproducibility – Extensive (physico)chemical and biological characterization program to compare follow-on and reference product
Non-clinical data	4. Equivalence of biological assay results: EAE assay considered to be the most useful biological assay	<ul style="list-style-type: none"> – EAE mouse model (considered of limited value) – Cell-based potency assay in THP-1 cells – Comparative toxicity studies
Clinical data	Not required	– Multicenter, randomized, double-blind, placebo-controlled, parallel group, 9-month equivalence trial
Additional evidence	FDA's own analytical testing via specifically developed methods to analyze the digestion products	Not provided
Guidance documents	FDA Draft Guidance on Glatiramer Acetate Injection (Apr 2016)	<ul style="list-style-type: none"> – Guideline on similar biological medicinal products (CHMP/437/04 Rev. 1) – CHMP guideline on Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2)

4.3 Low Molecular Weight Heparins - enoxaparin

The last example to be reviewed in this thesis are the low molecular weight heparins (LMWH), and specifically enoxaparin, and their follow-on products. LMWH are a new class of anticoagulants, consisting of a complex mixture of oligosaccharide chains. Although LMWH do not fall under the definition of NBCDs in all jurisdictions, but are classified as biologicals in Europe they should be considered here as borderline products with a similar complexity as NBCDs.

LMWH are manufactured from unfractionated heparin sodium by depolymerization. Both heparin and LMWH are anticoagulants, used for prevention and treatment of thromboembolic disorders, including deep vein thrombosis and pulmonary embolism. To understand the complexities around LMWH it is helpful to first have a look at heparin.

Heparin is a carbohydrate, a highly sulfated glycosaminoglycan usually extracted from porcine intestinal mucosa. Heparin is a mixture of linear polysaccharides, consisting of various repeating disaccharide units. The polysaccharides have an average molecular weight of about 15 kDa, ranging from 5 to 40 kDa (Oduah, Linhardt, & Sharfstein, 2016). The most representative disaccharide unit is an L-iduronic acid linked to D-glucosamine via 1-4 glycosidic bond, and in which position C2 of the iduronic acid and C6 of the glucosamine are O-sulfated and C2 of the glucosamine is N-sulfated. Heparin contains also a specific pentasaccharide sequence with a particular 3-O-sulfated glucosamine residue, which is important for binding of heparin to antithrombin III. This binding causes a conformational change in the antithrombin molecule (Gray, Mulloy, & Barrowcliffe, 2008).

Heparin prevents the coagulation of blood via activation of the enzyme inhibitor antithrombin III which then inactivates several coagulation factors such as thrombin and factor Xa. For many years heparin was the anticoagulant of choice. It is administered via intravenous injection or infusion, usually given to hospitalized patients. There are certain disadvantages associated with heparin, such as unintended bleeding and its inability to inactivate surface-bound factor IIa or factor Xa, which reduces its efficacy e.g. in coronary thrombolysis. Heparin is also associated with heparin-induced thrombocytopenia (HIT), a serious risk. Heparin

has a short half-life, which requires frequent or continuous administration as infusion. Because patients show an individual response to heparin, the anticoagulant activity should be monitored (Hirsh, et al., 2001) (FDA, 2010).

LMWH have been developed to overcome some of these disadvantages. LMWH are prepared from unfractionated heparin by various chemical or enzymatic depolymerization processes. Several LMWH are approved in Europe and in the U.S., e.g. enoxaparin, dalteparin, reviparin, tinzaparin. Enoxaparin is one of the most widely used anticoagulants and approved under the brand name Clexane® in Europe and Lovenox® in the U.S.. Enoxaparin sodium is obtained from heparin from porcine intestinal mucosa by alkaline depolymerization. It is a heterogenous mixture of oligosaccharides consisting mainly of less than 18 monosaccharide units. The heterogeneity of enoxaparin is characterized by three important criteria: (1) different chain lengths, (2) a diversity of disaccharide units and the distribution of disaccharide unit sequences in the chain and (3) differences in the modified terminal end of the oligosaccharide chain (FDA, 2010).

The shorter chain length of enoxaparin is responsible for the higher ratio of antithrombotic activity to anticoagulant activity compared to unfractionated heparin.

With regard to the LMWH and approval of their follow-on products different approaches are followed by the FDA and the EMA, based on the different classification of medicinal products derived from animal sources. The FDA considers the follow-on versions of LMWH as synthetic products and therefore they can be approved via the ANDA pathway if active ingredient sameness can be shown. The EMA considers LMWH as biological products, therefore – by definition - follow-on products are considered similar and have to be approved via the biosimilar way. These differences have led to controversial discussions, which then also triggered amendments to the applicable guidance documents. The different approaches are reviewed below.

4.3.1 U.S. approval of generic enoxaparin

Lovenox, the originator enoxaparin and therefore the reference product was approved by the FDA in 1993 (NDA 20-164). The first enoxaparin follow-on product was submitted to the FDA in 2003 (ANDA 76-684, Amphastar Pharmaceuticals,

Inc.), but it was only after several years of discussions that the first generic enoxaparin was approved in 2010 (ANDA 77-857, Sandoz Inc.), under the ANDA pathway which is usually applied for small molecules. The FDA acknowledges the complexity of LMWH and heterogenous nature of enoxaparin sodium. Therefore, in addition to compendial standards for enoxaparin sodium the following five criteria are must be met to demonstrate “active ingredient sameness”:

- i. Equivalence of physicochemical properties
- ii. Equivalence of heparin source material and mode of depolymerization
- iii. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
- iv. Equivalence in biological and biochemical assays
- v. Equivalence of *in vivo* pharmacodynamic (PD) profile

These five criteria are laid down in a Draft Guidance on Enoxaparin sodium, issued in Oct 2011, which has to be read in conjunction with the FDA response to Citizen Petition (Docket No. FDA-2003-P-0273) (FDA, 2011) (FDA, 2010). In this response document, the FDA provides their view on what is understood by the “same” active ingredient, emphasizing also the broad discretion they have regarding the information that needs to be considered to show that two active ingredients are the same. From an FDA point of view an active ingredient in a generic drug product is considered to be the same as that of the reference listed drug if it meets the same standards for identity. Usually the pharmacopoeial standards for identity are applied, however in certain cases, such as enoxaparin, additional standards are prescribed to ensure active ingredient sameness. The FDA response to Citizen Petition provides detailed background information on Criteria 1-4, i.e. why these tests are considered necessary and gives information how to conduct these tests.

Criterion 1, equivalence of physicochemical properties provides broad information on overall chemical composition and molecular weight distribution to ensure similar distribution of oligosaccharide chain lengths. The second criterion, equivalence of heparin source material and mode of depolymerization is considered important because the distribution of sequences of disaccharide units in enoxaparin depends on the sequences found in the heparin source material as well as on the sites for

the cleavage reaction. Also, the cleavage reaction introduces new chemical structures at the terminal ends of the cleaved oligosaccharide chains. Therefore, only an equivalent mode of depolymerization can ensure equivalent structures between the originator and the generic product. The third criterion, equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species, goes into further detailed structural analysis. Information on disaccharide building blocks can be achieved e.g. by exhaustive enzymatic digestion and further analytical identification. Fragment mapping is used to receive information on the distribution of sequences of disaccharide building block units in the oligosaccharide chains. Additional information on the distribution of sequences of disaccharide building block units can be obtained through direct sequencing of oligosaccharides.

Taken together, the first three criteria have to be met to ensure the source material, the chemical reactions in the depolymerization process and the structure are equivalent. The FDA considers that when the first two criteria are met, the third criterion provides crucial evidence on the equivalence of the molecular diversity of the originator and the generic product. The first three criteria are however not seen sufficient to demonstrate active ingredient sameness.

Criteria 4 and 5 focus on the anticoagulant activity. The fourth criterion establishes the equivalence in biological and biochemical assays. The *in vitro* biological assay measures relevant markers of anticoagulant activity, e.g. activated partial thromboplastin time and Heptest prolongation time. In the biochemical assay, the inhibitory effect on factor IIa and factor Xa in the coagulation cascade is measured. Equivalence in these biochemical characteristics provides further evidence on equivalent pharmacological activity and evidence of active ingredient sameness.

To demonstrate active ingredient sameness, in addition the fifth criterion, equivalence of the *in vivo* pharmacodynamic profile, needs to be fulfilled. For criterion 5 a single-dose, two-way crossover *in vivo* PD study must be conducted and factors anti-Xa and anti-IIa in plasma have to be measured. Equivalence is based on the test and reference data for anti-Xa area under the effect curve and anti-Xa peak effect, whereas the anti-IIa data are considered *in vivo* supportive evidence.

In summary, only if those five criteria are fulfilled collectively the FDA considers that the generic enoxaparin is the same as the originator product, based on equivalent molecular diversity of the generic enoxaparin and the originator enoxaparin.

In the Response to Citizen Petition the FDA also addresses the question of immunogenicity. A known adverse event associated with heparin and LMWH is thrombocytopenia, which can be caused by a non-specific electrostatic interaction between the oligosaccharide chain and platelet factor 4 and which depends on the oligosaccharide chain length and charge density. It is therefore assumed that in cases in which the immune response is thought to be stimulated by the active ingredient, like enoxaparin, a generic product with the same molecular diversity would not differ from the originator product regarding immunogenicity. However, to rule out a possible risk of immunogenicity due to potential impurities the FDA recommends additional *in vitro* and *in vivo* assays to address impurities. Details for such studies are laid down in the Guidance for Industry: Immunogenicity – Related Considerations for Low Molecular Weight Heparin, issued in February 2016 (FDA, 2016). The impurities and the immunogenicity risk should be established for both the reference and the generic product.

As already seen in the example of glatiramer acetate, also in the case of enoxaparin the FDA puts great weight on establishing active ingredient sameness, which is a prerequisite to follow the ANDA approval path.

4.3.2 European approval of follow-on enoxaparin

In contrast to the FDA, the EMA and the WHO consider LMWH as biological products, and consequently any follow-on products have to be approved via the biosimilar pathway. Directive 2001/83/EC as amended defines a biological substance as a substance that is produced by **or extracted** from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. Heparin and LMWH fall under the European definition of a biological substance because they are extracted from a biological source and their characterization is complex.

With the European Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular weight heparins (EMA/CHMP/BMWP/118264/2007 Rev. 1) a product-specific guideline is available. The guideline, last revised in Nov. 2016, briefly outlines the specific aspects of the quality comparison for LMWH, which should be applied in addition to compliance with the requirements of the Ph. Eur.:

- molecular weight distribution and overall chemical composition
- starting material (tissue type and species) and mode of depolymerisation
- disaccharide building blocks, fragment mapping profiles and sequences of selected unfragmented oligosaccharides
- biological and biochemical assays.

For the non-clinical studies, a risk-based approach is applied, which means the type and details of the required studies depend on how convincingly similarity was demonstrated during the physicochemical and biological characterization. The non-clinical studies (*in vitro* and *in vivo* pharmacodynamic studies) should be conducted to assess differences in the response between the biosimilar and the reference LMWH. *In vitro* pharmacodynamic studies should include at least evaluations of factors anti-Xa and anti-IIa. This information may already have been obtained in the bioassays as part of the above described quality comparison. Depending on the results, additional non-clinical *in vivo* pharmacodynamic studies may not be required.

With regard to clinical studies, a comparative pharmacodynamic study is required to compare anti-FXa, anti-FIIa and Tissue Factor Pathway Inhibitor (TFPI) activity. It should be noted that the first version of the guideline, which was valid until June 2017, contained also the requirement for a comparative clinical trial against the reference LMWH. This requirement was discussed in a concept paper on the revision of the guideline, and waived in the current version of the guideline, because scientific progress and improved possibilities for physicochemical characterization make it possible to show similar efficacy and safety between the biosimilar and the reference LMWH also via other means (EMA, 2011).

4.3.3 Comparison European and U.S. approach

In Europe LMWH follow-on products are handled as biosimilars via Article 10(4), while the FDA considers them as chemicals and approved them via the ANDA pathway. Despite this difference in the regulatory approval path, the scientific requirements and the dossier content in both jurisdictions appear to be aligned to a large extent. The FDA defined five criteria to establish active ingredient sameness. Criterion I-IV are essentially also found in the quality comparison section in the European guidance.

For criterion IV (biological and biochemical assays), which may be part of the quality or the non-clinical dossier, the U.S. requirements however strictly ask for equivalence, while in Europe, with the risk-based approach an additional *in vivo* PD study may have to be conducted to further support similarity. Here is a main difference between the two jurisdictions: with the FDA “active ingredient sameness” approach, a follow-on product which could not convincingly demonstrate equivalence in criteria 1-4 would not be considered for further evaluation, while with the European requirement to demonstrate “active ingredient similarity” and the risk-based approach the extent of further non-clinical studies depends on the similarity results obtained so far.

The clinical data requirements are harmonized with a more or less similar design and similar endpoints (anti-FXa and anti-FIIa) for the comparative *in vivo* PD study (corresponding to criterion V in the FDA guideline). The previous European requirement for a comparative efficacy trial was waived with the current guideline.

Regarding immunogenicity testing impurities the FDA recommends additional *in vitro* and *in vivo* assays to address impurities, but no detailed proposals for a suitable *in vivo* model are given. According to the EMA guideline, immunogenicity should be compared in appropriate non-clinical test because animal studies are not considered predictive for human immunogenicity. Only if the impurity profile raises concerns, additional comparative safety and immunogenicity data in patients will have to be generated. Here again the EMA approach is risk-based, whereas the FDA more strictly defines the test program. A comparison of the U.S. and European requirements is provided in **Table 3**.

Table 3: Comparison U.S. and European approach for approval of LMWH (enoxaparin) follow-on products

	U.S. approach	European approach
Legal basis	ANDA, section 505(j)	Biosimilar application, Article 10(4)
Justification	Active ingredient sameness based on five criteria (I-V)	LMWH considered biological substance Active ingredient similarity
Quality data	(I) Equivalence of physicochemical properties (II) Equivalence of heparin source material and mode of depolymerization (III) Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species (IV) Equivalence in biological and biochemical assays	– Molecular weight distribution and overall chemical composition – Starting material (tissue type and species) and mode of depolymerisation – Disaccharide building blocks, fragment mapping profiles and sequences of selected unfragmented oligosaccharides – Biological and biochemical assays
Non-clinical data	Equivalence of biochemical assay (see also criterion IV): comparative measurement of anti-Fxa and anti-FIIa	Risk-based approach – <i>In vitro</i> PD studies: comparative bioassays (evaluations of anti FXa and anti-FIIa), may already be part of the quality dossier – <i>In vivo</i> PD studies: not routinely required if similarity already convincingly demonstrated. Otherwise: o <i>In vivo</i> pharmacodynamic model for clinically relevant pharmacodynamic effects for LMWH or animal thrombosis model
Clinical data	(V) Equivalence of <i>in vivo</i> PD profile: o Fasting, single-dose, two-way crossover <i>in vivo</i> in healthy subjects (endpoints: anti-FXa and anti-FIIa)	– Comparative <i>in vivo</i> PD study: o Randomized, single-dose, two-way crossover in healthy volunteers (assessment of anti-FXa and anti-FIIa, Tissue Factor Pathway Inhibitor (TFPI) activity)

Table 3: Comparison U.S. and European approach for approval of LMWH (enoxaparin) follow-on products

	U.S. approach	European approach
		– Comparative efficacy trial not necessary
Immunogenicity	– <i>In vitro</i> and <i>in vivo</i> assays to address immunogenicity of LMWH and of impurities	– <i>In vitro</i> immunogenicity – Clinical immunogenicity assessment depends on impurity profile
Guidance documents	– FDA Draft Guidance on Enoxaparin Sodium, Oct 2011 – FDA Guidance for Industrie: Immunogenicity-Related Considerations for Low Molecular Weight Heparin, Feb 2016	Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins (EMA/CHMP/BMWP/118264/2007/Rev. 1, 10 Nov 2016)

5 Discussion

Lengthy approval times and controversies over the approval of follow-on NBCDs led to discussions whether for follow-on products of these complex medicinal products besides the established regulatory routes for approval of generics and biosimilars a separate category for NBCD-similars is required. Also, on a first look there does not seem to be a harmonized approach between Europe and the U.S., with European regulators going formally via the Article 10(3) hybrid route with data requirements like for biosimilars, while in the U.S. the follow-on products are approved via the conventional generic pathway with an apparently easier and faster ANDA approval.

Looking at Europe, many researchers have argued that (1) this new group of medicinal products should be formally recognized and a similar terminology applied and (2) that a dedicated regulatory scheme and clear guidance for approval of NBCD follow-on products is not available, causing uncertainty for generic companies who would like to bring follow-on products on the market (Crommelin, et al., 2014) (Garattini & Padula, 2017). There is also uncertainty when it comes to the question whether prescribers can switch their patients to an NBCD follow-on product, although the assessment of this aspect is not within the remit of the European regulatory bodies.

Appropriate legal basis for approval of NBCD follow-on products

In Europe, there are currently two regulatory options available for an abbreviated approval procedure of NBCD follow-on products:

- Generic pathway, if the follow-on product has the same qualitative and quantitative composition in active substance, the same pharmaceutical form and if bioequivalence against the reference product has been demonstrated
- Hybrid pathway, if bioequivalence against the reference product cannot be demonstrated, or in case of slight changes to the active substance, to the indications, strengths, pharmaceutical form or route of administration. In this case additional non-clinical and clinical data have to be provided

The generic pathway was followed for iron sucrose similars (ISS) and led to the approval of ISS, which showed different efficacy and safety in clinical practice compared to the originator. The problems arising from this approach and the increasing awareness for issues due to the complex chemical structures of NBCDs changed the understanding and nowadays the only possible regulatory option in Europe is the hybrid path with additional non-clinical and clinical studies.

Some researchers have requested that for NBCD follow-on products a biosimilar approach should be applied, with extensive comparability exercises to show similarity also with regard to efficacy and safety (Schellekens, et al., 2014). It should therefore be discussed whether a biosimilar approach is possible with a hybrid application according to article 10(3).

A look at the relevant legislation (Directive 2001/83/EC) shows that for both the article 10(3) hybrid approach and the article 10(4) biosimilar approach in a first step it needs to be determined whether the definition of a generic product is met. Only if this definition is not met the results of “*appropriate pre-clinical tests or clinical trials*” have to be provided. Article 10(4) gives details when biosimilars do not meet the definition of generic medicinal products, which is “*owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal products and the reference biological medicinal product.*” In this case “*the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.*” Likewise, article 10(3) states that “*in case of changes in the active substance(s) [...] vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.*”

The legal basis does not give any information per se on the extent and details of the appropriate additional tests that have to be conducted. Additional details for specific marketing authorization dossiers and requirements are given in Annex I, Part II, of Directive 2001/83/EC.

For biosimilars “*The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.*” For hybrid products, Annex I requires for “*different salt/ester complex/derivative evidence that there is no*

change in the pharmaco-kinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/ efficacy profile shall be demonstrated.”

Two of the products reviewed in this thesis, follow-on products for glatiramer acetate (GA) and LMWH are good examples for this case-by-case assessment and the weight-of-evidence approach applied in Europe. For the GA similar, a follow-on NBCD which was approved under the Article 10(3) hybrid path, a phase III clinical equivalence trial was required, while for the biosimilar enoxaparin a clinical study assessing PD parameters is deemed sufficient and a comparative efficacy trial is not considered necessary.

With teriparatide, a parathyroid hormone, there is also an example of a chemically synthesised follow-on product of a biological reference product. The reference product Forsteo® is derived from E.coli, whereas the follow-on product is manufactured synthetically and was therefore approved under the Article 10(3) hybrid path via decentralized procedure (DE/H/4291/01/DC, DE/H/4292/01/DC) (BfArM, 2017).

For both biosimilars and hybrid applications the extent and details of the additional information needs to be determined on a case-by-case basis, and in the end, is a matter of scientific assessment, and not a question of the legal basis. The requirements may also change over time due to scientific progress and new methodologies which allow alternative approaches to address certain scientific questions. The European hybrid pathway is therefore a suitable legal basis for approval of NBCD follow-on products, gives enough flexibility and allows a case-by-case assessment on the additional data needed for approval the products.

The U.S. regulatory approach differs from the European point of view insofar that the NBCD follow-on products reviewed in this thesis are approved under the generic ANDA pathway. The FDA puts great effort on the demonstration of active ingredient sameness and may even request equivalent manufacturing procedures. For generic GA and generic enoxaparin the FDA established a “thorough scientific approach for demonstrating active ingredient sameness”, and defined equivalence criteria and the order in which they have to be met. Only if the applicant can convincingly demonstrate equivalence in the first criterion the product is considered

for further evaluation in the next criterion. There is no option for a risk-based approach as applied in Europe for enoxaparin, i.e. the extent and details of further non-clinical studies depend on how convincingly similarity could be demonstrated in the previous steps. Instead, if equivalence is not convincingly demonstrated the product would not be considered for further evaluation. The FDA argues that these quality equivalence criteria are more sensitive to differences than clinical efficacy studies (FDA, 2016). With the U.S. ANDA approach a clinical efficacy study may not be needed, due to very strict quality equivalence criteria. However, this approach may prevent the development of similar products with minor quality differences without clinical relevance.

The question of terminology for NBCDs and their follow-on products

Although “NBCD” is not formally recognized in regulatory guidance documents it has become a commonly accepted term. However, for copy versions of NBCDs a variety of terms is used. The FDA uses the term of “complex generics”, which is appropriate given the active ingredient sameness approach under the ANDA pathway. For Europe, following the similarity approach, the term “NBCD-similar” seems to be most appropriate as it adequately reflects the underlying concept for the approval.

Is there progress towards a harmonized approach?

The differences in the approval requirements between the European and U.S. approach lead to the question whether different standards are applied and whether the follow-on products can be considered similarly safe and efficacious. With the U.S. ANDA approval path the focus is on active ingredient sameness and very strict quality equivalence criteria are applied. With this approach, the follow-on product is considered therapeutically equivalent (i.e. equivalent clinical effect and no differences in the adverse effects), and thus can be prescribed instead of the reference drug.

In Europe, the follow-on products are considered similar, but not the same. The question whether the originator product can be substituted by the follow-on product is not part of the assessment of the regulatory authorities, but is handled on a national level. For the European approval of the GA follow-on product, additional

non-clinical and clinical studies were required. An additional clinical phase III study requires considerable investment for applicants. However, despite the GA follow-on product and the reference product are regarded as therapeutic equivalent they may not be necessarily substituted in clinical practice.

Based on the different regulatory procedures in Europe and the U.S. the focus on how to demonstrate equivalence is different. But the example of the LMWH follow-on products reviewed in this thesis shows that there is progress towards harmonized scientific requirements across jurisdictions.

Marketing authorization procedures in Europe

Another point to look at is the question of centralized versus national marketing authorization procedures for NBCD-similars in Europe. Because they are so complex products one could argue that a centralized procedure like for biosimilars should be mandatory. Indeed, most biosimilars have been approved via the centralized procedure, because they fall under the mandatory scope (Article 3(1) of Regulation (EC) No 726/2004) as they are usually produced via biotechnological methods. But this is not always the case and therefore certain biosimilars may also be approved via national procedures. NBCD-similars may not fall under the mandatory scope, but they could still be eligible for the optional scope (Article 3(2) of Regulation (EC) No 726/2004), e.g. if the authorization is in the interest of patients at Community level. If the NBCD reference product is authorized via the centralized procedure a hybrid NBCD-similar will have automatic access to the centralized procedure (Article 3(3) of Regulation (EC) No 726/2004). But also for NBCD-similars approved via national procedures it needs to be ensured that the same scientific standards as for centralized procedures are applied. In some cases, product-specific guidance documents are available, like the CHMP reflection paper on nano-colloidal iron-based products, or disease-specific guidance documents, like the CHMP guideline on MS, which are applicable also for national marketing authorization procedures. There is also an increasing awareness among regulators for the complexities around the NBCD topic and it can be expected that the CMDh will consult with the CHMP on scientific questions, especially as new members of the NBCD category and their follow-on products are likely to come.

6 Conclusion and Outlook

NBCDs are a family of heterogenous medicinal products. The experience with the approval of NBCD-similars has shown that each product requires a case-by-case assessment. The approval procedures for follow-on products in the past were accompanied by lengthy discussions and sometimes took several years. To assist companies in the preparation of their applications for follow-on products in Europe, an overarching guidance documents which outlines the general principles and expectations on the data requirements would be helpful. This guidance document could include the following topics:

- Definition of NBCDs and their follow-on products; definition of the similarity concept for complex chemical medicinal products
- Appropriate legal basis for submission: Article 10(3) hybrid application with case-by-case assessment on required additional non-clinical tests and clinical trials
- Guidance on the appropriate marketing authorization procedure: centralized or national procedure
- Expectations on the data requirements based on the concept of a risk-based approach, with a stepwise evaluation of quality equivalence criteria, and additional non-clinical and clinical information depending on the weight of evidence

Such a guidance document – similar to the overarching biosimilars guideline – should define the position of the EMA for approval of NBCD-similars. There will however still be the need to develop product-specific guidance documents. For each new member of the NBCD group the first generic application will be challenging because product-specific criteria to demonstrate essential similarity have to be defined.

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Radolfzell, den

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