

T I T L E

Clinical Requirements for the Development of Biosimilar Products

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

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Bonn 2007

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*For Moritz
and
for you, Henning
with all my love.*

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List of Abbreviations

ANC	Absolute Neutrophil Count
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BIO	Biotechnology Industry Organization
BLA	Biologic License Application
BMWP	similar Biological Medicinal products Working Party
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CHMP	Committee on Medicinal Products for Human Use
CPMP	Committee on Proprietary Medicinal Products
DCP	Decentralized Procedure
DK	Denmark
DNA	Deoxyribonucleic Acid
EC	European Commission
E. coli	Escherichia coli
EFTA	European Free Trade Area
EGA	European Generic medicines Association
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPO	Erythropoietin
EU	European Union
FDA	Food and Drug Administration
FDCA	Food, Drug and Cosmetic Act
FOP	Follow-On Protein
G-CSF	Granulocyte-Colony Stimulating Factor
GH	Growth Hormone
GIR	Glucose Infusion Rate
hGH	human Growth Hormone
ICH	International Conference on Harmonization
IGF-1	Insulin-like Growth Factor 1
IGFBP-3	Insulin-like Growth Factor Binding Protein 3
IgG	Immunoglobulin G
INN	International Nonproprietary Name
IT	Italy
I.U.	International Units
i.v.	intravenous
LMWH	Low Molecular Weight Heparins
MA	Marketing Authorization
MAA	Marketing Authorization Application
MRP	Mutual Recognition Procedure
NDA	New Drug Application
NL	The Netherlands
NPH	Neutral Protein Hagedorn
PD	Pharmacodynamic
PhRMA	Pharmaceutical Research and Manufacturers of America
PHSA	Public Health Service Act
PK	Pharmacokinetic

PL	Patient information Leaflet
PSUR	Periodic Safety Update Report
RMS	Reference Member State
s.c.	subcutaneous
SmPC	Summary of Product Characteristics
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Executive Summary

As global sales of biologic products are growing rapidly this market represents a significant target for generic companies. The term “biosimilar product” is a new European term which came-up with the 2004 review of EU legislation. Biosimilar products can be regarded as a generic version of biologically or biotechnologically derived products situated in-between the pure generic approach and a full new application. The first biosimilar product in the EU was Somatotropin / Sandoz (Omnitrope®). In the EPAR of Omnitrope® a definition of the term “biosimilar product” can be found.

Due to several reasons in the USA the opportunities for the development of generic versions of biological products are much less developed : currently there is no approval pathway for biosimilar products in the USA. The FDA is considering a hybrid application between the regular NDA and the ANDA for particular biological products, which would include consideration of data from the innovator product and the potential for provision of additional data by the biosimilar applicant. But so far, in the USA the majority of biologics are approved after submission of a full Biologic License Application (BLAs) and there is currently no approval pathway for biosimilars of BLAs.

Contrary to the USA a legal framework for biosimilars exists in the EU since the review of EU legislation. Directive 2004/27/EC displaced the term “essential similarity” by two new terms: “generic medicinal products” and “similar biological medicinal product”. For authorization of all biotechnology products including biosimilars the centralized procedure is mandatory. The type and quantity of data needed depends on a case-by-case assessment. According to Directive 2003/63/EC, the usual generic approach is not sufficient. For the demonstration of the similar nature of two biological products, additional data regarding the toxicological and clinical profile have to be provided. The following three essential guidelines give advice for the pre-clinical and clinical sections of the biosimilar dossier:

- EMEA/CHMP/437/04
- EMEA/CPMP/3097/02 to be replaced by EMEA/CHMP/BMWP/101695/06 (draft)
- EMEA/CHMP/BMWP/42832/2005 and its four product specific annexes regarding epoetin, G-CSF, human insulin and somatropin.

Additionally, there are two draft guidelines regarding the specific concerns of

- immunogenicity (EMEA/CHMP/BMWP/14327/06) and
- LMWH (EMEA/CHMP/BMWP/496286/06).

According to this new legislation it may not be necessary to repeat all safety and efficacy studies of the originator if the biosimilar applicant can demonstrate that it is possible to characterize the product in detail with respect to physico-chemical properties and in vitro activity and comparability can be shown from a chemical-pharmaceutical perspective.

All pre-clinical and clinical studies should be comparative in nature and should be designed to detect differences in response between the biosimilar and the reference product and not just the response per se. The comparability exercise requires not only a comparable physico-chemical profile but also pre-clinical and clinical trials showing similarity between biosimilar and reference product. The chosen reference product must be a medicinal product authorized in the Community, on the basis of a complete dossier. The same reference product should be used throughout the whole comparability program.

1. Introduction

1.1 Market share

Global sales of biologic products are growing rapidly and therefore this market represents a significant target for generic companies. As biotechnology flourishes and produces more and more products for mainstream medicine, the price will become an even greater determinant of who gets what medicine (Zeid, 2000). However, the price difference between biogenerics and originator biotechnology products is not deemed to be as great as small molecule generic products since the development and production of biosimilar products is not as simple and low-priced. The question is, if and how substantially biosimilar products will be able to reduce therapy costs.

The specific cost savings will depend on each individual product. Current experience from non-EU markets tends to indicate price savings of 25 % to 40 % less than the costs of the originator product. Applying these levels of savings to the top six off-patent biopharmaceuticals today implies annual savings of over € 2 billion per year, creating the opportunity for greatly improving access to medicines across Europe. The savings potential was already demonstrated in Poland, where biosimilar human insulin reduced prices by 28 % in the first year after launch and now saves Poland over € 65 million per year (EGA FAQ).

Biosimilar medicines are already available in certain areas of the world such as Asia and Latin America. The major part of biotechnology products are derived from recombinant DNA technology. Further biotechnology products include antibodies, vaccines, cytokines, interleukines, hormones and in-vivo diagnostic allergenic products.

1.2 Barriers and skills for the development of biosimilar products

Probably, removing from the long-standing product = process dogma will bring biotech products and especially biosimilars faster to market and will help to open the door for multisource biotech products from non-innovator companies (Zeid, 2000). However, there are higher barriers (see Figure 1) to entering biosimilar markets than to the small molecule generic markets. Due to the complexity of the products, in comparison to small molecules it is more challenging to copy biotechnology products. Key factors affecting biosimilar markets include regulatory issues, marketing strategies, and the class of rDNA protein targeted. In the long term the emergence of biosimilars from low-cost manufacturing sites plus the next generation of so-called “super-biosimilars” is also expected to drive market growth (Belsey, 2006).

2. Problem statement

The term “biosimilar product” is a new European term which came-up with the review of the EU legislation called “Review 2004”. Biosimilar products can be regarded as a generic version of biologically or biotechnologically derived products situated in-between the pure generic approach and a full new application. The generic approach showing simply bioequivalence to a branded product is not considered being sufficient for this kind of products neither in the USA nor in the EU. While the FDA is still quarreling with an adequate

pathway and the kind and amount of data needed for such application, the EU separated the term “essentially similar” into “generic” and “biosimilar” and published some essential guidelines laying down the requirements on the quality, pre-clinical and clinical part of the dossier. Furthermore, there are already four product-specific guidelines, one draft guideline is released for consultation and more are likely to follow.

This master thesis is going to focus on the presentation and discussion of the clinical requirements for the development of biosimilar products. Therefore, the legal situation in the USA and the EU will be described and compared, evaluating why the situation for biogenerics is less promising in the USA than in the EU.

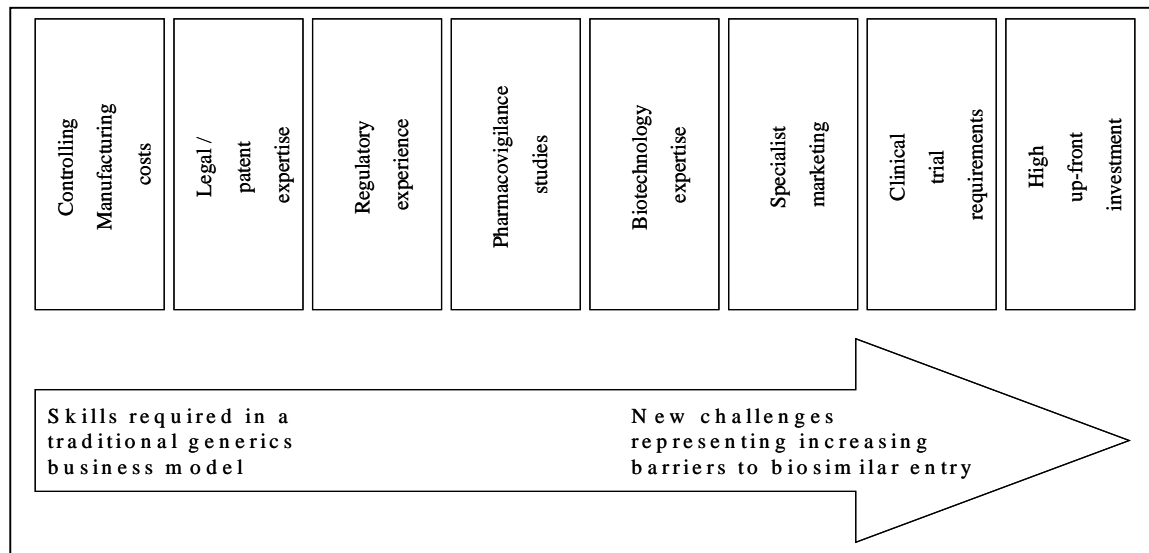


Figure 1: Skills and barriers required to develop biosimilars (Belsey, 2006).

3. Naming conventions

Steered by the originator industry the term “biogeneric” has not achieved acceptance yet and admittedly does not meet the full truth. The authorities are naming them “biosimilar” in the EU or “Follow-on Proteins (FOP)” in the USA. The US conservative position finds its expression in their different viewpoint regarding the naming convention for biosimilar products.

3.1 Definition and Synonyms

There is no definition of the term “biosimilar product” in the new EU legislation such as Directive 2001/83/EC as amended and its Annex Directive 2003/63/EC. However, in the EPAR of Omnitrope¹ a definition of this term can be found: “Omnitrope is a ‘biosimilar product’: this means that Omnitrope is similar to a biological medicine already authorized in the EU (also known as the ‘reference medicine’). Omnitrope has been compared to and matches the reference medicine (Genotropin) in terms of quality (how it is made), safety (for

¹ To simplify matters registered trade marks will not specifically be labeled in the scope of this master thesis.

example the side-effects that can occur when receiving treatment are similar), and effectiveness” (EPAR Omnitrope).

Due to the American requirements on the similarity of the Active Pharmaceutical Ingredient (API) for generic applications (see Chapter 4.2) the term ‘biosimilar product’ is not commonly used in the USA whereas the term Follow-on Protein product (FOP product) is rather familiar. The term is often used for a biotechnology product, that is developed later than the originator product and which is probably more advanced (Rader 9/20/2006). The industry organization BIO understands FOP as a product that pretends to be so similar to an innovator product that for a Marketing Authorization Application (MAA) for the FOP product safety and efficacy can be established with less non-clinical and human clinical data than the innovator had to submit (BIO, 2005) or that the follow-on manufacturer can rely on data and information developed by the innovator (BIO, 2004).

According to the FDA “the term follow-on protein products generally refers to protein and peptide products that are intended to be sufficiently similar to a product already approved or licensed to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. Follow-on protein products may be produced through biotechnology or be derived from natural sources” (FDA, 30 May 2006).

3.2 INN

On 13 November 2006 the World Health Organization (WHO) arranged a meeting in Geneva on the International Non-proprietary Name (INN) naming convention for biotechnology derived medicinal products including biosimilars. During the meeting it was considered whether biologics produced by different manufacturers should be given the same or a distinct INN as compared to the innovator product. The industry was represented by six trade associations (BIO, EBE, EFPIA, Europabio, PhRMA and IFPMA). The discussion about the naming convention for biotechnology products raised since this field is becoming more and more complex. Some stand-alone biologicals have the same INN even if there are slight differences, i.e. in glycosylation (WHO, 2006). Another naming approach is to require that both branded and biosimilar products bear brand names, i.e. INN + qualifier (Europabio, 2006).

For the FDA the naming convention is not just a discussion about chemical names. They feel that issues of interchangeability and substitution are playing a significant role in this matter. The FDA believes that nomenclature should not be used as a way to imply pharmacologic interchangeability: “To date, the USA does not use non-proprietary names as a vehicle for communicating pharmacologic interchangeability. ... The issue of interchangeability is not an issue of nomenclature but a scientific question that needs to be decided on its own merit.” The FDA sees examples in both small molecule products and more complex protein products having the same INN without sufficient scientific data establishing the interchangeability, i.e. interferon β -1a, insulin, or somatropin. The FDA notes further, that “it is beyond the role of the INN Expert Committee to make product interchangeability determinations. The INN should not be used as a determinant of interchangeability (FDA 1 September 2006).

The FDA has specific concerns with regard to biotechnology protein products including biosimilars and requires a specific naming convention for such products: “Biosimilars have

not been demonstrated to be interchangeable through any scientific process. The world community may ultimately decide that INN policy for this class of products should be treated differently than that for small molecule drugs. A different naming scheme for these products might involve utilizing a different level of granularity, which may be more detailed or less detailed depending upon the utility in the INN system” (FDA 1 September 2006). This point of view is supported by the industry organization BIO. They also require a unique INN to assure that physicians and patients are informed and aware of the unique identity of each FOP (BIO, 2005). This position is further supported by the originator industry: Roche states in its “Position on similar biological products” (Roche 2005), that for an effective pharmacovigilance monitoring of biosimilar products (traceability) it may be necessary to use the brand and not a common generic name with respect to the INN (Roche, 2006).

The European generic association EGA is concerned that delays in the review of WHO guidelines on the naming of proteins are creating confusion over naming conventions. They fear that this could lead to the EMEA refusing to grant the same INN to biosimilars as given to the reference product. EGA recommends that no changes are required to the nomenclature system per se (EGA, 2006; EGA 31/10/2006).

4. USA

There are several reasons why the future for biosimilars is less promising in the USA than in Europe. Currently there is no regulatory approval pathway for biosimilar products in the USA and due to safety reasons the FDA is very restricted with the regulation of biosimilars. On the one hand there are constraints with regard to interchangeability linked to the question of how identical must a generic version of a biologic protein be to have the same INN as the originator one. On the other hand, there is a conflict of responsibility and regulatory processes within the FDA since drugs are assessed by the Center for Drug Evaluation and Research (CDER) under the Food, Drug and Cosmetic Act (FDCA) after submission of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) whereas biologicals are assessed by the Center for Biologics Evaluation and Research (CBER) under the Public Health Service Act (PHSA) after submission of a Biologic License Application (BLA).

4.1 Legal framework / Application procedure

In 1991 an agreement between CDER and CBER created a regulatory framework for biotechnology products. Prior to this resolution all ethical products were reviewed by CDER. Afterwards the responsibility has been split: New and generic drug products are falling under CDER domain, while products from living organisms or tissues are governed by CBER licensed as biopharmaceuticals. (Coan, 2001).

Drug products are only considered to be therapeutically equivalent, if they are pharmaceutical equivalents and if they can be expected to have the same clinical efficacy and safety profile when administered to patients under the conditions specified in the labeling. The regulatory requirements for therapeutic equivalence are (Coan, 2001):

21 CFR 320 (c)	Pharmaceutical equivalents are drug products that contain the identical amount of identical API, i.e. the same salt or ester of the same therapeutic moiety in identical dosage form.
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There are three channels for regulatory approval of therapeutically equivalent products and two for biotechnology products including FOPs (Coan, 2001; Zeid, 2000):

Regulatory way	Characteristics	Therapeutically equivalents	FOPs
505 (b) (1) FDCA	Full NDA.	X	
505 (b) (2) FDCA	NDA where the applicant does not own or have a right of reference to all of the studies essential for approval; this is a NDA where the sponsor relies on data it does not own.	X	X
505 (j) FDCA	Generics, statutory authority for ANDAs for any drug product approved as safe and effective.	X	
351 PHSA	Full BLA.		X

An ANDA is always interchangeable with a listed drug, the other three ways may or may not.

4.3 Obstacles for biosimilar approval in the USA

Summarizing the above there are numerous arguments why generic biotechnology products would not be feasible in the USA. The main argument is the issue of safety, mainly because of immunogenicity. Additionally, there is the inherent difficulty in achieving and demonstrating comparability between generic biologics and innovator products (Coan, 2001).

The process is the product

The “process is the product” dogma has been initiated and supported by the innovator industry represented by PhRMA and BIO and means, that the manufacturing process determines the chemical contents and state of complex protein products as well as related safety and efficacy. According to this view all biopharmaceuticals (originator products or FOP) would require a full clinical program (Rader 2006, Rader 9/20/2006). Analytical tests are deemed to be very limited in their ability to substitute for experience with a particular manufacturing process and to predict the clinical safety and effectiveness of a FOP (BIO, 2004).

Regulatory conflicts

The FDA decided that the traditional ANDA route under CDER does not allow sufficient evidence to approve a generic biopharmaceutical. This is partly because under an ANDA CDER cannot ask for additional preclinical or clinical testing. By using the 505 (b) (2) route the FDA has applied a compromise application, which allows the FOP applicant to refer to innovator data and to provide additional data. This approach can be considered as a hybrid between the regular NDA with full, independent data and the ANDA. This hybrid regulation is not specifically intended for generic biologics and only addresses those products regulated by CDER.. This way – giving the generic industry the chance to refer to innovator’s data - is extensively opposed by BIO and the biotechnology innovator industry. BIO strongly disagrees with the FDA’s interpretation of 505 (b) (2) and emphasizes that the FDA should

not reveal or rely on any proprietary information submitted by an innovator to review or approve a FOP. They feel that in important respects all protein products are deemed to be unique and tests performed by an innovator to demonstrate safety and effectiveness of its own product may not be relevant to a follow-on manufacturer's product (Coan, 2001; BIO, 2004; BIO, 2005).

Another factor impeding wide-scale biosimilar launches in the USA is the fact, that the majority of biologics were approved as BLAs and there is currently no regulatory approval pathway for biosimilar versions of BLAs with a reduced clinical program.

Caused by the refusal of Miacalcin from Natestch in July 2006, four US-governors signed a citizen petition calling for the immediate release of guidelines for generic versions of human insulin and hGH to be sold in America (Roumeliotis, 17/08/2006).

Data protection

Although the PHSA regulations authorize the FDA to make the safety and efficacy data and further information on protein products publicly available immediately after licensure, the agency repeatedly assured innovators that a license "is under no circumstances granted ... to a second manufacturer based on published or otherwise publicly available data and information based on another manufacturer's version of the same product" (US Freedom of Information Act). BIO requires that the FDA must continue to protect that data and information from inappropriate disclosure and use. This illustrates the difficulty the FDA will face in determining whether it can segregate trade secrets and confidential commercial information from other public data when reviewing applications for FOPs (BIO, 2004). Furthermore, a product approved under 505 (b) (2) receives NDA patent protection. The sponsor of the FOP, therefore, would create a branded generic (Coan, 2001).

Sameness / Similarity / Interchangeability

The FDA considers an API to be the same as that of the reference listed drug if it meets the same standards for identity. Under section 314.93 of the FDCA, the FDA determines the suitability of products for ANDAs by determining that two products are the same, meaning *identical* in API, dosage form, strengths, route of administration and condition of use. Contrary to that definition the European perspective offers a broader view of how "sameness" or "similarity" are being defined judicially (Coan, 2001): According to CHMP Guideline CHMP/437/04 the API of a biosimilar product must be *similar* not *identical* in molecular and biological terms to the API of the reference product. Especially in the field of biotechnology, where the API is deeply determined by the manufacturing process, an identical version would hardly be possible during innovator's patent protection period.

As described in Section 3.2 above, the FDA's view of interchangeability is linked to their opinion on granting of INNs. According to their point of view "interchangeability is a term used ... to ... demonstrate that two products ... can be safely substituted for one another.... With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins" (FDA, 1 September 2006). The industry organization BIO supports this point of view. In their comments on the European Guideline EMEA/CHMP/437/04 they say, that FOP should not be considered interchangeable unless robust data including comparative clinical data justify claims of interchangeability or substitutability (BIO, 2005).

With regard to the interchangeability of generic versions of erythropoietin the President of the Biotechnology Information Institute Ronald Rader asked provocatively: “Ask yourself, presuming cost was not a factor and you required EPO, would you prefer to receive, products with nearly two decades of manufacturing, clinical and post-marketing experience, or a new biogeneric version ruled by the FDA as identical for all practical purposes and, therefore, just as safe and effective, but likely not tested in large-scale safety and efficacy trials, for which little or no post-approval surveillance studies are likely yet available, and likely manufactured by a new entrant to the field, perhaps, even manufactured in Eastern Europe, China or another lesser-developed country?” (Rader, 9/20/2006).

5. European Union

5.1 Legal framework

Contrary to the USA a legal framework for biosimilar products exists in the EU since the review of EU legislation called “Review 2004”. Directive 2004/27/EC displaced the term “essential similarity” by two new terms: “generic medicinal products” and “similar biological medicinal product”. With the issuing of guidelines for biosimilars, Europe has a more advanced framework for biological products than the USA. However, as for the USA, applications are assessed on a case-by-case basis and are based upon how well the products are characterized (Belsey, 2006). In contrary to the USA approach the EU legislation forbids reference to the innovator’s file in deciding whether to approve a biosimilar product (BIO, 2004).

The legal basis for a biosimilar approval is article 10 (4) of Directive 2001/83/EC as amended and Section 4, Part II of Annex I to this Directive. The requirements for the MAA are based on the demonstration of the similar nature of the biosimilar and the reference product and are laid down in the said Annex.

5.2 Application Procedure

For all biotechnology medicinal products including biosimilars the Centralized Procedure is mandatory. They fall within the scope of Regulation EC 726/2004. When using the Centralized Procedure a single MAA has to be submitted to the EMEA resulting in one single MA valid throughout the EU. The EFTA countries will grant national MAs subject to a positive CHMP opinion.

Generic applications to centralized registered products - provided that the Centralized Procedure is not mandatory - can be made either by the Centralized Procedure or via the Mutual Recognition Procedure (MRP), the Decentralized Procedure or the national route (i.e. biological products extracted from a biologic source like LMWH).

5.3 Dossier requirements

The Commission published a new version of Annex I to Directive 2001/83/EC which went into effect on 1 November 2003 establishing a legal framework for biosimilar products. Comparability studies are needed to substantiate the similar nature, in terms of quality, safety

and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorized in the Community (EMA/CHMP/437/04). The requirements for the dossier include a full quality dossier, non-clinical and clinical studies, comparative PK and immunogenicity studies as well as the comparability exercise. Ideally, the clinical trials should be performed using the product made by the final manufacturing process.

The type and quantity of data needed depends on a case-by-case assessment. This provision coupled with the detailed requirements of Directive 2003/63/EC and the relevant guidelines cast doubt on whether there truly will be a reduction of data required for the approval of biosimilars in comparison to new products (BIO 2004).

5.3.1 Directive 2003/63/EC, Part II, Section 4

In June 2003 the European Commission issued Directive 2003/63/EC as Annex I of Directive 2001/83/EC as amended, defining the approval requirements for biological medicinal products including biosimilars.

According to this Directive, the usual generic approach is not sufficient in the case of biological medicinal products. For the “demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.” Consequently, the “Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data” as the usual generic approach, but “the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product”.

The Directive says further: “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”. There is further a clear request for seeking of scientific advice: “Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority [= EMA], taking into account the specific characteristic of each individual medicinal product.” To achieve a MA for more than one indication, it is required: “the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.”

5.4 Guidance documents

Guidance to the European regulatory processes is provided on the EMA homepage in form of Concept Papers, draft Guidelines, adopted Guidelines and Overview of Comments. The following papers can be found:

5.4.1 Concept Papers

- Concept Paper on Guideline on Comparability of Biotechnology-Derived Medicinal Products after a Change in the Manufacturing Process - Non-Clinical and Clinical Issues

(CHMP/BMWP/9437/06); Replaces Guideline CPMP/3097/02

Publication date: Feb 2006; Deadline for comments June 2006. Final version expected

- Concept Paper on Guideline on Immunogenicity Assessment of Therapeutic Proteins (CHMP/BMWP/246511/05)
Publication date: Feb 2006; Deadline for comments Jun 2006. Final version expected
- Concept Paper on the Development of a CPMP Guideline on Comparability of Biotechnology-derived Products (CPMP/BWP/1113/98)

5.4.2 Valid Guidelines

Two guidelines help with the quality requirements of the dossier:

- Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMA/CHMP/49348/05)
Publication date: Feb 2006; Effective date: Jun 2006
- Guideline on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active Substance -Quality Issues (EMA/CPMP/BWP/3207/00 Rev. 1)
Publication date: Dec 2003; Effective date: Dec 2003

The following three essential guidelines give advice for the pre-clinical and clinical section of the dossier. They will be summarized in Section 6:

- Note for Guidance on Comparability of Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance - Non Clinical and Clinical Issues (EMA/CPMP/3097/02)
Publication date: Dec 2003; Effective date: June 2004
- Guideline on Similar Biological Medicinal Product (EMA/CHMP/437/04)
Publication date: Sep 2005; Effective date: Oct 2005
- Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMA/CHMP/42832/05); Publication date: Feb 2006; Effective date: June 2006
and its four product specific annexes:
 - Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products Containing Recombinant Erythropoietins (EMA/CHMP/94526/05); Publication date: Mar 2006; Effective date: July 2006
 - Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Biosimilar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor (EMA/CHMP/31329/05)
Publication date: Feb 2006; Effective date: Jun 2006
 - Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products Containing Somatropin (EMA/CHMP/94528/05)
Publication date: Feb 2006; Effective date: Jun 2006

- Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products Containing Recombinant Human Insulin (EMA/CHMP/32775/05); Publication date: Feb 2006; Effective date: Jun 2006

5.4.3 Draft Guidelines

In January 2007, three further guidelines have been published for consultation:

- Similar biological medicinal products containing low molecular weight heparins - Non-Clinical Issues (EMA/CHMP/BMWP/496286/06)
Release for consultation Jan 2007; Deadline for comments 30 Apr 2007
- Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (EMA/CHMP/BMWP/14327/06)
Release for consultation Jan 2007; Deadline for comments 31 July 2007.

These two draft guidelines are summarized under Section 6.

- Comparability of Biotechnology-Derived Medicinal Products after a change in the Manufacturing Process - Non-Clinical and Clinical Issues (EMA/CHMP/BMWP/101695/06)
Release for consultation Jan 2007; Deadline for comments 30 Apr 2007.
Replaces Guideline EMA/CPMP/3097/02.
For the scope of this master thesis the requirements of the valid guideline EMA/CPMP/3097/02 are summarized and discussed under Section 6.4.

6 Clinical requirements

The CHMP guidelines stipulate the need to demonstrate clinical efficacy and safety. Data from standard confirmatory and comparative efficacy and safety studies are needed to compare the biosimilar product with the originator's one. The comparability exercise requires a comparable physico-chemical profile as well as pre-clinical and clinical studies showing similarity between biosimilar and reference product.

Though each situation is case-dependent, the application should be evaluated first on a product class basis and then on a case-by-case basis using a tiered approach of combined physico-chemical characterization, PK / PD assessment, surrogate endpoint equivalence and assessment of immunogenicity. Demonstrating therapeutic equivalence will be applied on product complexity, clinical indications and additional safety data for observed changes (Zeid, 2000).

There is a particular problem with physico-chemical characterization: even if the product can be fully characterized and the chemical characterization is similar, the PD profile will be a cumulative biologic response, obtained in animal models or clinical trials, and which may or may not be similar. That means that the clinical relevance of such physico-chemical characterization data has to be questioned. Therefore, chemical characterization alone without biologic profiling and toxicological considerations of a complex multi-component drug is not

deemed to be sufficient (Fareed, 2005). This has been described for LMWHs but is exactly the same for protein products.

Usually, wide lot-to-lot variations were observed among batches of biologic products. The impact of these batch inconsistencies on the clinical outcome should be documented. There are several biological actions and clinical characteristics that are not readily detectable and these may influence the product profile (Fareed, 2004). Eventually, during the development of a biosimilar product the batch-to-batch consistency of the innovator product should be taken into account.

Furthermore, any company – drug or biotech, innovator or biosimilar - needs to establish and maintain a Structure Activity Relationship database to scientifically justify manufacturing changes later (Zeid, 2000).

Summarizing the above, the consequences are: clinical efficacy studies will always be required either to assess any undetected differences or to evaluate the clinical impact of any observed differences in the physico-chemical characterization and the PK studies assuming that current analytical and PK studies are not discriminating enough to detect any differences that could impact safety and efficacy between biosimilar and reference product (Zeid, 2000). On the other hand, clinical trial programs are associated with significant costs and, moreover, considerable ethical constraints. Therefore, there is a compelling need to optimize the clinical program and to keep trial sizes to a minimum (Nick, 2004). In any case, the applicant should justify the approach taken during the development and is well advised to contact the EMEA before starting the development for scientific and regulatory advice. In the following the clinical requirements as laid down in valid guidelines on biosimilar products will be summarized and discussed.

6.1 Guideline on similar biological medicinal products (EMA/CHMP/437/04)

The purpose of the guideline is to introduce the concept of biosimilar products, to outline the basic principles and to provide applicants with a ‘user guide’, showing where to find relevant scientific information in the various CHMP guidelines, in order to substantiate the claim of similarity.

6.1.1 Requirements of the guideline

The biosimilar approach

The success of a biosimilar development program will deeply depend on the ability to characterize the product and to demonstrate the similar nature of the concerned products in terms of quality, safety and efficacy. Whether a medicinal product would be acceptable using the biosimilar approach depends on the state of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences. It should be recognized that, by definition, biosimilar products are not generics.

With regard to the quality part of the dossier biosimilar just as innovator biotechnology products have to fulfill all requirements of Module 3. A full quality dossier (as defined in Annex I to Directive 2001/83/EC) is needed. Module 3 should satisfy the technical

requirements of the monographs of the European Pharmacopeia and any additional requirements, such as defined in relevant CHMP and ICH guidelines.

With regard to the comparability exercise, the normal generic approach is scientifically not appropriate due to the complexity of biologically / biotechnologically derived products. Instead, the biosimilar approach, based on a comparability exercise, has to be followed to demonstrate similarity, i.e. for highly purified products, which can be thoroughly characterized (such as some biotechnology derived medicinal products). The biosimilar approach is more difficult to apply to other types of biological medicinal products, which by their nature are more difficult to characterize, such as biological substances arising from extraction from biological sources (i.e. LMWH) and / or those for which little clinical and regulatory experience has been gained.

The safety / efficacy profile of biosimilar products is highly dependent on the robustness and the monitoring of quality aspects. Generally, the requirements to demonstrate safety and efficacy of biosimilar products have to comply with the data requirements laid down in Annex I to Directive 2001/83/EC. General technical and product-class specific provisions are addressed in the specific EMEA/CHMP guidelines. For situations where product-class specific guidance is not available, the applicant is encouraged to seek Scientific Advice from the EMEA or national health authorities.

In order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified, since it could be expected that there may be subtle differences between biosimilar products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established (traceability).

Choice of reference product

The chosen reference product must be a medicinal product authorized in the Community, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended.

The chosen reference product, defined on the basis of its MA in the Community, should be used throughout the whole comparability program for quality, safety and efficacy studies during the development of a biosimilar product in order to allow the generation of coherent data and conclusions. Data generated with medicinal products authorized outside the Community may only provide supportive information.

The API of a biosimilar product must be similar in molecular and biological terms to the API of the reference product. For example, a medicinal product containing interferon alfa-2a claiming to be similar to another biological product should refer to a reference product containing also interferon alfa-2a. In other words: a product containing interferon alfa-2b could not be considered as reference product.

The pharmaceutical form, strength and route of administration of the biosimilar product should be the same as that of the reference product. When the pharmaceutical form, the strength or the route of administration is not the same, additional data in the context of the comparability exercise should be provided. Any differences between the biosimilar and the

reference product will have to be justified by appropriate studies on a case-by-case basis. Consultation with the EMEA is highly recommended to discuss all those issues.

Relevant guidelines

This guideline on similar biological medicinal products lists a couple of further relevant guidelines. Some are of general nature for the development of biotechnology products, i.e. stability testing. The relevant guidelines with regard to clinical testing will be introduced below.

6.1.2 Comments and discussion

The above presented EU guideline raised challenging comments from the industry organization BIO (BIO, 2005):

For biosimilar products the simple generic approach based on bioequivalence to a reference product is not appropriate because of the critical fact that biotechnology derived APIs are large molecules with a complex three dimensional structure, patterns of glycosylation, and other characteristics that may greatly affect their clinical properties. Critical changes in proteins may hardly be detectable and, moreover, the clinical relevance of such physico-chemical changes is more or less in question. Judgment on safety is difficult as for many proteins no reliable animal models are presently available for predicting effects in humans.

BIO cautions against the use of the word “comparability” in describing the relationship between innovator and manufacturers of biosimilar products. At least in the USA, comparability is a term that has long been associated with “intra-manufacturer” situations, e.g. to describe the relationship between a manufacturer’s product before and after manufacturing changes and hence, guidance on demonstrating comparability between biosimilar and reference product should be kept clearly distinct from guidance on the demonstration of comparability when changes are made in the manufacturing process of already approved products.

It is recommended that the biosimilar applicant should develop appropriate quality information to support its choice of the reference product before any trials are initiated in humans. Even if there are applicable monographs in the European Pharmacopeia, compliance with these should not necessarily be considered sufficient for approval. It should be considered that for reference products not approved via the Centralized Procedure, there might be differences between the member states, in which case it is advisable to consistently source the reference product from the same EU member state. There are a number of other factors that will need to be considered in making the choice of reference product; these include (Nick, 2004):

- the extent of physico-chemical and biological similarity. A biosimilar approach will only be possible if few or no differences exist and the same name can be applied to both the biosimilar and reference product (see Section 3 above);
- the current clinical perception of efficacy and safety relative to competitor products;
- the potential for future clinical problems or advantages;
- the patent status, not just in terms of the molecular entity but also there may be patents covering formulations, delivery devices and processes;

- the remaining period of data exclusivity, which will determine when a submission can be filed and when the product can be marketed;
- the relative market share of the reference product;
- the price of the reference product relative to competitor products;
- the potential for competition from other manufacturers and innovations.

Due to the complexity of these products the guideline provides no specific help regarding the amount or type of data that will be required for biosimilar development. What is “appropriate” and what is “sufficient” in the context of the guideline? However, there are four product specific annexes to the guideline on clinical issues (EMA/CHMP/BMWP/42832/2005), that give more concrete recommendations.

6.2 Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues (EMA/CHMP/BMWP/42832/2005)

This guideline lays down the general requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy. Therefore, the guideline addresses the general principles for the non-clinical and clinical development and assessment of the dossier of biosimilar products containing recombinant proteins as API. The guideline provides the non-clinical and clinical requirements:

- The non-clinical section addresses the pharmaco-toxicological assessment.
- The clinical section addresses the requirements for PK, PD and efficacy studies.
- The section on clinical safety and pharmacovigilance addresses clinical safety studies as well as the risk management plan with special emphasis on studying the immunogenicity of the similar biological medicinal product.

Today, four product class specific annexes supplement this guideline.

6.2.1 Requirements of the guideline

All studies should be comparative in nature and should be designed to detect differences in response between the biosimilar and the reference product and not just the response per se.

Biosimilar products are manufactured and controlled according to their own development. An appropriate comparability exercise is required to demonstrate that the biosimilar and the reference product have similar profiles in terms of quality, safety and efficacy. The principles for the comparability exercise are laid down in this guideline. The same reference product should be used for all three parts of the dossier (i.e. quality, safety and efficacy).

The dossier of a biosimilar product shall provide a full quality dossier. The quality issues relevant for demonstration of comparability for biosimilar products are addressed in a specific guideline (EMA/CHMP/49348/05).

In case the originally authorized medicinal product has more than one indication, the efficacy and safety of the biosimilar product has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications. Justification will depend on e.g. clinical experience, available literature data, whether or not the same

mechanisms of action or the same receptors are involved in all indications. Possible safety issues in different subpopulations should also be addressed.

Non-clinical data

Non-clinical studies should be performed before initiating clinical trials in humans. Results from physico-chemical and biological characterization studies should be reviewed with respect to the potential impact on efficacy and safety. Relevant guidance documents (CPMP/ICH/302/95) as well as emerging technologies should be taken into consideration. The approach taken will need to be fully justified in the non-clinical overview. The following may be considered:

- In vitro studies: Bio-assays like receptor-binding studies or cell-based assays (which may already be available from quality-related bioassays) should normally be undertaken in order to establish comparability in reactivity and the likely causative factors if comparability cannot be established.
- In vivo studies: Animal studies should be designed to maximize the information obtained and to compare reference and biosimilar product intended to be used in the clinical trials. The species used should be known to be relevant and employ state of the art technology. Where the model allows, consideration should be given to monitoring a number of endpoints such as:
 - PD effect / activity relevant to the clinical application.
 - Non-clinical toxicity as determined in at least one repeat dose toxicity study including toxicokinetic measurements. Toxicokinetic measurements should include determination of antibody titres, cross reactivity and neutralizing capacity. The duration of the studies should be sufficiently long to allow detection of relevant differences in toxicity and / or immune responses between biosimilar and reference medicinal product.
 - If there are specific safety concerns, these might be addressed by including relevant observations i.e. local tolerance in the same repeat dose toxicity study.

Normally other routine toxicological studies such as safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not required for biosimilar products, unless results of repeat dose studies indicate this.

Clinical studies

The clinical requirements depend on the existing knowledge about the reference product and the claimed therapeutic indications. Available product or disease specific guidelines should be taken into account. It is acknowledged that the manufacturing process should be optimized during development. It is further recommended to generate the required clinical data for the comparability study with the test product as produced with the final manufacturing process and therefore representing the quality profile of the batches to become commercialized.

The clinical comparability exercise is a stepwise procedure that should begin with PK and PD studies followed by clinical efficacy and safety trials or, in certain cases, PK/PD studies for demonstrating clinical comparability. For all clinical comparability trial designs, assay sensitivity (ICH topic E10) has to be ensured.

Pharmacokinetic studies

Comparative PK studies designed to demonstrate clinical comparability between the biosimilar and the reference product with regard to key PK parameters are an essential part of the comparability exercise. Specific considerations related to the inherent characteristics of proteins are described in a specific guideline (EMEACHMP/89249/2004/in prep). Similarity or differences in terms of absorption, bioavailability, elimination characteristics (e.g. clearance and elimination half-life) should be explored. The ordinary crossover design is not appropriate for therapeutic proteins with a long half-life (e.g. therapeutic antibodies and pegylated proteins) or for proteins for which formation of anti-drug antibodies is likely. The choice of the design for single dose, steady-state or repeated dose studies should be justified. The criteria and acceptance limits used in standard bioequivalence studies are also not appropriate. The acceptance range to conclude clinical comparability with respect to any PK parameter should be based on clinical judgment, taking into consideration all available efficacy and safety information on the test and reference products.

Pharmacodynamic studies

The PD markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy of the product. The PD effects of test and reference product should be compared in a population where the possible differences can be best observed. Combined PK / PD studies may provide useful information on the relationship between exposure and effect. The selected dose should be in the steep part of the dose-response curve. Studies at more than one dose level may be useful. The design and duration of the studies must be justified.

Confirmatory pharmacokinetic / pharmacodynamic studies

Normally comparative clinical trials are required for the demonstration of clinical comparability. However, in certain cases comparative PK / PD studies between biosimilar and reference product may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met:

- The PK of the reference product is well characterized. There is sufficient knowledge of the PD properties of the reference product including binding to its target receptors and intrinsic activity. Sometimes, the mechanism of action of the biological product will be disease-specific.
- The relationship between dose and exposure as well as response and efficacy of the reference product (therapeutic “concentration-response” curve) is sufficiently characterized.
- At least one PD marker is accepted as a surrogate marker for efficacy and the relationship between dose and exposure to the product and this surrogate marker is well known. A PD marker may be considered as a surrogate marker for efficacy if therapy-induced changes of that marker can explain changes in clinical outcome to a large extent (i.e. absolute neutrophil count to assess the effect of G-CSF or early viral load reduction in chronic hepatitis C to assess the effect of alpha interferon). The choice of the surrogate marker for use in PK / PD studies should be thoroughly justified.

If PK / PD studies are used to demonstrate comparability of the biological products, the relevant dose range to demonstrate assay sensitivity should be investigated carefully (ICH E10). The margins defining clinical comparability of PK and PD parameters must be defined a priori and justified.

Efficacy trials

Usually comparative clinical trials will be necessary to demonstrate clinical comparability between the biosimilar and the reference product. Clinical comparability margins should be pre-specified and justified, primarily on clinical grounds. If a clinical comparability trial design is not feasible, other designs should be explored and their use discussed with the competent authorities.

Clinical safety requirements

Even if the efficacy is shown to be comparable, the biosimilar product may exhibit a difference in the safety profile in terms of nature, seriousness, or incidence of adverse reactions. Pre-licensing safety data should be obtained in a number of patients sufficient to address the adverse effect profiles of the test and the reference product with respect to type, severity and frequency of the adverse reactions.

Pharmacovigilance requirements

Data from pre-authorization clinical studies normally are insufficient to identify all potential differences. Therefore, clinical safety of biosimilar products must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment. A risk specification should be given in the dossier including a description of possible safety issues related to tolerability of the biosimilar product that may result from a manufacturing process different from that of the originator. A risk management program or pharmacovigilance plan should be presented taking into account the risks identified during product development and further potential risks. The pharmacovigilance system and procedure including traceability to achieve this monitoring should be in place when the biosimilar MA is granted. Any specific safety monitoring imposed on the reference product or product class should be taken into consideration in the risk management plan. In the Periodic Safety Update Reports (PSUR), the MA holder should address reports and any other information on tolerability that the company has received. These reports or information must be evaluated and assessed by the MA holder in a scientific manner with regard to causality of adverse events or adverse drug reactions and related frequencies.

Immunogenicity

For many proteins and peptides, a number of patients develop clinically relevant anti-drug antibodies.

Factors affecting immunogenicity

The immune response against therapeutic proteins is product specific, since the immunogenic potential is influenced by many factors, such as

- the nature of the API
- product- and process-related impurities
- excipients
- stability of the product
- route of administration
- dosing regimen
- target patient population.

The patient-related factors may have a genetic basis, e.g. lack of tolerance to the normal endogenous protein, or are acquired, such as immunosuppression, due to the disease or its concomitant medication. There is a considerable inter-individual variability in antibody response in terms of different antibody classes, affinities, and specificities. Thus, data should be collected from a sufficient number of patients to characterize the variability in antibody response.

Consequences of an immune response

The consequences of immunogenicity may vary considerably, ranging from irrelevant for therapy to serious and life-threatening. Therefore, the immunogenicity issue has become a subject of concern in the development and approval of biopharmaceuticals. An immune response to the product may have a significant impact on its clinical safety and efficacy. Although only neutralizing antibodies directly alter the PD effect, any binding antibody may affect the PK. Thus, an altered effect of the product due to anti-drug antibody formation might be a composite of PK, pharmacological and safety changes. Antibody formation can cause increased or decreased clearance of the therapeutic protein, although the former effect is the most common.

Principles for evaluation of immunogenicity

Normally an antibody response in humans cannot be predicted from animal studies. Thus, immunogenicity of a biosimilar product must always be investigated. The assessment of immunogenicity requires an optimal antibody testing strategy, characterization of the observed immune response, as well as evaluation of the correlation between antibodies and PK or PD effects relevant for clinical safety and efficacy in all aspects. It is important to consider the risk of immunogenicity in different therapeutic indications separately.

Testing

The applicant should present a rationale for the proposed antibody-testing strategy. Testing for immunogenicity should be performed by state of the art methods using assays with appropriate specificity and sensitivity. The screening assays should be validated and sensitive enough to detect low titre and low affinity antibodies. An assay for neutralizing antibodies should be available for further characterization of antibodies detected by the screening assays. Standard methods and international standards should be used whenever possible. The possible interference of the circulating antigen with the antibody assays should be taken into account. The periodicity and timing of sampling for testing of antibodies should be justified.

In view of the unpredictability of the onset and incidence of immunogenicity, long term results of monitoring of antibodies at predetermined intervals will be required. In case of chronic administration, one-year follow-up data will be required pre-licensing.

Evaluation of the clinical significance of the observed immune response

If a different immune response to the biosimilar product is observed as compared to the innovator product, further analyses to characterize the antibodies and their implications to clinical safety, efficacy and PK parameters are required. Special consideration should be given to those products where there is a chance that the immune response could seriously affect the endogenous protein and its unique biological function. Antibody testing should be

considered as part of all clinical trials protocols. The role of immunogenicity in certain events, such as hypersensitivity, infusion reactions, autoimmunity and loss of efficacy should be considered. The sponsor needs to discuss possibilities to encourage the reporting of relevant adverse events, including events related to loss of efficacy.

6.2.2 Comments and discussion

Generally, for the complete comparability exercises the pharmaceutical form, strengths, route of administration and dose regimen as recommended for the reference product should be used.

Phase 1 studies

As for any clinical development program a clinical Phase 1 study to be completed prior to the confirmatory efficacy and safety studies should be considered also for the biosimilar development program. The purpose of Phase 1 is to demonstrate equivalent PKs particularly in terms of AUC, C_{\max} and elimination characteristics. The Phase 1 study should compare the formulation intended for marketing and the EU sourced reference product. If the variability is high, as may be the case (i.e. if there is the need to rely on a biological assay) data of a sufficient number of patients (more than 30) should be collected. The equivalence margins as for small molecules are not appropriate and will need to be decided on a case-by-case basis taking into consideration the route of administration, the therapeutic window and the precision and sensitivity of the available assays. The Phase 1 study may also be useful in examining comparative PD effects (Nick, 2004). Different biotech classes may require different models depending upon the dose-response-relationship. A key aspect in biotherapeutics is receptor kinetics. Some considerations for evaluating the PK / PD relationship with biotherapeutics are (Zeid, 2000):

- the shape of the dose-response curve,
- the duration of response to develop and persist in relation to PK,
- the concentration as well as dose to separate PK and PD components.

Comparative clinical trials

Comparative PK / PD studies may be adequate if sufficient is known of the biological product and an acceptable surrogate marker exists (e.g. for insulin). The use of surrogate markers is clearly one way of reducing the number of trial subjects and shortening the duration of the trial, but surrogate markers need to be validated and their use as a primary end-point needs very careful consideration. Supposedly, this should be discussed in advance with the regulatory authorities. However, the real value of a surrogate endpoint is how well it correlates to the clinical outcome. (Zeid, 2000; Nick, 2004).

Regarding efficacy, equivalence or at least non-inferiority in terms of dosage should be demonstrated, particularly in situations where a clear inter-dependence between dose and efficacy exists, e.g. for epoetin and insulin. Equivalence limits will have to be defined a priori and justified. Generally, the equivalence margin should be defined in terms of a clinically meaningful endpoint and will need to be sufficiently narrow as to ensure that any potential differences will not be of clinical significance (Nick, 2004).

It could be helpful to know, if the effect of the test product is distinguishable from that of placebo provided the biosimilar developer is acquainted with this kind of innovator data, i.e.

following a comprehensive literature search or, when ethically acceptable, by using a placebo control (Nick, 2004).

The number of patients needed to demonstrate equivalence statistically depends on the variability of the endpoint. It could be estimated by an estimation of the common standard deviation, which may be obtained from literature or a pilot study may be required (Nick, 2004).

Depending on how the risk of a failed trial should be balanced against the need for increased numbers of patients the power of the study is usually set between 80 and 90 %. The trial size will also be influenced by the allocation of patients between the two groups. Equal distribution requires the least number of patients. In order to increase the safety data base or to reduce the cost of purchasing the reference product it might be considerable to relatively increase the number of patients receiving the biosimilar product and consequently, the trials size has to be adjusted accordingly (Nick, 2004). It is further important, that clinical trials are powered to detect clinically significant differences and that they are sufficiently sized to make a comparison to immunogenicity (Schering, 2004).

With regard to multiple indications the guideline requires, that “efficacy and safety has to be justified, or if necessary, demonstrated separately for each of the claimed indications”, whereas the product specific annexes to EMEA/CHMP/BMWP/42832/2005 for somatropin, erythropoietin and G-CSF indicate, that results from one study can be extrapolated to other indications.

Safety aspects

Generally, the risks associated with the pharmacological activity of the biosimilar API should be compared with and should be comparable to those of the reference product. Differences in the risk profile e.g. due to changes in the manufacturing process or the immunogenicity profile should be subject to further safety monitoring. Where the potential for serious adverse effects exist (e.g. epoetin), at least twelve month's data in 300 patients would be required (EMA/CHMP/BMWP/94526/2005 Corr.).

Pharmacovigilance

The detection of rare adverse reactions requires a sufficient number of patients. Therefore, post approval safety monitoring and pharmacovigilance strategies including regular PSUR reporting are necessary.

Generally, for biosimilars the pharmacovigilance requirements are the same as for all medicinal products. In accordance with Directive 2001/83/EC as amended, Article 8.3 (ia) “a detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce” should be part of the dossier. The pharmacovigilance strategy for medicinal products covers further the regular PSUR submission (Regulation 726/2004, Article 24 (3)). The pharmacovigilance activities are described in detail in the Notice to Applicants, Volume 9.

The risk-management system should cover pharmacovigilance activities and necessary interventions, where the possible risks should be identified and characterized in order to prevent them in the future. The effectiveness of the interventions should be assessed. A risk

minimization plan should cover minimization actions like amendments to specific sections of the SmPC, PL or labeling and / or additional information to health care professionals. A risk specification should describe possible safety issues due to differences in the manufacturing process. The cycle of PSURs has probably to be restarted after a variation. A new post-marketing requirement for biosimilar products is traceability. This means, that the specific (biosimilar) product given to the patient should be clearly identified and additional safety measures (e.g. special monitoring system) may be necessary.

Immunogenicity

There are a lot of factors triggering immunogenicity effects, e.g. (Schering, 2004):

- route, dose, frequency and duration of administration with the s.c. route being associated with the greatest immunogenicity
- chemical structure including amino acid sequence, glycosylation
- contaminants and impurities
- formulation and stability, physical and chemical degradation
- underlying disease / indication
- patient genotype
- prior treatment with the same product
- unknown factors which include associated diseases and concomitant therapies.

Furthermore, there can be a cross-immunogenicity with natural compounds. The clinical consequences of immunogenicity can be: no effect, reduced or enhanced efficacy, neutralization of a natural host protein or general effects of antigen – antibody complexes (Schering, 2004).

Repeated administration of biologics often needs assessment of immunogenicity. In comparison to the reference product a changed immunogenicity profile is the most important safety aspect. This can have profound safety implications in terms of hypersensitivity reactions or by breaking tolerance to self-antigens and inducing the formation of auto antibodies. Immunogenicity studies, therefore, represent a pivotal part of any comparability program (Zeid, 2000; Nick 2004).

Today, there are no established pre-clinical (animal) models that can safely predict the immunogenicity potential of a protein in humans. Eventually, the information gained from human clinical trials to evaluate immunogenicity is indispensable and hence, immunogenicity studies should be part of the comparability program. It is the crux of immunogenicity effects, that the incidence in humans is often low, but if it occurs the consequences are rather severe. Therefore, prior to large-scale Phase III studies smaller studies should be conducted to evaluate possible immunogenic reactions or other side effects. Furthermore, immunogenicity has to be assessed in post-marketing monitoring due to unpredictability of its onset.

Of key importance is the need to distinguish between neutralizing and non-neutralizing antibodies. Neutralizing antibodies are of particular concern because - as it has been reported in several studies - the appearance of them can be associated with reduced clinical efficacy or auto-antigenicity due to their capacity to neutralize important host factors. Therefore, safety studies should generally include comparative antibody testing. For products that can induce neutralizing antibodies immunogenicity testing should be included in the Phase III registration trial and in Phase IV post-marketing studies in order to take care of pharmacovigilance aspects and long-term monitoring (Nick, 2004; Schering, 2004).

For further and more detailed aspects on immunogenicity the new guideline “Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins” (EMA/CHMP/BMWP/14327/06) published as draft in January 2007 should be taken into account.

6.3 Product-specific Annexes

The four product-specific annexes to this guideline lay down the non-clinical and clinical requirements for the four specific products. The non-clinical section addresses the pharmacotoxicological assessment. The clinical section addresses the requirements for PK, PD, efficacy and safety studies as well as the risk management plan.

All four guidelines confirm that the dossier must provide the demonstration of comparability of the product to an EU reference product. All studies should be comparative in nature and should be designed to detect differences in the pharmacotoxicological response between the biosimilar and the reference product and should not just assess the response per se. In general, the sponsor is well advised to seek for scientific advice, i.e. for study design, duration, choice of doses, efficacy / pharmacodynamic endpoints, and comparability margins.

Non-clinical studies

The non-clinical requirements for the four products are comparable:

Pharmacodynamic studies

- In vitro studies: In order to assess any differences in properties between the biosimilar and the reference product, comparative studies such as in vitro bioassays (e.g. receptor-binding studies) should be provided. Many of them may already be available from quality-related bioassays. It is important that assays used for comparability will have appropriate sensitivity to detect differences and that experiments are based on a sufficient number of dilutions per curve to fully characterize the concentration-response relationship.
- In vivo studies: The PD effects of the biosimilar and the reference product should be quantitatively compared in an appropriate animal model. Data may be already available from quality-related bioassays. For insulin comparative studies of PD effects would not be anticipated to be sensitive enough to detect any non-equivalence not identified by in vitro assays and are normally not required as part of the comparability exercise.

Toxicology

Data from at least one repeat dose toxicity study in a relevant species should be provided. Study duration should be at least 4 weeks. The studies should be performed in accordance with CPMP/SWP/1042/99 and include pharmacodynamic measurements and appropriate toxicokinetic measurements in accordance CPMP/ICH/384/95. In this context, special emphasis should be laid on the investigation of immune responses to the products.

Data on local tolerance in at least one species should be provided in accordance with CPMP/SWP/2145/00. If feasible, local tolerance testing can be performed as part of the described repeat dose toxicity study.

Pharmacovigilance

In addition to the requirements of the superior guideline (see Section 6.2.1) the risk management program should detail how risks (identified during product development and further potential risks) will be addressed in post-marketing follow-up. Special attention should be paid to immunogenicity and potential rare serious adverse events. In order to further study the safety profile of the biosimilar product, particularly rare serious adverse events safety data should be collected from a cohort of patients representing all approved therapeutic indications.

6.3.1 Erythropoietin (EMEA/CHMP/BMWP/94526/2005 Corr.)

Human erythropoietin is a 165 amino acid glycoprotein, mainly produced in the kidneys and is responsible for the stimulation of red blood cell production. Erythropoietin for clinical use is produced by recombinant DNA technology (epoetin) using mammalian cells as expression system. All epoetins in clinical use have a similar amino acid sequence as endogenous erythropoietin but differ in the glycosylation pattern. Glycosylation influences PK and may affect efficacy, safety and particularly immunogenicity. Physico-chemical and biological methods for the characterization of the protein are available.

Clinical studies

Epoetin-containing medicinal products are indicated for several conditions such as

- anaemia in patients with chronic renal failure,
- chemotherapy-induced anaemia in cancer patients, and for
- increasing the yield of autologous blood from patients in a pre-donation program.

The mechanism of action is the same in all indications but the doses required to achieve the response may vary considerably and are highest in the oncology indications. Epoetin can be administered i.v. or s.c.

Pharmacokinetic studies

The relative PK properties of the biosimilar and the reference product should be determined in single dose crossover studies using s.c. and i.v. administration in healthy subjects as appropriate study population. The selected dose should be in the sensitive part of the dose-response curve. The primary PK parameter is AUC and the secondary parameters are C_{\max} and $t_{1/2}$ or CL/F. Equivalence margins have to be defined a priori and appropriately justified. Differences in $t_{1/2}$ for the i.v. and the s.c. routes and the dose-dependence of clearance should be taken into account when designing the studies.

Pharmacodynamic studies

PD should preferably be evaluated as part of the comparative PK studies. The selected dose should be in the linear ascending part of the dose-response curve. In single dose studies, reticulocyte count is the most relevant and therefore recommended PD marker for assessment of the activity of epoetin. On the other hand, reticulocyte count is not an established surrogate marker for efficacy of epoetin and therefore no suitable endpoint in clinical trials.

Clinical efficacy studies - General requirements

Comparable clinical efficacy between the biosimilar and the reference product should be demonstrated in at least two adequately powered, randomized, parallel group clinical trials. Equivalence margins for both co-primary endpoints have to be pre-specified and appropriately justified and serve as the basis for powering the studies. Transfusion requirements should be included as an important secondary endpoint. The clinical comparability has to be demonstrated for both routes of administration. This is best achieved by performing separate studies:

- s.c. epoetin: a correction phase study in a pre-dialysis population
- i.v. epoetin: maintenance phase study in a haemodialysis using population.

Confirmatory studies should be double-blind to avoid bias. If this is not possible, at minimum the decision-making people (e.g. dose adjustment) should be effectively masked to treatment allocation.

Sensitivity to the effects of epoetin is higher in erythropoietin-deficient than non erythropoietin-deficient conditions and is also dependent on the responsiveness of the bone marrow. Patients with renal anaemia are therefore recommended as the target study population as this would provide the most sensitive model. Other reasons for anaemia should be excluded. Demonstration of efficacy and safety in renal anaemia may allow extrapolation to other indications of the reference product if appropriately justified. Since epoetin doses necessary to achieve target haemoglobin levels differ in pre-dialysis and dialysis patients, these two populations should not be mixed in the same study.

Clinical efficacy studies - Particular specifics

The clinical trials should include a ‘correction phase’ study during anaemia correction and a ‘maintenance phase’ study in patients on epoetin maintenance therapy. A correction phase study is important to determine response dynamics and dosing during the anaemia correction phase. It should only include treatment-naïve patients or previously treated patients after a suitably long epoetin-free and transfusion-free period (e.g. 3 months). It is recommended that the comparative phase be 6 months in order to establish comparable clinical efficacy of the biosimilar and the reference product in patients with stabilized haemoglobin levels and epoetin dose. Shorter study duration should be justified.

The study design for a maintenance phase study should minimize baseline heterogeneity and carry over effects of previous treatments. Patients included in a maintenance phase study should be optimally titrated on the reference product (stable haemoglobin in the target range on stable epoetin dose and regimen without transfusions) for three month. Thereafter, study subjects should be randomized to the biosimilar or the reference product and followed up for at least three and ideally 6 months to avoid carry over effects.

In the course of both studies, epoetin doses should be closely titrated to achieve (correction phase study) or maintain (maintenance phase study) target haemoglobin concentrations. The protocol should clearly pre-define the dose adjustment algorithm. Haemoglobin target range and titration schedule should be in accordance with current clinical practice.

In the correction phase study ‘haemoglobin responder rate’ (proportion of patients achieving a prespecified haemoglobin target) or ‘change in haemoglobin’ are the preferred primary

endpoints. In the maintenance phase study ‘haemoglobin maintenance rate’ (proportion of patients maintaining haemoglobin levels within a pre-specified range without transfusion) or ‘change in haemoglobin’ are the preferred primary endpoints. Epoetin dosage should be a co-primary endpoint in both studies. The fact that epoetin dose is titrated to achieve the desired response reduces the sensitivity of the haemoglobin-related endpoints to detect possible differences in the efficacy of the treatment arms.

Clinical safety

Recombinant erythropoietins have a relatively wide therapeutic window and are usually well tolerated provided, that the stimulation of bone marrow is controlled by limiting the amount and rate of haemoglobin increase. The rate of haemoglobin increase may vary considerably between patients and is dependent not only on the dose and dosing regimen of epoetin, but also other factors, such as iron stores, baseline haemoglobin and erythropoietin levels, and the presence of concurrent medical conditions such as inflammation. Exaggerated pharmacodynamic response may result in hypertension and thrombotic complications.

Comparative safety data from the efficacy trials are sufficient to provide an adequate pre-marketing safety database. At least 12-months comparative immunogenicity data pre-authorisation should be submitted. Retention samples for both correction phase and maintenance phase studies are recommended. For detection of anti-epoetin antibodies, a validated, highly sensitive assay should be used.

Immunogenicity

Moreover, pure red cell aplasia, due to neutralizing anti-erythropoietin antibodies, has been observed predominantly in renal anaemia patients treated with s.c. administered epoetin. Because antibody-induced pure red cell aplasia is a very rare event and usually takes months to years of epoetin treatment to develop, such events are unlikely to be identified in pre-authorization studies. In addition, possible angiogenic and tumor promoting effects of epoetin might be of importance in selected populations.

6.3.2 G-CSF (EMA/CHMP/BMWP/31329/2005)

Human G-CSF is a single polypeptide chain protein of 174 amino acids with O-glycosylation at one threonine residue. Recombinant G-CSFs produced in *E. coli* (filgrastim) and in CHO (lenograstim) are in clinical use. Compared to the human and to the mammalian cell culture derived G-CSF, the *E. coli* protein has an additional amino-terminal methionine and no glycosylation. The recombinant G-CSF protein contains one free cysteinyl residue and two disulphide bonds. Physico-chemical and biological methods are available for characterization of the protein.

Effects of G-CSF on the target cells are mediated through its transmembrane receptor that forms homo-oligomeric complexes upon ligand binding. Several isoforms of the G-CSF receptor arising from alternative RNA splicing leading to differences in the intracytoplasmic sequences have been isolated. One soluble isoform is known. However, the extracellular, ligand-binding domains of the known isoforms are identical. Consequently, the effects of rG-CSF are mediated via a single affinity class of receptors. Antibodies to the currently marketed *E. coli* derived recombinant G-CSF occur infrequently. These have not been described to have

major consequences for efficacy or safety. RG-CSF is administered s.c. or i.v. Possible patient-related risk factors of an immune response are unknown.

Clinical studies

Recombinant G-CSF can be used for several purposes such as:

- Reduction in the duration of neutropenia after cancer chemotherapy or myelo-ablative therapy followed by bone marrow transplantation.
- Mobilization of peripheral blood progenitor cells (PBPCs);
- For treatment of severe congenital, cyclic, or idiopathic neutropenia
- Treatment of persistent neutropenia in patients with advanced human immunodeficiency virus infection.

The posology varies between these conditions.

Pharmacokinetic studies

The PK properties of the biosimilar and the reference product should be compared in single dose crossover studies using s.c. and i.v. administration. The primary parameter is AUC and the secondary parameters are C_{max} and $t_{1/2}$. The general principles for demonstration of bioequivalence are applicable.

Pharmacodynamic studies

The absolute neutrophil count (ANC) is the relevant PD marker for the activity of rG-CSF. The PD effect of the test and the reference products should be compared in healthy subjects. The selected dose should be in the linear ascending part of the dose-response curve. Studies at more than one dose level may be useful. The CD34+ cell count should be reported as a secondary PD endpoint. The comparability range should be justified.

Clinical efficacy studies

The recommended clinical model for the demonstration of comparability is the prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group (e.g. tumor type, previous and planned chemotherapy as well as disease stage). This model requires a chemotherapy regimen that is known to induce a severe neutropenia in patients.

A two-arm comparability study is sufficient in chemotherapy models with known frequency and duration of severe neutropenia. If other chemotherapy regimens are used, a three arms trial, including placebo, may be needed. The comparability delta for the primary efficacy variable, the duration of severe neutropenia (ANC below $0.5 \times 10^9/l$) have to be justified. The incidence of febrile neutropenia, infections and the cumulative recombinant G-CSF dose are secondary variables. The main emphasis is on the first chemotherapy cycle. Demonstration of the clinical comparability in the chemotherapy-induced neutropenia model will allow the extrapolation of the results to the other indications of the reference product if the mechanism of action is the same. Alternative models, including PD studies in healthy subjects, may be pursued for the demonstration of comparability if justified.

Clinical Safety

Safety data should be collected from a cohort of patients after repeated dosing, preferably in a comparative clinical trial. The total exposure should correspond to the exposure of a conventional chemotherapeutic treatment course with several cycles. The total follow-up of patients should be at least six months. The number of patients should be sufficient for the evaluation of the adverse effect profile, including bone pain and laboratory abnormalities.

Immunogenicity

Immunogenicity data should be collected according to the principles described in the guideline EMEA/CPMP/42832/05.

6.3.3 Insulin (EMEA/CHMP/BMWP/32775/2005)

Human insulin for therapeutic use is a non-glycosylated, disulphide-bonded heterodimer of 51 amino acids. The effects of insulin are mediated predominantly via stimulation of the insulin receptor but insulin is also a weak natural ligand of the IGF-1 receptor. The same receptors are known to be involved in the mechanism of action relevant for the currently approved therapeutic indications of recombinant human insulins. Antibodies to recombinant human insulin occur frequently, mainly as cross-reacting antibodies. These have been rarely described to have major consequences for efficacy or safety. The potential for development of product / impurity-specific antibodies needs to be evaluated. Recombinant human insulin is administered s.c. or i.v. Possible patient-related risk factors of immune response are unknown.

6.3.3.1 Requirements of the Guideline

Clinical studies

Pharmacokinetic studies

The relative PK properties of the biosimilar and the reference product should be determined in a single-dose crossover study using s.c. administration. Comprehensive comparative data should be provided on the time-concentration profile (AUC as the primary endpoint and C_{max} , t_{max} , and $t_{1/2}$ as secondary endpoints). Studies should be performed preferably in patients with type1 diabetes. Factors contributing to PK variability e.g. insulin dose and site of injection / thickness of subcutaneous fat should be taken into account.

Pharmacodynamic studies

The clinical activity of an insulin preparation is determined by its time-effect profile of hypoglycaemic response, which incorporates components of PD and PK. PD data are of primary importance to demonstrate comparability of a similar recombinant human insulin with the reference product. The double-blind, crossover hyperinsulinaemic euglycaemic clamp study is suitable for this characterization. Data on comparability regarding glucose infusion rate and serum insulin concentrations should be made available. The choice of study population and study duration should be justified. Plasma glucose levels should be obtained as part of the PK study following s.c. administration.

Clinical efficacy studies

Provided that clinical comparability can be concluded from PK and PD data, there is no anticipated need for efficacy studies on intermediary or clinical variables.

Clinical safety

The safety concerns with a similar recombinant human insulin relate mainly to the potential for immunogenicity.

Immunogenicity

The issue of immunogenicity can only be settled through clinical trials of sufficient duration, i.e. at least 12 months using s.c. administration. The comparative phase of this study should be at least six months, to be completed pre-approval. Data at the end of 12 months could be presented as part of post-marketing commitment. The primary outcome measure should be the incidence of antibodies to the test and reference medicinal product. The plans for these trials should take into account:

- Justification of study population including history of previous insulin exposure
- Definitions of pre-specified analyses of the immunogenicity data with respect to effects on clinical findings (glycaemic control, insulin dose requirements, local and systemic allergic reactions).

Local reactions

If any concern is raised through non-clinical and short-term clinical studies outlined above, additional evaluation of local tolerability may be needed pre-marketing. Otherwise, such reactions should be monitored and recorded within immunogenicity trials.

6.3.3.2 Aspects of the Insuman EU application dossier

Insuman is produced by recombinant DNA technology. The structure and activity are shown to be identical as compared to the semi-synthetic human insulin produced by enzymatic conversion of porcine insulin but the manufacturing process of the API differs (EPAR Insuman).

The company Hoechst AG submitted on 29 November 1995 to the EMEA an application for MA for the medicinal product Insuman falling within the scope of Part A of the Annex to Council Regulation No (EC) 2309/93. The MA was granted 450 days later on 21 February 1997 (EPAR Insuman).

Insuman, annex II application of Commission regulation (EC) No 542/95 was submitted in order to introduce a second generation of recombinant human insulin (Insulin HPR or Insulin HR1799). This centralized application differed from the first generation of recombinant human insulin (insulin HGT) in its manufacturing process.

On two occasions (12 May 1995 and 15 May 1996) the applicant requested scientific advice from the CPMP on the sufficiency to perform a reduced clinical program. The CPMP emphasized that “in order to demonstrate that the two recombinant human insulins have the

same characteristics, the company should conduct intensive comparative studies on physico-chemical characterization. Evidence should be provided that the two recombinant human insulins produced with different means have the same quality in terms of both impurities and characteristics of the active compound. On basis of comparative PD and PK studies, the company have to demonstrate that similar biologic activity and similar PK parameters can support identical therapeutic activity. Furthermore, the company should provide information on the level of antigenicity of the different types of insulin. Provided that the results obtained with proper studies are satisfactory, a reduced clinical package of information can be considered.” (EPAR Insuman).

Insuman was presented as six different preparations depending on the ratio short/prolonged duration of action: Insuman Rapid, Comb 50, Comb 25, Comb 15, Basal, Infusat (EPAR Insuman). The composition of the six formulations differed in relationship to the excipients. Clinical studies were performed with 3-ml cartridges of the 100 IU/ml formulations, which were identical to the formulations to be marketed. The following studies were carried out (EPAR Insuman):

Toxico-pharmacological aspects

Pharmacodynamics

- Related to the proposed indication: The blood glucose lowering effect of Insuman formulations were indistinguishable from that of semisynthetic human insulin preparations after s.c. administration in rats, dogs and rabbits. In the rat and dog studies, a statistically significant difference in depot effect between three preparations was demonstrated.
- Safety: The general cardiovascular PD was studied in anaesthetized dogs. The observed and expected cardiovascular effects were shown to be due to induced hypoglycemia.

Pharmacokinetics

No PK studies were performed in laboratory animals. This information was considered to be not necessary for the products at hand.

Toxicology

- Single dose toxicity was studied in Wistar rats. The animals were observed for three weeks. No signs of toxicity occurred.
- Repeated dose toxicity was not studied because of the low level of impurities and the biological and chemical identity of the drug to natural insulin.
- Reproduction studies were not performed, because it was known from the literature that insulin-induced hypoglycaemia provokes birth defects in mice, rats and rabbits. In addition, it is well known that diabetic hyperglycaemia causes congenital malformations and increased neonatal mortality.
- Mutagenicity testing was not required for recombinant human insulin because of its peptidic nature and well-characterized impurity profile. Nevertheless the following tests were performed: Ames test and E. coli WP2 uvrA test.
- Carcinogenicity: No studies were performed.
- Local tolerance (e.g. phototoxicity, photosensitivity) of s.c. injection of Insuman Rapid was tested in rabbits.

- Special toxicity studies: Immunotoxicity, the induction of anti-insulin antibodies, will be discussed in the clinical part.

These findings might have lead to the recommendation in the guideline, that safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not routine requirements for non-clinical testing.

Environmental risk assessment

Since natural human insulin is rapidly and completely degraded by enzymatic hydrolysis, the injected drug was not considered as a environmental risk factor.

Clinical aspects

The clinical part of the dossier for the approval of Insuman consisted of four bioequivalence studies carried out studying the comparison of the biosynthetic human insulin from Hoechst Marion Roussel GmbH, *versus* the corresponding recombinant human insulin manufactured by a competitor. The dossier further cross-referred to the clinical data presented for the approval of Insuman (Insulin HGT).

Bioequivalence studies

1. Study A1: Comparison of the PD and PK parameters of test (Insuman Rapid fast acting) and reference product using the euglycaemic clamp technique. The two insulin preparations compared well with regard to all variables calculated for the Glucose Infusion Rate (GIR) and the exogenous insulin serum concentrations. Based on these results it could be concluded that the two insulin preparations studied were bioequivalent.
2. Study A2: Comparison of the PD and PK parameters of test (human intermediate 30 % dissolved insulin and 70 % crystalline insulin) and reference product by using the euglycaemic clamp technique. The two tested insulin preparations also compared well with regard to all variables calculated for GIR and the exogenous insulin serum concentrations. Based on these results one could conclude that the two insulin preparations studied were bioequivalent.
3. Study A3: Comparison of the PD and PK parameters of test (Insuman Basal, intermediate acting) and reference product by using the euglycaemic clamp technique. Bio-equivalence was not fully demonstrated due to the well-known high intra-individual coefficients of variation of Neutral Protein Hagedorn (NPH). After the assessment of the responses provided by the applicant, the slight differences could be considered as clinically not relevant.
4. Study A4: Comparison of the PD and PK parameters of test (Insuman Rapid, fast acting) and reference product by using the euglycaemic clamp technique. The three insulin preparations compared well with regard to all variables calculated for the GIR and the exogenous insulin serum concentrations.

Based on these results, it could be concluded that the three insulin preparations studied (two test products Insuman Rapid (insulin HPR 1799) and Insuman Rapid (insulin HGT)) and another human insulin fast acting (reference) were mutually bioequivalent. The results from studies A1 to A4 based on both the PD effect and PK profile, indicate that the three insulin formulations had comparable benefit/risk profiles when administered i.v. Based on this

assessment a new route of administration (i.v.) was added for Insuman Rapid for treatment of hyperglycaemic coma and ketoacidosis, as well as for achieving pre-, intra- and post-operative stabilization in patients with diabetes mellitus.

For Insuman Infusat a solution of regular insulin for i.v. infusion, bioequivalence studies were not required according to the EU guidelines. For Insuman Comb 15, Insuman Comb 25 and Insuman Comb 50 no bio-equivalence studies were presented.

Pharmacodynamics and pharmacokinetics

PD and PK studies were performed in healthy volunteers after single administration of one of the Insuman preparations. A total of five Phase I studies were submitted. In these studies, five different biosynthetic formulations were compared to those of the corresponding semi-synthetic insulins. Insulin was injected s.c. In all studies the PD action of insulin was assessed using the euglycaemic clamp technique. As conclusion no significant differences in the PD values were found between semi-synthetic and recombinant insulin.

Clinical efficacy

In order to assess the clinical safety and efficacy of Insuman, two phase III trials (B1-B2) were performed involving a total 611 patients with either type I or type II diabetes mellitus.

B1 was a multi-center parallel-group study. Men and woman of ages 18-70 were enrolled in the study. Patients were stratified either to a free combination of NPH (crystalline, basal) with or without regular insulin or to a fixed combination Insuman Comb 25. Patients were randomized to either biosynthetic or semi-synthetic insulin preparations in each group. A total of 288 patients were treated daily with biosynthetic insulin for a range of 2-266 (median of 176) days and 289 patients were treated daily with semi-synthetic insulin for a range of 2-247 (median of 176) days.

There was no significant difference between biosynthetic and semisynthetic insulins during the 24-week study. After 10 week treatment more than 40 % patients both semi-synthetic and biosynthetic group experienced hypoglycaemic episodes. No statistically significant difference between these two groups was seen.

B2 was a small multi-center open non-controlled trial including 34 patients. Men and women aged 18 - 65 years suffering from type I diabetes mellitus were included in the study. Patients received continuous infusion of biosynthetic human pump insulin designed for use in an external insulin pump. The duration of treatment was 12 weeks. Glycated hemoglobin and hypoglycaemia were chosen as primary efficacy parameters.

Immunogenicity

Furthermore, no studies were included in the dossier dealing with product immunogenicity in humans. Chemically, a new insulin like by-product was found, although in low concentrations. Some pre-clinical data were available in the dossier, but these data were insufficient to assess the lack of immunogenicity in humans. The applicant agreed to provide the human data on immunogenicity during the post-marketing phase.

Apart from routine analysis of adverse events and blood chemistry and hematology, IgG antibodies to insulin and antibodies to E. coli peptides were measured in the phase III trials B1 and B2. As in all studies with human insulin, the immunogenicity was quite low.

6.3.4 Somatropin (EMA/CHMP/BMWP/94528/2005)

The principal bioactive hGH is a single chain non-glycosylated 191 amino acid, 22 kD polypeptide produced in the anterior pituitary gland. Growth hormone for clinical use has an identical amino acid sequence and is produced by recombinant technology using E. coli, mammalian cells or yeast cells as expression system. The structure and biological activity of somatropin can be characterized by appropriate physico-chemical and biological methods. Several techniques and bioassays are available to characterize both the active substance and product-related substances / impurities such as deamidated and oxidized forms and aggregates.

6.3.4.1 Requirements of the Guideline

Clinical studies

Growth hormone has potent anabolic, lipolytic and anti-insulin effects (acute insulin-like effect). The effects of hGH are mediated both directly (e.g. on adipocytes and hepatocytes) and indirectly via stimulation of insulin-like growth factors (principally IGF-1). Somatropin-containing medicinal products are currently licensed for normalizing or improving linear growth and / or body composition in hGH-deficient and certain non hGH-deficient states. The same receptors are thought to be involved in all currently approved therapeutic indications of recombinant hGHs.

Pharmacokinetic studies

The relative PK properties of the biosimilar and the reference product should be determined in a single-dose crossover study using s.c. administration. Healthy subjects are considered appropriate but suppression of endogenous GH production e.g. with a somatostatin analogue should be considered. The primary PK parameter is AUC and the secondary parameters are C_{max} and $t_{1/2}$. Comparability margins have to be defined a priori and appropriately justified.

Pharmacodynamic studies

PD should preferably be evaluated as part of the comparative PK study. The selected dose should be in the linear ascending part of the dose-response curve. IGF-1 is the preferred PD marker for the activity of somatropin and is recommended to be used in comparative PD studies. In addition, other markers such as IGFBP-3 may be used. On the other hand, due to the lack of a clear relationship between serum IGF-1 levels and growth response, IGF-1 is not a suitable surrogate marker for the efficacy of a somatropin in clinical trials.

Clinical efficacy studies

Comparable clinical efficacy between the biosimilar and the reference product should be demonstrated in at least one adequately powered, randomized, parallel group clinical trial.

Comparability margins have to be pre-specified and appropriately justified, primarily on clinical grounds, and serve as the basis for powering the study.

Clinical studies should be double-blind to avoid bias. If this is not possible, at minimum the person performing height measurements should be effectively masked to treatment allocation.

Sensitivity to the effects of somatropin is higher in hGH-deficient than non-hGH-deficient conditions. Treatment-naïve children with hGH deficiency are recommended as the target study population as this provides a sensitive and well-known model. Study subjects should be pre-pubertal before and during the comparative phase of the trial to avoid interference of the pubertal growth spurt with the treatment effect. This may be achieved e.g. by limiting the age / bone age at study entry. It is important that the study groups are thoroughly balanced for baseline characteristics, as this will affect the sensitivity of the trial and the accuracy of the endpoints.

(Change in) height velocity or (change in) height velocity standard deviation score from baseline to the pre-specified end of the comparative phase of the trial is the recommended primary efficacy endpoint. Height standard deviation score is a recommended secondary endpoint. Adjustment for factors known to affect the growth response to somatropin should be considered.

During the comparative phase of the study, standing height should be measured at least 3 times per subject at each time point and the results averaged for analyses. The use of a validated measuring device is mandatory. Consecutive height measurements should be standardized and performed approximately at the same time of the day, by the same measuring device and preferably by the same trained observer. These recommendations aim to reduce measurement errors and variability.

Calculation of pre-treatment growth rates should be based on observation periods of no less than 6 and no more than 18 months. For the determination of reliable baseline growth rates, it is important that also height measurements during the pre-treatment phase are obtained in a standardized manner using a validated measuring device.

Due to significant variability in short-term growth, seasonal variability in growth and measurement errors inherent in short-term growth measurements, the recommended duration of the comparative phase is at least 6 months and may have to be up to 12 months.

Demonstration of efficacy and safety in hGH-deficient children may allow extrapolation to other indications of the reference medicinal product if appropriately justified by the applicant.

Clinical safety

Somatropin has a wide therapeutic window in children during the growth phase whereas adults may be more sensitive for certain adverse effects. Antibodies to somatropin have been described, including, very rarely, neutralizing antibodies. Problems have been associated with the purity and stability of the formulations. Somatropin is administered s.c.; possible patient-related risk factors of immune response are unknown.

Data from patients in the efficacy trials are usually sufficient to provide an adequate pre-marketing safety database. Comparative 12-month immunogenicity data of patients who

participated in the efficacy trials with sampling at 3-month intervals and testing using validated assays of adequate specificity and sensitivity should be provided. In addition, adequate blood tests including IGF-1, IGFBP-3, fasting insulin and blood glucose should be performed.

6.3.4.2 Aspects of the Omnitrope EU application dossier

Sandoz submitted on 1 July 2004 their MAA to the EMEA under the legal base of similar biological medicinal product referring to Article 10.4 of Directive 2004/27/EC. The reference product to which Omnitrope claimed to be similar was Genotropin produced by Pfizer, originally authorized in the EU in 1988. Genotropin was presented in the same qualitative and quantitative composition and the same pharmaceutical dosage form. As required for a biosimilar application, the dossier contained a full quality Module 3 and reduced non-clinical and clinical Modules 4 and 5. The MA was finally granted 651 days after the application on 12 April 2006. Sandoz carried out the following studies as part of the comparability exercise (EPAR Omnitrope):

Physico-chemical characterization

Omnitrope was compared to the reference product Genotropin from a number of EU markets by a variety of spectrometric, sequence and physico-chemical data. No significant differences were identified. Omnitrope was shown to be comparable to the reference product, both quantitatively with regard to the overall purity and qualitatively with regard to the impurity profile.

Non-clinical aspects

Comparing with a full new application the pre-clinical program was reduced. It covered the following studies:

Pharmacodynamic studies

- Rat weight gain bioassays were performed to analyze the PD of batches of the API and the finished product.
- Potency assays: The purpose of rat tibial width assay was to estimate the potency of different recombinant hGH products, each with a high and low content of product-related impurities.

No specific PK studies were performed.

Toxicology

- Repeat dose toxicity (with toxicokinetics) 14 days s.c. toxicity test in the rat. The overall conclusion was that Omnitrope had no relevant toxic effect.
- Toxicokinetics: Serum was collected from selected animals in all groups post-dosing. The hGH concentration was measured. There was slight accumulation of GH over the 14 days of treatment indicated.
- Local tolerance: Two formulations of Omnitrope were given daily for seven days to male and female rabbits.

- Ecotoxicity / environmental risk assessment: The peptide was considered to be rapidly and completely degraded in the human organism. Thus, the therapeutically administered compound was not released into the environment.

Clinical aspects

During the clinical development program two formulations of growth hormone were used (powder for solution for injection and liquid) with two API sources (Covance and Sandoz). The formulation to be marketed (Omnitrope) was powder with the API of Sandoz.

Phase I: Pharmacokinetic studies

Three pharmacokinetic studies performed in healthy subjects were submitted. All PD assessments were part of the PK studies.

- Study EP2K-99-PhISUSA was an exploratory PK study assessing the PK profile of Somatropin Sandoz powder (API Covance) compared to placebo. Aim of the study was to assess the safety, tolerance and PK of somatropin after single s.c. administration. In the double blind, randomized, placebo-controlled, two-way crossover study, a total of 12 healthy subjects (six male and six female, 18 - 45 years) received either 5 mg Somatropin Sandoz powder (API Covance) or placebo (water for injection) s.c. The washout period between treatments was one week. The study further demonstrated that continuous infusion of octreotide was effective in suppressing endogenous GH secretion in healthy human subjects.
- In study EP2K-99-PhIUSA the PK profiles of Somatropin Sandoz powder (API Covance) and Genotropin USA were compared. The study was designed as a double blind, randomized, two-way crossover, comparative study. A total of 25 healthy subjects (12 male and 13 female, 18 - 45 years) received either 5 mg Somatropin Sandoz powder (API Covance) or Genotropin s.c. The washout period between treatments was one week. The PK of Somatropin Sandoz (API Covance) and Genotropin USA could be considered as comparable with respect to the rate and extent of absorption as well as elimination rate after a single dose.
- EP2K-00-PhI^{AQ}: This study demonstrated the equivalence between Somatropin Sandoz powder (API Covance) with Somatropin Sandoz 3.3 mg/ml solution for injection (API Sandoz). In this double blind, randomized, two-way crossover study, a total of 24 healthy subjects (12 male and 12 female, 23 - 48 years) received either 5 mg Somatropin Sandoz powder (API Covance) or Somatropin Sandoz Liquid (API Sandoz) s.c. The washout period between treatments was at least one week. Somatropin Sandoz Liquid (API Sandoz) and Somatropin Sandoz powder (API Covance) formulation were considered comparable with respect to the rate and extent of absorption.

Phase III: Pivotal study (efficacy and safety)

The study was a phase III study consisting of three sub-studies (EP2K-99-PhIII, EP2K-99-PhIIIFo and EP2K-00-PhIIIFo). Initially, the study was designed as a superiority study and was later re-designed to show similarity between Somatropin Sandoz powder (API Covance) and Genotropin. Two of the three sub-studies (EP2K-99-PhIII / EP2K-00-PhIIIFo) compared the effects of the EU reference product Genotropin and Somatropin Sandoz powder (API Covance) in an open design over a period of nine months on the growth in 89 treatment-naïve pre-pubertal children with GH deficiency. The third study compared the effects of Omnitrope

and Somatropin Sandoz liquid (API Sandoz) during the first six months of the study (month nine to 15 of the complete trial) after which all patients were transferred to Somatropin Sandoz liquid (API Sandoz).

The same patients were included in EP2K-00-PhIII^{AQ}, an open, multi-center, comparative, follow-up trial evaluating the efficacy and safety of two formulations of Somatropin Sandoz, i.e. Omnitrope and Somatropin Sandoz liquid (API Sandoz) formulation.

Besides these studies a pivotal safety study EP2K-02-PhIII-Lyo was carried out. The study is an ongoing, open, multicentre, non-comparative, non-controlled study using Omnitrope s.c. Twelve months data were evaluated. The study duration is planned for 24 months. As study subjects 51 treatment naïve children with GH deficiency were enrolled.

In conclusion, study EP2K-99-PhIII / EP2K-00-PhIIIFo demonstrated comparable efficacy between Somatropin Sandoz powder (API Covance) and Genotropin. Somatropin Sandoz powder (API Covance) and Omnitrope were similar, except for two additional purification steps for Omnitrope which were not expected to affect bioavailability or efficacy. The results from study EP2K-99-PhIII / EP2K-00-PhIIIFo showing comparable efficacy of these products were transferable to Omnitrope, the product to be marketed. The almost superimposable growth response curves during treatment with Omnitrope (in study EP2K-02-PhIII-Lyo) or Somatropin Sandoz powder (API Covance) (in study EP2K-99-PhIII / EP2K-00-PhIIIFo) further supported this conclusion.

Pivotal safety study

- The most important difference between Somatropin Sandoz powder (API Covance) and Genotropin in study EP2K-99-PhIII / EP2K-00-PhIIIFo was the formation of antibodies in 57 % and 2 % of the patients, respectively. However, no statistically significant or clinically relevant differences at any time-point between patients with and without anti-GH antibodies could be detected. This result indicated that the presence of anti-GH antibodies had no effect on efficacy. The formation of anti-GH antibodies was most likely related to the presence of an increased level of host cell proteins. Somatropin Sandoz powder (API Covance) and Omnitrope (API Sandoz) were similar, except for two additional purification steps for Omnitrope to reduce the amount of E. coli proteins.
- The submitted data from study EP2K-02-PhIII-Lyo confirmed that the issue of antibody induction was solved.

The clinical comparability in terms of safety and immunogenicity between Omnitrope and Genotropin was demonstrated.

6.4 Guideline on comparability of medicinal products containing biotechnology derived proteins as active substance, non-clinical and clinical issues (EMA/CPMP/3097/02/final)

The guideline addresses primarily the comparability exercise whereas the guideline EMA/CHMP/42832/2005 lays down the general principles for the non-clinical and clinical development and assessment of biosimilar products (see Section 6.2). Two situations are indicated in which comparability might become an issue:

- a variation procedure with regard to a change in the manufacturing process or
- a new application of a biosimilar product.

In either case it has to be demonstrated or justified that the “new” and the “original / reference” product have similar profiles in terms of quality, safety and efficacy. The purpose of the guideline is to explore which non-clinical and clinical data will be required. The data requirements and timing of submission of these data will have to be judged on a case-by-case basis and will mainly be guided by:

- the extent to which the product may be characterized,
- the nature of the changes,
- the observed potential differences between the two products,
- the clinical experience pertaining to the particular class of products.

The clinical requirements supporting the variation procedure on changes in the manufacturing process are not within the main focus of this master thesis.

This guideline will be replaced by EMEA/CHMP/BMWP/101695/06. In future, the issues of immunogenicity will be addressed by a separate guideline (EMA/CHMP/BMWP/14327/06), which is currently also a draft for consultation.

6.4.1 Requirements of the guideline

It may not be necessary to repeat all safety and efficacy studies of the originator if the biosimilar applicant can demonstrate that

1. it is possible to characterize the product in detail with respect to physico-chemical properties and in vitro activity and
2. comparability can be shown from a chemical-pharmaceutical perspective.

During the whole comparability exercise the same reference product should be used for all three parts of the dossier.

In case the reference product has more than one indication, the efficacy and safety of the biosimilar product has to be justified or demonstrated separately for each of the claimed indications. Justification will depend on e.g. clinical experience, available literature data for the reference product, whether or not the same receptors are involved in all indications, pre-clinical data and immunogenicity.

Safety data will be needed prior to MA but also post-marketing as possible differences might become evident later.

Non-clinical data

Data from non-clinical studies can provide useful pointers to potential therapeutic differences in the biological properties. Non-clinical studies should be comparative in nature and may be used to highlight differences between the biosimilar and the reference product particularly regarding immunogenicity. All points of the guideline CPMP/ICH/302/95 will need to be addressed in the dossier. The following approach may be considered:

- In vitro studies: A battery of receptor binding studies should be undertaken in order to assess if any alterations in reactivity have occurred and to determine the likely causative factors.
- In vivo studies: If there are specific uncertainties or concerns regarding safety in vivo studies in one or more suitable animal model may be considered, ideally a species shown for the reference product to be a good model for man. The biosimilar and the reference product should be compared in the final product composition and at several dose levels to allow a comparison of the dose-response curve.

The duration of the studies should be sufficiently long to detect any differences in toxicity and immunogenicity and should take into account the intended duration of use.

Clinical data

Important issues that should be taken into account when designing and justifying the clinical program include experience gained with the originator product with respect to:

- the stage of development of the product,
- the relationship between dose and response as well as efficacy and safety,
- whether a dynamic marker has been accepted as a surrogate marker,
- the relationship between dose / exposure and this surrogate marker,
- drug receptor interaction,
- disease specific mechanism of action,
- target organ for activity,
- mode of administration,
- PK properties including biological barriers of relevance.

The clinical requirements showing comparability depend on the type of product and the therapeutic areas. Generally, demonstration of equivalence concerning bioavailability and PD actions using equivalent doses is required. Equivalence has to be defined a priori and the choice of the PD parameters justified. In addition, clinical trials demonstrating equal efficacy (equivalence trials) will generally be necessary between the biosimilar and the reference product. The kind of trials, the duration and the type of endpoint (e.g. clinical or surrogate) depend on experience, type of product, therapeutic area and the availability of accepted surrogate endpoints. Assay sensitivity has to be ensured.

Surrogate markers

Usually in clinical trials efficacy is defined by a clinical endpoint. Sometimes surrogate markers are used. Surrogate markers are usually more sensitive to changes in activity and can be assessed earlier than clinical endpoints and therefore may be more useful when comparability has to be shown. However, data are needed concerning the quantitative relationship between the surrogate and the clinical endpoint to enable defining and justifying the equivalence margins.

Comparability exercise

The applicant has to demonstrate that the product is similar in terms of quality, safety and efficacy to a medicinal product already authorized in the EU. It may not be necessary to repeat all safety and efficacy studies if the applicant can demonstrate that

1. it is possible to characterize the product in detail with respect to physico-chemical properties and
 2. comparability can be shown from a chemical-pharmaceutical perspective.
- During the whole comparability exercise the same reference product should be used for all three parts of the dossier.

In case the reference product has more than one indication, efficacy and safety of the biosimilar product has to be justified or if necessary demonstrated separately for each of the claimed indications. Justification will depend on e.g. clinical experience, available literature data for the reference, whether or not the same receptors are involved in all indications, pre-clinical data and immunogenicity.

Safety

Safety data will be needed prior to MA, but also post-marketing including risk-to-benefit assessment. A risk specification should be presented in the dossier. This includes a description of possible safety issues related to tolerability that may result from a manufacturing process different from that of the innovator. A pharmacovigilance plan should be presented. In the PSURs submitted during the first five years tolerability should be particularly addressed.

Immunogenicity

Immunogenicity must always be addressed by clinical data with special emphasis on differences in the quantity or type of antibodies, unless immunogenicity can be excluded. The issues regarding immunogenicity are already summarized in Section 6.2 above. In addition, the following important issues are laid down in this guideline.

Prediction of immunogenicity

The factors triggering immune reactions are often not fully understood. In general, however, the occurrence of immunogenicity is influenced by the properties of the API and the finished product. Changes to the manufacturing process, i.e. from the originator process to the biosimilar process, may lead to changes that can trigger an immune response. Furthermore, host factors including genotype and concomitant disease associated with immune dysregulation, previous exposure to other therapeutic proteins that may cause cross reactivity may also play a part. The route of administration can modify the host immune reaction. Repeated administration of an antigen may increase the likelihood of an immune response as compared to on-off treatment.

Changes to the API and the finished product

Changes induced by an altered manufacturing process may not always be detected by physico-chemical methods but may still cause immunogenicity.

Investigation of immunogenicity

Virtually, all biotechnology derived proteins elicit some level of antibody response. Those antibodies associated with clinical consequences require closer monitoring. The assessment of immunogenicity requires validated antibody assays, characterization of the observed immune

response as well as evaluation of the correlation between antibodies, PK / PD and efficacy and safety. Especially the role of immunogenicity in events related to hypersensitivity, infusion reactions, autoimmunity and loss of efficacy should be considered. In addition, a post-marketing program may be required as discussed below.

A rationale for the proposed antibody strategy should be presented. The screening assays should be sensitive enough to detect low titre antibodies as well as antibodies to conformational and linear epitopes. An assay for neutralizing antibodies should be available for further characterization of antibodies detected. The assays should be validated. Standard methods and international standards should be used whenever possible. The duration of the studies must be sufficiently long; the periodicity and timing of sampling for testing of antibodies should be justified. The value of the antibody testing in the monitoring of the individual patient should be critically evaluated and recommended as a routine measure only if it can affect therapeutic decision-making.

When to study immunogenicity?

The issue of immunogenicity must always be considered when a claim of comparability is made, especially when repeated administration is proposed. Immunological studies are expected if physico-chemical characterization is not sufficient and an impact on immunogenicity cannot be excluded with reasonable certainty.

In principle, pre-authorization studies are required for a claim of comparability. In view of the unpredictability of the onset and incidence of immunogenicity post-marketing monitoring of antibodies at predetermined intervals will be required for at least one year for a biosimilar product. A pharmacovigilance plan and a pharmacovigilance specification for post-marketing should be included in the MAA. If the risk for serious but rare immune response is considered to be high, either because of signals detected before the authorization or previous experience with similar products a special risk management program may be required. Special consideration should be given to those products where there is a risk that the immune response could affect the endogenous protein that has unique biological functions.

6.4.2 Comments and discussion

The standard generic approach of simply showing bioequivalence to a reference product is not feasible for biosimilar products. In addition to the quality data required for all biotechnology products, the biosimilar dossier must contain a comparability exercise. The applicant is well advised to agree on the comparability program with the EMEA in advance.

The biosimilar product and the originator reference product have to be well characterized and it has to be shown that the products are comparable in terms of quality, pre-clinical and clinical profile. The comparability exercise is triggered by changes in the manufacturing process between biosimilar and reference product (process = product): any alteration to the originator's process can impact safety and efficacy. On the other hand, due to patent reasons it is impossible to replicate the originator's process exactly, which makes it difficult to prove similarity or equivalence.

The focus of the comparability exercise is to assess the impact of the combined observed and unobserved product changes on safety and efficacy using an established test battery. That this

can be done has been proven by innovator firms (i.e. for LMWH) supporting a variations procedure for manufacturing changes without repeating extensive clinical trials (Zeid, 2000, Fareed, 2004).

In cases, where satisfactory comparability may not be demonstrable, a full pre-clinical and clinical data package will be required. If a change in the primary sequence of the API is detected the concept of comparability cannot be applied anymore.

Physico-chemical characterization

Since the comparability exercise covers also a physico-chemical characterization of the biosimilar and the reference product the pharmaceutical part of a biosimilar dossier contains a full Module 3 and additionally a comprehensive comparative physico-chemical characterization of test and reference product.

The physico-chemical comparability includes similarities in structure and activity between biosimilar and reference product. Due to nowadays available highly sophisticated analytical possibilities and capacity the physico-chemical characterization should be carefully evaluated and aligned with the specification of the reference product. On the other hand, clinical experience cannot be extrapolated from physico-chemical comparability. Even if all analytical data appear identical, they do not prove that similar products are identical in terms of safety, immunogenicity or efficacy. Since the structure of proteins is usually too complex for a complete physico-chemical characterization, the clinical relevance of all physico-chemical parameters has to be evaluated carefully.

In most cases analytical methods alone without any further clinical data are not sufficient to support a biosimilar application. Furthermore, differences in the purity and impurity profile between biosimilar and reference product could be a safety risk, if they are not properly assessed via preclinical or clinical studies. Actually, the criteria for “similarity” does not lie solely in analytical equivalence but in demonstrating therapeutic equivalence to a standard test battery that has been shown to be sensitive enough to detect subtle differences in the safety profile and have some value in predicting impact on safety and efficacy (Zeid, 2000).

Clinical studies

With regard to clinical studies there are several factors that will need to be considered including (Nick C, 2004):

- the physico-chemical and biological similarity to the reference medicinal product
- the relationship between the pharmacodynamic effect, the clinical effect and the administered dose
- the existence of suitably validated surrogate markers and their relationship to dose and resulting drug tissue levels
- the statistical burden for proof of efficacy at the 95% confidence level in terms of the acceptability of the equivalence margin, the need for assay sensitivity, the variability in terms of the common standard deviation, and the required power of the study
- the potential for immunogenicity and the potential impact of neutralizing antibodies.

For most biologics, depending on the nature of the protein, comparability can be demonstrated using some or all of the following parameters: in vitro studies, PK studies, surrogate markers or clinical outcome (Rakoczy, 2004). For the therapeutic interchangeability

of LMWH there have been six criteria described, which should be scientifically justifiable and pharmaco-economically beneficial (Fareed, 2004; Leong, 2003):

- pharmacological equivalence,
- clinical evidence supporting therapeutic interchange in a given indication,
- cost / availability,
- thorough evaluation process,
- regular monitoring of patient outcomes and
- response variations.

However, the bioequivalence margins suitable for small molecules may not be appropriate for biosimilars and will need to be decided on a case-by-case basis taking into consideration the route of administration, the therapeutic window and the precision and sensitivity of the available assays (Nick C, 2004).

6.5 LMWH

Low molecular weight heparins (LMWH) offer certain advantages as compared to unfractionated heparin, including longer dose intervals and more predictable PK and PD. LMWH are prepared from unfractionated heparin by various depolymerization processes. Thus, the starting material of LMWHs is of biological origin. There is a manufacturing process that defines the characteristics of the drug substance. The drug substance is a very complex mixture of glycosaminoglycans of different sizes that can be characterized with difficulties by using state of the art analytical methods. In addition the quantitative composition of the polysaccharide chains vary from preparation to preparation. Due to this heterogeneity, conventional PK studies cannot be performed. Instead, the absorption and elimination of LMWHs can be studied by using PD tests, including anti-FXa and anti-FIIa activity (EMA/CHMP/BMWP/496286/2006).

6.5.1 Requirements of the Draft Guideline (EMA/CHMP/BMWP/496286/2006)

There are several licensed LMWHs that differ in their source material, manufacturing process, PD properties and therapeutic indications, which include treatment and prophylaxis of deep venous thrombosis and prevention of complications of unstable angina and non-Q wave cardiac infarction.

MAAs for LMWH have been submitted in several EU Member States. Assessment of these applications is difficult for several reasons: the physico-chemical characterization of the LMWHs is limited due to the high complexity of the molecules and the limited knowledge about qualitative and quantitative contribution to safety and efficacy of each fraction

The kinetics of LMWH are based on PD measurements. However, the quantitative correlation between the PD and clinical efficacy has not been demonstrated. Furthermore, the relative contribution of various interactions with proteins and cells of LMWHs to the efficacy in different therapeutic indications is controversial.

Classical bioequivalence studies are not sufficient to establish therapeutic equivalence between LMWHs. The design of an appropriate comparability program is complicated by the unknown PD and clinical significance of the numerous interactions with plasma components

and cells and by the rather complex mixture of the drug substances. Regulatory guidelines are regarded as a useful tool to harmonize the requirements across the EU.

The Working Party on similar biological medicinal products (BMWP) recommend drafting a guideline on the non-clinical aspects of the development and assessment of similar biological medicinal products containing LMWH. The guideline should address:

- Role of non-clinical studies in demonstration of comparability of two LMWHs
- Demonstration of comparable pharmacokinetics and pharmacodynamics
- Possibility of using pharmacodynamic markers only in demonstration of equivalent efficacy
- Need for and design of clinical studies to demonstrate comparable efficacy and safety.
- Extrapolation of clinical data from one therapeutic indication to others
- Risk Managements Plans

A joint drafting group consisting of BPWP experts will develop the guideline. At least three formal meetings of the drafting group will be required in the margins of the working party meetings. Contributions from experts from EWP, BWP, QWP, BPWP, SWP and PhVWP will be required.

Guidance on the investigation and assessment of immunogenicity may contribute to a predictable and consistent assessment of the national MAA and facilitate the MRPs or DCPs involving LMWHs.

6.5.2 Comments and discussion

Besides the draft as mentioned above there are no valid guidelines neither in the USA nor in Europe for the clinical requirements on the generic development of LMWH. The above mentioned Guideline has been published in January 2007 for consultation until 30 April 2007. A joint drafting group consisting of BPWP experts should develop the non-clinical recommendations to be laid down in this guideline. The time frame for this has not been fixed yet.

When the different LMWHs (i.e. Fraxiparin, Dalteparin, Enoxaparin) were initially developed, they were envisaged as generic drugs to each other. However, results gained during product development assigned them as not being bioequivalent. The agents exhibit substantial molecular structural heterogeneity. Today, they are considered as distinct drugs, whose safety and efficacy profile has been determined separately. Obviously, the individual composition of each LMWH determines its PK and PD in vivo behavior, which may account for the different safety / efficacy ratios observed in clinical trials. Eventually, LMWH from different sources can neither be considered as bioequivalent nor as interchangeable. Each of the commercial LMWHs has been individually developed in specific clinical indications which may be dosage and product dependent (Fareed, 1988, Fareed, 2003).

The strongest argument against generic competition relies on the unique LMWH manufacturing process and the lack of full characterization of this drug class (Leong, 2003). This hurdle unifies the fortune of LMWs and biosimilar products: if regulatory requirements do not consider all of the originator's specifications, it may be very likely that a generic product will not behave in a similar way as the original drug. And the other way round: if a

generic version copies exactly the originator's process and specifications, it is likely that it is patent infringing. In order to prevent generic competition Aventis submitted a citizen's petition on February 19, 2003 to the FDA, supplemented on February 12, 2004 emphasizing the unique manufacturing process for its product. The citizen's petition and its supplements have stipulated that several requirements should be met before the FDA gives any considerations to the generic LMWH (Fareed, 2004).

Because of the complex PD profile of these agents, basic bioequivalence studies like for small molecules are not considered sufficient. Minor compositional differences in the generic version may have an impact on the PK and PD data. Additional testing in animal models for safety and efficacy and PD parameters may be mandatory. Bioequivalence and PD comparative data have been described and should include antithrombotic markers such as anti-Xa-, anti-IIa-activity, anti-Xa to anti-IIa ratio, activated partial thromboplastin time, international normalized ratio, comparable effect on INR, USP activity, pharmacologic characterization (Fareed, 2004; Leong, 2003).

In order to achieve the desired clinical equivalence physical, chemical, biochemical, and PK / PD parameters should be compared for test and reference product as well as drug interaction studies including antithrombotic activity (Leong, 2003). In addition, head-to-head clinical trials for specific indications will also prove safety and efficacy of the generic LMWH in comparison to branded products (Fareed, 2004; Leong, 2003).

6.6 Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (EMA/CHMP/BWP/14327/06)

This draft guideline is valid not just for biosimilar but for all biotechnology products. In the following some key aspects of the draft guideline will be summarized:

Sampling

Several factors such as dose, schedule and treatment modalities influence the development of an immune response against a therapeutic protein. Therefore, the sampling schedule for detection of an immune response should be adapted and selected individually for each product. Baseline samples should always be collected.

For products intended for chronic use, more frequent sampling will be employed in the earlier phase of treatment, where patients are usually most at risk of antibody development. Sampling schedules should include repetitive sampling and be designed to clearly distinguish patients being transiently positive from patients developing a persistent antibody response.

Since longer-term treatment is more likely to result in an immune response, routine sampling later in the treatment course for a sufficient number of patients should be implemented in clinical trials. In case of continuous chronic treatment, immunogenicity data in general for one year should be available pre-authorization.

Efforts should be engaged to collect data on potential changes in the character of the antibody response over time, e.g. change from non-neutralizing to neutralizing in a given patient, where applicable.

To enable intra-product comparison, applicants should endeavor to standardize sampling schedules, assays, definitions etc. However, for some therapeutic proteins, different timings for antibody formation have been reported depending on the underlying disease. Applicants should consult relevant bibliographical data relating to other products to identify the appropriate timing of measurements in relation to the underlying disease, and scheduling might have to be adapted accordingly. If feasible, sampling should be done after completion of the treatment regimen to determine persistence of response. Adequate follow-up of patients for measuring an immune response after discontinuation of treatment should be implemented to evaluate immunogenicity in absence of the therapeutic protein.

Sampling should take into account both the half-life of the therapeutic protein and the duration of PD effects. While a decrease of anti-drug antibodies might occur over time in patients initially positive for such antibodies, also a rise in such antibodies might occur, e.g. if the therapeutic protein has immunosuppressive properties and by its mechanism of action suppresses an immune response against itself.

Impact on PK of the product

Both neutralizing and non-neutralizing antibodies can impact on the PK of the product. If antibodies are detected during the clinical program, the applicant should investigate the impact on the PK in the individual patient. The binding characteristics (binding vs. neutralizing) should be linked to this evaluation. The half-life may be prolonged, but not necessarily associated with the prolonged therapeutic effect. A change in PK may be an early indication of antibody formation.

Methodology aspects to assess comparability of immunogenicity potential

During comparability testing either for changes in the manufacturing process or to a reference product in case of the development of a biosimilar product immunogenicity evaluation should be part of clinical efficacy and safety studies. Studies should be carefully planned and data should be systematically collected from a sufficiently large number of patients to characterize the variability in antibody response. Since the comparative evaluation of immunogenicity both inter-product (i.e. biosimilar products or products in the same class) and intra-product (i.e. between different versions of the product, indications or different patient populations for a given product) is of relevance, applicants should make an effort to select a homogeneous patient population that allows for such comparisons.

A patient population should be chosen that is representative of the target population intended for clinical practice. Due to expected differential susceptibility, immunogenicity data from healthy volunteers are not suitable substitutes. For most products, immunogenicity is studied in previously unexposed patients. Children should be studied separately, if applicable, stratified by age. A sufficient washout period for previous treatments potentially influencing the immune response should be included, taking into account not only elimination, but also reversal of the pharmacodynamic effect, where appropriate.

Recommendations for routine monitoring of changes in clinical response and linking immunological findings to clinical events

Antibody testing should be considered as part of all clinical trial protocols. For a clinical trial, applicants are encouraged to evaluate immunogenicity in all patients and not only in a

symptom-driven manner (i.e. only for patients when a change in safety or efficacy profile is suspected).

However, further to scheduled routine repetitive sampling patients should also be evaluated in a symptom-driven manner, when the occurrence of an antibody is suspected. Applicants should collect data and provide guidance for the prescriber as part of the MAA on how a patient with loss of efficacy should be handled over time, e.g. by an increase of dose or a reduced dosing interval or cessation of treatment. The results of the immunological studies should be included in the relevant sections of the SmPC.

Immunogenicity in paediatric indications

Recombinant technology has allowed the development of proteins for use in genetic disorders where previous substitution treatment has not been available. Children are the most likely subjects exposed to these products and may be at high risk for antibody development. When studying the product in a paediatric indication, posology and treatment schedules should be selected and justified accordingly. Patients should be stratified by age, and immunogenicity data should be evaluated and presented separately for each age stratum.

Risk management Plan

The extent of data on immunogenicity that can be obtained during the clinical development program depends on the event rate, driven both by the immunogenic potential of the protein and the rarity of the disease. Therefore, further systematic immunogenicity testing might become necessary after MA, and may be included in the risk management plan. The extent of immunogenicity data to be collected in the post-marketing setting will depend on various factors including:

- Disease-related factors like its prevalence, the vulnerability of the patients, availability of alternative therapies, duration of treatment, etc.
- Pre-authorization immunogenicity findings including impact on efficacy and safety.
- Experience on immunogenicity with similar proteins or related members from that class of proteins, including proteins manufactured with similar production processes.

6.7 Example for implementation of the biosimilar legislation in an EU member state: Germany

Directive 2004/27/EC (of 31 March 2004) amending Directive 2001/83/EC has been implemented into German national law with the 14. amendment of the German Drug Law (Arzneimittelgesetz, AMG), which has come into force one and a half year later on 06 September 2005.

In particular, the legal basis as defined in article 10 (4) of Directive 2001/83/EC as amended was implemented in German national law by adding a new article § 24 b (5) to the German Drug Law. The wording of this article is substantially the German translation of the Directive article with just one difference: Regarding the type and quantity of supplementary data to be provided the Directive refers to the requirements as laid down in Annex 1 (Directive 2003/63/EC) and the related guidelines, whereas the German Drug Law is a bit more vague by referring to the “state of the art” and the relevant criteria thereunto.

The requirements on the registration dossier are further laid down in a general administrative provision enacted by the ministry of health on the basis of § 26 German Drug Law called “Arzneimittelprüfrichtlinien” (Arzneimittelprüfrichtlinien, 2004). The general administrative provision has been amended on 11 October 2004 implementing the EU requirements of the so called “Review 2004”. Section 3, Article 4 deals with biosimilar products. The wording of this article is the direct translation of Directive 2003/63/EC, Part II, Section 4 (see Section 5.3.1).

According to this document, the dossier of a biosimilar product must not be limited to Module 1, 2 and 3 like normal generics, but has to contain data on bioequivalence and bioavailability additionally. The extend of such additional data (toxicological, pre-clinical and clinical data) will be assessed on a case-by-case basis according to the scientific guidelines. In case of more than one indications of the originator product efficacy and safety of the biosimilar product have to be justified or demonstrated for each of the indications separately. Based on the differences of the biological medicinal products the authority has to assess the types of studies of Module 4 and 5 on a case-by-case basis. With regard to the basic principles of biosimilar products, the general administrative provision refers to the guideline/s published by the EMEA on this subject.

7. Case studies

7.1 Epoetin

Currently there are two product ranges of Epoetin alpha (Erypo / Janssen-Cilag and NeoRecormon / Roche) and one product range of Epoetin beta (NeoRecormon / Roche) on the German market without any generic competition both in various dosage strengths, see Annex 1. The Roche products are authorized via Centralized Procedure.

Mid of 2006 Stada Arzneimittel AG has filed an MAA at the EMEA on behalf of Bioceuticals Arzneimittel AG for Erythropoietin-zeta. The launch is envisaged at the beginning of 2008 (Stada 2006). BioGeneriX - a company belonging to the ratiopharm group – as well as Biopartners GmbH are both developing a formulation of epoetin, too. Biopartners in-licensed and targets to start the development program in the second half of 2006 and to start Phase I clinical trials in the second half of 2007.

7.2 G-CSF

Currently the originator product is on the German market in two dosage strengths without generic competition, see Annex 2. Stada / Bioceuticals Arzneimittel AG and BioGeneriX are developing a biosimilar version of Filgrastim / G-CSF (Stada 2006).

7.3 Human Insulin

Annex 3 gives an overview over the products currently on the German / European market. Most of the products are authorized via the Centralized Procedure and manufactured by

recombinant DNA technology. The first product licensed throughout the EU was Insuman from Aventis. The clinical program is summarized under Section 6.3.3.2.

7.4 Interferon

For Interferon alpha-2a a reduction in efficacy has been reported due to immunogenicity. Therefore, for interferon immunogenicity is an issue and should essentially be included in pre-approval studies (Schering, 2004).

Currently there is no generic competition on the German market for any interferon products, see Annex 4. Biopartner's interferon beta is currently in advanced Phase III clinical trials and the company expects to submit a MAA to the EMEA in the first quarter of 2007. Biopartners GmbH in-licensed its interferon beta formulation from Rentschler in September 2002. On June 30, 2006, the CHMP issued a negative opinion for a biosimilar application filed in December 2003 by the company due to issues concerning basic manufacturing aspects and biosimilarity (Rader 2006). BioGeneriX is developing interferon beta-1b for the treatment of multiple sclerosis. Stada has stopped their interferon-beta development (Stada 2006).

7.5 LMWH

Today, due to patent reasons there is no generic competition on the LMWH market. The various LMWH products currently registered in Germany are listed in Annex 6. Although neither the FDA nor any European authority has approved a generic LMWH yet, there is a lot of generic competition on the development of enoxaparin, the most important LMWH:

- Teva Pharmaceutical submitted an ANDA on June 30, 2003.
- The FDA accepted the application from Amphastar, Inc. on June 26, 2004.
- Momenta Pharmaceuticals in collaboration with Sandoz submitted an ANDA for M-Enoxaparin as generic equivalent to Lovenox™ in August 2005.
- Gland Pharma has already introduced Cutenox in India.
- A generic version of enoxaparin is available in Brazil.

LMWHs are not protein drugs, thus none of these products are registered following the Centralized Procedure. Since LMWHs are a complex mixture of linear polysaccharides extracted from biologic material, it is very likely that generic versions would not be accepted with a simple bioequivalence study and without further clinical and toxicological data. The content of the draft guideline on non-clinical issues is summarized under Section 6.5.

7.6 Somatropin

Currently, in Germany nine product ranges (Annex 5) in various dosage strengths are marketed: three as solution for injection and six as powder for solution for injection. All products are produced by recombinant DNA technology. Two products are authorized via the Centralized Procedure (Omnitrope / Sandoz, NutropinAQ / Ipsen Pharma GmbH).

The first biosimilar product in the EU was Somatropin (Omnitrope / Sandoz). The EMEA issued a favorable opinion in mid-2003, but did not approve the product at that time. Sandoz sued the EMEA in January 2004 to force a decision (Brown, 2005). Sandoz finally submitted

on 1 July 2004 their MAA to the EMEA again, now under the legal base of similar biological medicinal product referring to Article 10.4 of Directive 2004/27/EC. The MA was finally granted 651 days after the application on 12 April 2006. The clinical program of Omnitrope is described under Section 6.3.4.2.

A second biosimilar product, Valtropin from Biopartners GmbH, was authorized on 24 April 2006 in exactly the same terms. Biopartners is further developing a sustained release formulation of Valtropin that requires less frequent administration. Biopartners targets to submit a MAA to the EMEA in the second half of 2008.

In the USA Sandoz filed in July 2003 under 505 (b) (2). Omnitrope has finally been approved on 30 May 2006. According to the FDA Omnitrope is not officially called a generic, because it is not rated as therapeutically equivalent to any of the other approved hGH products. It is, however, sufficiently similar to the originator's product Genotropin from Pfizer and is thus given the term follow-on protein product. Sandoz sued the FDA and the Department of Health and Human Service in September 2005 and on April 10, 2006, a federal judge in Washington, D.C. ruled that the FDA must make a decision on the application. The FDA approved the drug, because they assessed hGH as a fairly simple and well-understood protein. However, the FDA stressed that the Omnitrope approval does not establish a pathway for approval of biological FOPs, nor does it mean that more complex and / or less understood proteins could be approved as FOP (Barnes, 2006; FDA 30 May 2006).

7.7 Further biosimilar approaches

Sicor / Teva has already developed a biosimilar version of Novartis' Sandostatin (octreotide acetate). Octreotide is an octapeptide that mimics the effects of human somatostatin.

Besides Omnitrope, recent examples of 505 (b) (2) biogeneric-like approvals include recombinant calcitonin (Fortical), glucagon (GlucaGen) and multiple animal-derived (Vitrace and Amphadase) and recombinant hyaluronidase (Hylenex) products. The FDA has avoided the issue of therapeutic equivalence / substitution by designating each as a new chemical entity, recognizing each as unique, not substitutable in terms of filling prescriptions, forcing each to be marketed as a branded product (Rader, 9/20/2006). In July 2006, the FDA refused to approve an ANDA filed by Natestch for its generic form of Miacalcin nasal spray (Calcitonin). The FDA cited potential immunogenicity concerns (due to chlorobutanol, used as an antimicrobial preservative) 30 months after filing. From a regulatory point of view, antigenicity data cannot be used in a generic drug application in the USA. (Rader, 2006).

8. Outlook

Several important recombinant proteins are already or will be coming off patent during the next years. For example for Buserelin (Aventis) the patent has already expired. In the next couple of years the various interferons and interleukin antagonists as well as oxytocin and its antagonist and the most important LMWH enoxaparin will go off patent in Europe, see Annex 7. Thus, it could be expected, that the EMEA will extend the list of product specific annexes to EMEA/CHMP/42832/05 probably on the clinical requirements for the development of biosimilar interferon products, interleukin antagonists and LMWHs.

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Annex 1

Products with Epoetin alpha marketed in Germany / Europe²

Product strengths, pharmaceutical form	Manufacturing technology	Registration Procedure	Company
ERYPO 2000 I.E./ml/ -4000 I.E./ml Solution for injection for i.v. or s.c. administration (Mono)	Chinese Hamster Ovary-cells	national	Janssen-Cilag
ERYPO 40 000 I.E./ml Solution for injection (Mono)	Chinese Hamster Ovary-cells	national	Janssen-Cilag
ERYPO FS 1000 I.E./0,5 ml, 2000 I.E./0,5 ml, 3000 I.E./0,3 ml, 4000 I.E./0,4 ml Solution for injection for i.v. or s.c. administration, prefilled syringes	Chinese Hamster Ovary-cells	national	Janssen-Cilag
ERYPO FS 10 000 I.E./ml solution for injection for i.v. or s.c. administration, prefilled syringes	Chinese Hamster Ovary-cells	national	Janssen-Cilag
NeoRecormon 500/-1000/-2000/-3000/-4000/-5000/-6000/-10 000/-20 000/-30 000 IE Solution for injection, prefilled syringes (Mono)	recombinant DNA	centralized	Roche
NeoRecormon 500 IE Powder and solvent for solution for injection (Mono)	recombinant DNA	centralized	Roche
NeoRecormon 10 000/-20 000/-60 000 IE Powder and solvent for solution for injection (Mono)	recombinant DNA	centralized	Roche
NeoRecormon Multidose 50 000/-100 000 IE Powder and solvent for solution for injection (Mono)	recombinant DNA	centralized	Roche

² Source: Rote Liste online

Products with Epoetin beta marketed in Germany / Europe²

Product strengths, pharmaceutical form	Manufacturing technology	Registration Procedure	Company
NeoRecormon 500/-1000/-2000/-3000/-4000/-5000/-6000/-10 000/-20 000/-30 000 IE Solution for injection, prefilled syringes (Mono)	recombinant DNA	centralized	Roche
NeoRecormon 500 IE Powder and solvent for solution for injection (Mono)	recombinant DNA	centralized	Roche
NeoRecormon 10 000/-20 000/-60 000 IE Powder and solvent for solution for injection (Mono)	recombinant DNA	centralized	Roche
NeoRecormon Multidose 50 000/-100 000 IE Powder and solvent for solution for injection (Mono)	recombinant DNA	centralized	Roche

Annex 2

Products with G-CSF / Filgrastim marketed in Germany / Europe²

Product strengths, pharmaceutical form	Manufacturing technology	Registration Procedure	Company
Neupogen 30 Mio.E. (300 µg/0,5 ml) / -48 Mio.E. (480 µg/0,5 ml) Solution for injection, prefilled syringes (Mono)	recombinant DNA from E. coli K 12	MRP RMS: UK	Amgen
Neupogen 30 Mio.E. (300 µg/1,0 ml) Solution for injection (Mono)	recombinant DNA from E. coli K 12	MRP RMS: UK	Amgen

Annex 3

Products with human Insulin (injectable) marketed in Germany / Europe²

Product strengths, pharmaceutical form	Manufacturing technology	Registration Procedure	Company
Actrapid® 40 I.E./ml Solution for injection (Mono)	recombinant DNA (<i>Saccharomyces cerevisiae</i>).	centralized	Novo Nordisk
Actrapid® Penfill® 100 I.E./ml Solution for injection (Mono)	recombinant DNA (<i>Saccharomyces cerevisiae</i>).	centralized	Novo Nordisk
Actrapid® NovoLet® 100 I.E./ml Solution for injection (Mono)	recombinant DNA (<i>Saccharomyces cerevisiae</i>).	centralized	Novo Nordisk
Actrapid® InnoLet® 100 I.E./ml Solution for injection (Mono)	recombinant DNA (<i>Saccharomyces cerevisiae</i>).	centralized	Novo Nordisk
Berlinsulin® H Normal 3 ml Pen Solution for injection (Mono)	recombinant DNA (<i>E. coli</i>)	national	Berlin Chemie
Huminsulin® Normal 100/ -für Pen 3 ml Solution for injection (Mono)	recombinant DNA	MRP RMS: UK	Lilly
Insulin B. Braun ratiopharm® Rapid 40 I.E./ml Solution for injection 10 ml (Mono)	enzymatical from porcine insulin	national	B. Braun ratiopharm
Insulin B. Braun ratiopharm® Rapid 100 I.E./ml Solution for injection 3 ml (Mono)	enzymatical from porcine insulin	national	B. Braun ratiopharm
Insuman® Infusat 100 I.E./ml Solution for injection (Mono)	genetically by <i>E. coli</i> K 12	centralized	Aventis Pharma
Insuman® Infusat 100 I.E./ml Solution for injection (Mono)	genetically by <i>E. coli</i> K 12	centralized	Aventis Pharma
Insuman® Rapid 40 I.E./ml Solution for injection (Mono)	genetically by <i>E. coli</i> K 12	centralized	Aventis Pharma
Insuman® Rapid 100 I.E./ml Solution for injection (Mono)	genetically by <i>E. coli</i> K 12	centralized	Aventis Pharma
Insuman® Rapid® 100 I.E./ml OptiSet Solution for injection (Mono)	genetically by <i>E. coli</i> K 12	centralized	Aventis Pharma
Velosulin® 100 I.E./ml Solution for injection or infusion (Mono)	recombinant DNA (<i>Saccharomyces cerevisiae</i>).	centralized	Novo Nordisk

Annex 4

Products with Interferon marketed in Germany / Europe²

Interferon	Product strengths, pharmaceutical form	Manufacturing technology	Registration Procedure	Company
Interferon alfa 2a	Roferon-A 3/-4,5/-6/-9/ - 18 Mio. I.E./0,5 ml Solution for injection, prefilled syringes (Mono)	recombinant DNA, E. coli	MRP RMS: UK	Roche
Interferon alfa 2a	Roferon-A 18 Mio. I.E./0,6 ml Solution for injection, (Mono)	recombinant DNA, E. coli	MRP RMS: UK	Roche
Interferon alfa 2b	IntronA 18/-25 Mio I.E. Solution for injection (Mono)	recombinant DNA, E. coli	centralized	Essex Pharma
Interferon alfa 2b	IntronA 18/-30/-60 Mio I.E. Solution for injection, Multi dose, (Mono)	recombinant DNA, E. coli.	centralized	Essex Pharma
Interferon alfacon-1	Inferax 9 µg Solution for injection (Mono)	recombinant DNA, E. coli.	centralized	Astellas Pharma
Interferon beta	Fiblaferon 3/-5 Powder and solvent for solution for injection (Mono)		national	biosyn
Interferon beta-1a	AVONEX 30 µg/0,5 ml Solution for injection (Mono)		centralized	Biogen Idec
Interferon beta-1a	AVONEX 30 µg Powder and solvent for solution for injection BIO-SET (Mono)		centralized	Biogen Idec
Interferon beta-1a	Rebif 8,8 µg/ 22 µg/ -44 µg Solution for injection (Mono)	recombinant DNA, Chinese Hamster Ovary-cells CHO-K1	centralized	Serono
Interferon beta-1b	Betaferon Powder and solvent for solution for injection (Mono)	recombinant DNA	centralized	Schering
Interferon gamma-1b	Imukin Solution for injection (Mono)	recombinant DNA, genetically modified E. coli.	MRP RMS: NL	Boehringer Ingelheim

Annex 5

Products with hGH marketed in Germany / Europe²

Medicinal product strengths, pharmaceutical form, mg/I.U.	Manufacturing technology	Registration Procedure	Company
Genotropin MiniQuick 0,2 mg/-0,4 mg/-0,6 mg/-0,8 mg/-1,0 mg/-1,2 mg/-1,4 mg/-1,6 mg/-1,8 mg/-2,0 mg Powder and solvent for s.c. injection	recombinant DNA, E. coli	MRP RMS: DK	Pharmacia
Genotropin 5 mg/ml/-12 mg Powder and solvent for s.c. injection	recombinant DNA, E. coli	MRP RMS: DK	Pharmacia
Humatrope for Pen 6 mg/-12 mg/-24 mg Powder and solvent for solution for injection	recombinant DNA, E. coli	MRP RMS: NL	Lilly
Norditropin NordiFlex 5 mg/1,5 ml/-10 mg/1,5 ml/-15 mg/1,5 ml with injector Solution for injection 1 mg is equivalent to 3 I.U. Somatropin	recombinant DNA, E. coli MC 1061	MRP RMS: DK	Novo Nordisk
Norditropin SimpleXx 5 mg/1,5 ml/-10 mg/1,5 ml/-15 mg/1,5 ml Solution for injection 1 mg is equivalent to 3 I.U. Somatropin	recombinant DNA, E. coli MC 1061	MRP RMS: DK	Novo Nordisk
NutropinAq 10 mg/2 ml (30 I.E.) Solution for injection 1 mg is equivalent to 3 I.U. Somatropin	recombinant DNA, E. coli	centralized	Ipsen Pharma
Omnitrope 5 mg/ml Lyophilisate and solvent for solution for injection 1 mg is equivalent to 3 I.U. Somatropin	recombinant DNA, genetically modified E. coli	centralized	Sandoz
Saizen 8 mg click.easy Powder and solvent	recombinant DNA, mammalian cells	MRP RMS: IT	Serono
Zomacton 4 mg Powder and solvent for solution for injection	recombinant DNA, E. coli	MRP RMS: FR	Ferring Arzneimittel

The second centralized registered biosimilar product Valtropin / Biopartners GmbH is not listed in the German product index (Rote Liste) yet (18 April 2007).

Annex 6

Products with LMWH marketed in Germany / Europe²

Medicinal product strengths, pharmaceutical form	LMWH	Registration Procedure	Company
Mono-Embolex 8000 I.E. THERAPIE Solution for injection (Mono)	Certoparin-Sodium		Novartis
Mono-Embolex NM Fertigspritzen Solution for injection (Mono)	Certoparin-Sodium		Novartis
Mono-Embolex® NM/-multi/-PEN Solution for injection (Mono)	Certoparin-Sodium		Novartis
Fragmin/-D Solution for injection (Mono)	Dalteparin-Sodium		Pharmacia
Fragmin 4 ml/-10 ml Multidose Solution for injection (Mono)	Dalteparin-Sodium		Pharmacia
Fragmin P/-P Forte Solution for injection (Mono)	Dalteparin-Sodium		Pharmacia
Clexane 20 mg/-40 mg/-40 mg Duo Solution for injection (Mono)	Enoxaparin- Sodium		Aventis Pharma
Clexane multidose 100 mg/ml Solution for injection (Mono)	Enoxaparin- Sodium		Aventis Pharma
Clexane 60 mg/-80 mg/-100 mg Therapie Solution for injection (Mono)	Enoxaparin- Sodium		Aventis Pharma
Arixtra 2,5 mg/0,5 ml/-5,0 mg/0,4 ml/- 7,5 mg/0,6 ml/-10,0 mg/0,8 ml Solution for injection (Mono)	Fondaparinux	centralized	Glaxo Smith Cline
Fraxiparin 0,2/-0,3/-0,4/-0,6/-0,8/-1,0 Solution for injection (Mono)	Nadroparin- Calcium		Glaxo Smith Cline
Fraxiparin 0,3 duo Solution for injection (Mono)	Nadroparin- Calcium		Glaxo Smith Cline
Fraxiparin multi Solution for injection (Mono)	Nadroparin- Calcium		Glaxo Smith Cline
FRAXODI 19.000 I.E. anti-Xa/ml Solution for injection (Mono)	Nadroparin- Calcium		Glaxo Smith Cline
Clivarin 1.750 Solution for injection (Mono)	Reviparin-Sodium	MRP RMS: SE	Abbott
Clivarin multi Solution for injection (Mono)	Reviparin-Sodium	MRP RMS: SE	Abbott
innohep 3.500/-multi Solution for injection (Mono)	Tinzaparin- Sodium	MRP RMS: DK	LEO / ZLB Behring
innohep 20.000 Anti-Xa I.E./ml Solution for injection (Mono)	Tinzaparin- Sodium	MRP RMS: DK	LEO / ZLB Behring

Annex 7

Important biotechnology products going off patent in the next couple of years:

	Innovator company	Patent expiry incl. SPC
<u>Interferon</u>		
Interferon alpha	Schering-Plough (USA)	2002 (USA)
Interferon alpha 2a	Roche	
Interferon alpha 2b	Essex Pharma	
Interferon alfacon-1	Astellas Pharma	2008 (EU)
Interferon beta	biosyn	
Interferon beta 1a	Biogen Idec, Serono	
Interferon beta 1b	Schering	2008 (EU)
Interferon gamma	Böhringer Ingelheim	
<u>Interleukin antagonists</u>		
Aldesleukin	Novartis	
Anakinra	Amgen	2014 (EU)
<u>LMWH</u>		
Enoxaparin	Aventis	2009 (EU)
<u>Oxitocin / - antagonist</u>		
Atosiban	Ferring	2008 (EU)
Oxitocin	Novartis	2008 (EU)

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

Köln, 15. Mai 2007

Dr. Katja Schepper

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