What are the prospects for a global „biosimilar"development? Comparison of the regulatory requirements for the marketing authorisation of biosimilar products using the example of implemented or proposed legislation in the EU, Canada, Japan and the proposed WHO guidance

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Abbreviations

ANDS	Abbreviated New Drug Submission	Canada
AUC	Area under blood-concentration curve	Global
BWP	Biologics Working Party	EU
CHMP	Committee for Medicinal Products for Human Use	EU
CTD	Common Technical Document	Global
DIN	Drug Identification Number	Canada
EC	European Commission	EU
ECBS	Expert Committee on Biological Standardization	WHO
EMEA	European Medicines Agency	EU
ER-PAL	Enforcement Regulation	Japan
GCP	Good Clinical Practice	Global
GLP	Good Laboratory Practice	Global
GMP	Good Manufacturing Practice	Global
INN	International Nonproprietary Name	Global
LMWH	Low Molecular Weight Heparin	Global
MAH	Marketing Authorization Holder	Global
MHLW	Ministry of Health, Labour and Welfare	Japan
MO	Micro-Organism	Global
MS	Member State	Europe
NDS	New Drug Submission	Canada
NOC	Notice of Compliance	Canada
OTC	Over the counter	Global
PAL	Pharmaceutical Affairs Law	Japan
PFSB	Pharmaceutical and Food Safety Bureau of MHLW	Japan
PFSB/ELD	Evaluation and Licensing Davison of PFSB	Japan
PFSB/SD	Safety Division of PFSB	Japan
PMDA	Pharmaceuticals and Medicinal Devices Agency	Japan
PD	Pharmacodynamic	Global
PK	Pharmacokinetic	Global
PK/PD	Pharmacokinetic/Pharmacodynamic	Global
R&D	Research and Development	Global
RBP	Reference Biotherapeutic Product	WHO
SBPs	Similar Biotherapeutic Products	WHO
SEB	Subsequent Entry Biologic	Canada
SMBP	Similar Biological Medicinal Products	EU
SPC	Supplementary Protection Certificate	EU
TRIPS	Trade-Related Aspects of Intellectual Property Rights	Global
USD	US Dollar	USA
WHO	World Health Organization	Global
WTO	World Trade Organization	Global

1 Executive Summary

Biopharmaceutical drugs which are defined as medicines made by or derived from living organisms by applying biotechnological methods, are one of the fasted growing segments of the pharmaceutical industry.

Development of new drugs and biologic drugs in particular is a lengthy and cost intensive process. Although one of the most challenging aspects of drug discovery is identifying candidate compounds, the most expensive part is the process of taking the candidate through all the required stages of pre-clinical and clinical research and the regulatory process. The overall costs for the development of a biological drug range from 1.24 – 1.33 billion USD and exceed the development costs for new chemical entities (e.g. 802 million USD) by far.

Whereas in developed countries, the rapidly rising costs of health care, including supplies of medicines, are a matter of intense public concern (costs per year for biotherapeutic drug treatment is on average 16'425 USD), the cost of medicines in developing countries can be matter of life and death. Measures to stimulate price competition with innovator drugs and to keep the balance between the continuous development of better innovative medicines and the reduction of public health care costs, include the establishment of a legislation for abbreviated regulatory application pathways for follow-on versions of innovator drugs, thereby facilitating their market entry after expiry of patent protection and data exclusivity.

Follow-on versions of biotechnological medicines are commonly known as biosimilar medicines. The concept of biosimilar medicines is the approval for marketing authorization of a biosimilar product with a reduced non-clinical and clinical data package based on a thorough demonstration of comparability of the biosimilar product to an existing approved product in terms of quality, safety and efficacy. The costs to develop biosimilar medicines are consequentially less compared to the development costs for the innovator product, thereby allowing biosimilar products to enter the market at reduced prices. Biosimilar medicines are therefore considered a major opportunity to provide better access to affordable life-saving medicines. The significance of the introduction of biosimilar medicines may be equal to the emergence of generic medicines.

An important factor for the success of a biosimilar development program, set up by a global acting pharmaceutical company is the ability to access global markets. The European Union (EU) created a policy and legal framework for the marketing approval of biosimilar products with the introduction of the concept of biosimilar products into the EU legislation in 2003 and the biosimilar concept and legislation is evolving rapidly in other countries since. At the global level divergent approaches exist with regards to the regulatory oversight of this type of product for which a variety of terms such as biosimilars, follow-on biologics, follow-on proteins and subsequent entry biologics are used. Legislation for regulatory oversight is either implemented or currently under discussion in an increasing number of countries worldwide.

In March 2009 for example the Japan Minister of Health issued a biosimilar guidance providing instructions on the development and registration of biosimilar products. A regulatory framework for biosimilars is currently in preparation in Canada. The World Health Organization (WHO) has also started to establish a guideline on the evaluation of similar

biotherapeutic products in 2008. Countries, mainly less developed countries, which don't have the knowledge and resources to develop their own guidelines, may implement and employ the principles provided by the WHO for the evaluation and licensing of biosimilar products.

Global acting pharmaceutical companies which intend to set up global biosimilar development programs and marketing strategies need therefore to take the regional differences in the regulatory requirements for the abbreviated licensing application early in development into account. Regulatory differences in these regions may dictate the need for replicate programs resulting in increased effort and expenditure and longer time to market.

In order to investigate the prospects of a global biosimilar development program, this master thesis compares the principles and regulatory requirements for abbreviated marketing authorization procedures for similar biological medicinal products in the EU, Canada, Japan and as proposed by the WHO. Differences, in particular in the scope of the respective regulatory frameworks, the intellectual property rights, the reference product requirements, the comparability program requirements, the possibility to extrapolate clinical data, and their impact on a global biosimilar registration strategy by means of a globally acceptable data package suitable for the said jurisdictions are presented.

In conclusion, the regulatory requirements for biosimilar products appear to be very similar in the high regulated markets of the EU, Canada and Japan. Also the proposed WHO guideline, demonstrates a high scientific level which is comparable to other high regulated markets. All regulatory pathways share the same scientific and regulatory principles. Never the less, early consultation with the regulatory authorities in the regions concerned is recommended in order to determine whether the data are compliant with the requirements of the specific regions. The impact of ethnic differences on the required clinical data package should be evaluated on a case by case basis. However, the requirement that the reference product, which should be used during the whole development, should be approved in the individual territory has been identified as a major obstacle to a global biosimilar development. Whereas the Canadian and the WHO guideline do not strictly require or propose the use of a reference product approved in the individual territory, it is required in the EU and Japan.

2 Problem statement

In the European Union similar biological medicinal products are classified as biological medicinal products developed and proven to be similar in terms of quality, safety and efficacy to an already registered and well established medicinal product. A product of this type can be approved by an abbreviated regulatory process with a reduced non-clinical and clinical data package based on demonstrated similarity to the existing licensed reference product in terms of quality, safety and efficacy.

An important factor for the success of a biosimilar program set up by a global acting pharmaceutical company is the ability to access global markets. Experience with marketing authorization procedures for biosimilars across the world varies. In the EU the most developed regulatory framework for similar biological medicinal products exists. At the global level divergent approaches exist with regards to the regulatory oversight of this type of product for

which a variety of terms such as biosimilars, follow-on biologics, follow-on proteins and subsequent entry biologics are used. Legislation for regulatory oversight is either implemented or currently under discussion in an increasing number of countries worldwide.

Global acting pharmaceutical companies which are trying to set up global biosimilar development programs and marketing strategies need therefore to take the regional differences in the regulatory requirements for the abbreviated licensing application early in development into account. These regulatory differences may dictate the need for replicate programs resulting in increased effort and expenditure and longer time to market.

In this master thesis differences in the principles and regulatory requirements for abbreviated marketing authorization procedures for similar biological medicinal products are compared. Differences and their impact on the generation of a global data package suitable for countries with an existing or proposed abbreviated licensing application pathway using the example of the EU, Japan, Canada and the WHO are discussed.

3 Introduction

Biopharmaceutical drugs which are defined as medicines made by or derived from living organisms by applying biotechnological methods, are one of the fasted growing segments of the pharmaceutical industry. About 200 biopharmaceutical drugs are currently on the market and most of them are indicated for the prevention or treatment of severe diseases and critical illnesses including arthritis, asthma, Alzheimer disease, heart diseases, stroke, Cohn's disease, breast cancers, leukaemia, hepatitis, diabetes, psoriasis, multiple sclerosis, Lou Gehring's disease, AIDS and many more in development. Biotechnological medicines are estimated to account for more than 20% of all marketed medicines (1; 6).

Development of new drugs and biologic drugs in particular is a lengthy and cost intensive process (2;3;4). Although one of the most challenging aspects of drug discovery is identifying candidate compounds, the most expensive part is the process of taking the candidate through all the required stages of pre-clinical and clinical research and the regulatory process.

The average development time for new biological drugs is 97.7 months and therefore approximately 7.4 months longer than for new chemical entities. Compared to the development of new chemical entities, biologics have longer mean clinical development times (62). The overall costs for the development of a biological drug range from 1.24 – 1.33 billion USD and exceed the development costs for new chemical entities (e.g. 802 million USD) by far (62). These costs even exclude the costs for post marketing commitments and R&D costs for additional indications 5. In particular the pre-clinical and clinical costs appear to exceed 500 million USD on average (62).

Whereas in developed countries, the rapidly rising costs of health care, including supplies of medicines, are a matter of intense public concern (costs per year for biotherapeutic drug treatment is on average 16'425 USD), the cost of medicines in developing countries can be matter of life and death. Measures to stimulate price competition with innovator drugs and to keep the balance between the continuous development of better innovative medicines and the reduction of public health care costs due to price competition, include the establishment of a

legislation for abbreviated regulatory application pathways for follow-on versions of innovator drugs thereby facilitating their market entry after expiry of patent protection and data exclusivity.

By now, manufacturers other than the originator companies have the scientific capability to produce biopharmaceuticals similar to the originator products. These follow-on versions of biotechnological medicines are commonly known as biosimilar medicines. The concept of biosimilar medicines is the approval for marketing authorization of a biosimilar product with a reduced non-clinical and clinical data package based on a thorough demonstration of comparability of the biosimilar product to an existing approved product in terms of quality, safety and efficacy. The main difference is that the costs to develop biosimilar medicines are less compared to the development costs for the innovator product, thereby allowing biosimilar products to enter the market at reduced prices. Biosimilar medicines are therefore considered a major opportunity to provide better access to affordable life-saving medicines. The significance of the introduction of biosimilar medicines may be equal to the emergence of generic medicines over the past decades (6).

Europe has taken the lead amongst regulated markets in creating a policy and legal framework for the marketing approval of biosimilar products with the introduction of the concept of biosimilar products into the EU legislation in 2003. The biosimilar concept and legislation is evolving rapidly in other countries since. Other countries followed the EU and developed their own principles and guidelines for biosimilar medicinal products including Turkey "Instruction Manual on Biosimilar medical products" issued in August 2008; Taiwan "Review Criteria for Registration and Market Approval of Pharmaceuticals – Registration and Market Approval of Biological Products" issued in November 2008; Malaysia "Guidance Document for Registration of Biosimilars in Malaysia" issued in July 2008; Singapore "Guidance on Registration of Similar Biological Products in Singapore" issued in August 2009.

In March 2009 the Japan Minister of Health issued a biosimilar guidance providing instructions on the development and registration of biosimilar products. A regulatory framework for biosimilars is currently in preparation in Canada. The World Health Organization (WHO) has also started to establish a guideline on the evaluation of similar biotherapeutic products in October 2009. Countries, mainly less developed countries, which don't have the knowledge and resources to develop their own guidelines, may implement and employ the principles provided by the WHO for the evaluation and licensing of biosimilar products.

"Similar biological medicinal products" (SBMP), is the term which has been officially adopted by the European Commission (EC) together with the Biotechnology Working Party (BWP) at the European Medicines Agency (EMEA). However, the more programmatic term "biosimilar" product is more widely used, instead. A variety of terms for follow-on versions of biological drugs have been generated in other jurisdictions to describe these products eligibly for the abbreviated approval pathway: e.g. Subsequent-entry Biologic (SEB) in Canada, Biosimilar Product in Japan, Similar Biotherapeutic Product (SBP) by WHO.

In order to investigate the prospects of a global biosimilar development program, this master thesis compares the principles and regulatory requirements for abbreviated marketing

authorization procedures for similar biological medicinal products in the EU, Canada, Japan and as proposed by the WHO. Differences, in particular in the scope of the respective regulatory frameworks, the intellectual property rights, the reference product requirements, the comparability program requirements, the possibility to extrapolate clinical data, and their impact on a global biosimilar registration strategy by means of a globally acceptable data package suitable for the said jurisdictions are investigated.

4 Legislation and regulatory frameworks for abbreviated licensing pathways

4.1 European Union

4.1.1 Legislation and regulatory framework

The EU is the first region in the world, which defined a policy and legal framework for the approval of biosimilar products. With the amendment of Directive 2001/83/EC with Commission Directive 2003/63/EC dated June 25, 2003, the notion of "biosimilar products" has been introduced in the EU legislation. The Directive became effective as from July 01, 2003. Among others, the detailed scientific and technical requirements of Annex I to Directive 2001/83 has been adapted to take account of scientific and technical progress and in particular of the large set of new requirements resulting from recent legislation (7). In section 4, Part II of Annex I to Directive 2001/83/EC "Analytical, Pharmacotoxicological and Clinical Standards and Protocols in Respect of the Testing of Medicinal Products", the requirements for the presentation and the content of the marketing authorization application dossier to be prepared for "Similar Biological Medicinal Products", are laid down. The specific features of this category of medicinal product have been taken into account when the requirements of the marketing authorization application dossier as laid down in Part I of the Annex I were adapted.

In essence:

- For biological medicinal products which claim to be similar to an original medicinal product having been granted a marketing authorization in the Community, the requirements for an application for marketing authorization, after the expiry of data protection period, shall exceed the requirements for medicinal product which claim to be essentially similar "generic products" (8).
- Information to supply shall not be limited to Modules 1, 2 and 3, supplemented with bioequivalence and bioavailability data. 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 (see section 4.1.2).
- These guidelines, which shall take into account the diversity of biological medicinal products and the characteristics of the concerned biological medicinal product, should be published by the Agency (i.e. EMEA).

- The updated Annex I already provided the notion of extrapolation of indications i.e. in case where the originally authorized medicinal product has more than one indication approved the comparability of efficacy and safety ("therapeutic similarity") of similar biological medicinal product demonstrated in one indication may be extrapolated to other indications, if justified.

The concept of similar biological medicinal products was further elaborated with the adoption of the EU "Pharmaceutical Review in June 2003 (9). With Directive 2004/27/EC the regulatory approval pathway or licensing route for similar biological medicinal products was introduced in Article 10 of Directive 2001/83/EC.

- With regards to biological medicinal products which are similar to a reference biological product but which *do not meet the conditions in the definition of a generic medicinal product* (10) *results of appropriate pre-clinical or clinical tests relating to these conditions, should be provided when applying for marketing authorization application* (Article 10(4) of Directive 2001/83/EC as amended). With regards to the relevant criteria applicable to the marketing authorization application reference is made to Annex I as well as to product-class specific guidelines as introduced into Directive 2001/83/EC with Directive 2003/63/EC (see above). Non compliance of similar medicinal biological products with the conditions in the definition of generic medicinal products is expected due to differences relating to raw materials or differences in the manufacturing process of the biosimilar product and its reference product (Article 10(4) of Directive 2001/83/EC as amended).

In conclusion, Article 10(4) of Directive 2001/83/EC and Section 4, Part II Annex I to the said Directive forms the legal basis for the approval of similar biological medicinal products. The licensing route as stipulated in Article 10(4) of Directive 2001/83/EC applies to biological products, which claim to be similar to a biologic reference product, approved in the European Union but which do not meet the conditions in the definition of generics. The marketing authorization application is based on the demonstration of the similar nature of the two biological medicinal products. Application of marketing authorization is only allowed after the expiry of data exclusivity. Consequentially, results from pre-clinical and clinical studies are required to demonstrate safety and efficacy.

The "generic route" remains legally open for biological products, as non-compliance of similar biological medicinal products with the conditions in definition of generics is "usually" expected (11). Still, it has been declared by Nicolas Rossignol, a former Administrator within the European Commission in charge of the pharmaceutical legislation, that it is virtually impossible for applicants to produce an identical copy of a reference biological product taken the complexity of biological molecules and their production in living organisms into account (12).

As all 13 similar biological medicinal products currently approved on the basis of Article 10(4) of Directive 2001/83/EC are manufactured by means of one of the biotechnological processes listed in the Annex of Regulation (EC) No 726/2004 (13), the centralised procedure according to above mentioned regulation was mandatory in each case. Applications submitted in compliance with to Regulation (EC) No 726/2004 are assessed by the European Medicines

Agency (EMEA), which constitutes the scientific body of the European Commission responsible for the evaluation of the application. Based on a positive opinion issued by the EMEA it is the European Commissions may issue the approval.

Table 4-1 Biosimilar Products approved in the EU according to Article 10(4) of Directive 2001/83 EC

Active (INN)	Brand name/MAH	Date of approval	Reference Product
Somatropin	Omnitrope/Sandoz	April 12, 2006	Genotropin
	Valtropin/Biopartners	April 24, 2006	Humatrope
Epoetin alfa	Binocrit/Sandoz	Aug 28, 2007	Eprex/Erypo
	Epoetin alfa Hexal/Hexal	Aug 28, 2007	Eprex/Erypo
	Abseamed/Medice	Aug 28, 2007	Eprex/Erypo
Epoetin zeta	Silapo/Stada	Dec 18, 2007	Eprex/Erypo
	Retacrit/Hospira	Dec 18, 2007	Eprex/Erypo
Filgrastim	Filgrastim Ratiopharm/Ratiopharm	Sept 15, 2008	Neupogen
	Ratiograstim/Ratiopharm	Sept 15, 2008	Neupogen
	Biograstim/CT Arzneimittel	Sept 15, 2008	Neupogen
	Tevagrastim/Teva	Sept 15, 2008	Neupogen
	Filgrastim Hexal/Hexal	Feb 06, 2009	Neupogen
	Zarzio/Sandoz	Feb 06, 2009	Neupogen
Interferon alfa 1	Alpheon/Biopartners	Negative	-
Human Insulin	Insulin Marvel Short/Marvel Life Sci'	Withdrawn	-
	Insulin Marvel Intermediate/Marvel Life Sci'	Withdrawn	-
	Insulin Marvel Long/Marvel Life Sci'	Withdrawn	-

4.1.2 Guidance documents

The type and amount of quality, pre-clinical and clinical data required to substantiate the claim of similarity as required for marketing authorization are not pre-defined in the legislation as discussed in section 4.1.1, but are determined on a case by case basis and on the basis of product-class specific guidelines. Although Section 4 Part II Annex I of Directive 2001/83/EC refers

The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data (i.e. quality, pre-clinical and clinical data) to be provided for marketing authorization of a similar biological medicinal product. By developing general and product-class specific guidance documents the EMEA accounts for the wide spectrum of molecular complexity among the potential products eligible to the abbreviated licensing. These Annex guidelines present the current view of the CHMP on the non-clinical and clinical requirements for a marketing authorization application of the respective products.

The framework of the European biosimilar guidelines comprises three levels (14):

1 Level: The "overarching" guideline designed to introduce the concept of biosimilarity in scientific terms and to define its principles

2 Level: General guidelines concerning

- Quality aspects (24)
- Non-clinical and clinical aspects (15) including specific Annexes:

3 Level: Specific Annex guidelines designed to addressing specific non-clinical and clinical data requirements for defined product-classes:

- Insulin - Non-clinical and clinical aspects (16)
- Somatropin - Non-clinical and clinical aspects (17)
- Granulocyte-Colony Stimulating Factor (G-CSF) - Non-clinical and clinical aspects (18)
- Epoetin - Non-clinical and clinical aspects (19)
- Interferon (IFN)-alpha - Non-clinical and clinical aspects (20 21)
- Low Molecular Weight Heparins (LMWH) - Non-clinical and clinical aspects (22)
- Concept Paper: Monoclonal Antibodies (23)

General "overarching" guideline (CHMP/437/04) "Guideline on Similar Biological Medicinal Products" dated 30 October 2005 (24), designed to introduce the concept of biosimilarity in scientific terms and to define it's principles (please refer to section 5.1.1).

Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Quality Issues" EMEA/CHMP/BWP/49348/2005) (25), designed to lay down the requirements related to the manufacturing and control of the biosimilar medicinal products in general, including details pertaining to the comparability exercise versus the reference medicinal product, which is an additional element to the normal requirements of the quality dossier. Unlike the "overarching" guideline which states that the concept of biosimilars applies to any biological products, the scope of this guideline is limited to Similar Biological Products containing recombinant DNA- derived proteins.

The currently available spectrum of product-class specific guidance documents comprise "simple" molecules such as insulin to far more "complex" molecules such as epoetin, as far as molecular characteristics (structure, glycosylation and variability due to other post-translational modifications) are concerned. The majority of the product-classes covered by the guidelines are manufactured by means of recombinant DNA technology. Low Molecular Weight Heparin, however is a biological manufactured by extraction from biological sources.

Further product-class specific guidance documents for products which are of complex nature such as monoclonal antibodies are currently under discussion (23). Even gene or cell therapy medicinal products will be considered in the future when scientific knowledge and regulatory experience is gained (24).

Besides guidance documents specific for the development of similar biological medicinal products, multiple other guidance documents issued or implemented by the EMEA should be

considered during the development and maintenance of a similar biological medicinal product e.g.:

CHMP "Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process – non-clinical and clinical issues" (EMEA/CHMP/BMWP/101695/2006) dated 19 July 2007. The scope of this guideline comprises manufacturing process changes made either in development of for which a marketing authorization has been granted.

CHMP "Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins" (EMEA/CHMP/BMWP/14327/2006) dated 13 December 2007.

CHMP Note for Guidance on Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" ICH Topic Q 6 B (CHMP/ICH/365/96) dated September 1999.

4.2 Japan

4.2.1 Legislation and regulatory framework

Pharmaceutical administration in Japan is governed by a number of laws and primarily by the Pharmaceutical Affairs Law (PAL) that controls clinical research, manufacturing, marketing, labeling and safety of drugs, diagnostics and medical devices. The PAL has been enacted in 1943 and has been revised several times since. The current PAL (PAL, last revision June 11, 2003) is the results of several revisions, which became necessary to include for example legislation related to the re-examination of new drugs, the direct manufacturing and marketing approval applications by overseas pharmaceutical manufacturers or the establishment of the Pharmaceutical and Medical Devices Agency (PMDA) to conduct approval reviews and surveys of the reliability of application data.

For the enforcement and management of these laws, regulations with legal force are issued by the government in the form of "Enforcement Ordinances of the PAL" issued by the Japanese Cabinet and "Enforcement Regulations of the PAL" issued by the Minister of the Ministry of Health, Labor and Welfare (MHLW). "Notifications" with administrative directions and detailed explanations or operation statements about laws are issued by the Director General of the Bureau or the Directors of the Division in charge in the MHLW (26, 27).

Classification of medicinal products

Medicinal products are defined in Chapter I "General Provisions" Article 1 and 2 of the PAL and comprise drugs (28), quasi-drugs, cosmetics and medical devices (29). All of the before mentioned products with few exceptions, require marketing approval by the Minister of the MHLW before marketing (PAL Article 14 clause 1).

With regards to the introduction of a regulatory pathway for biosimilar products it should be noted that drugs in particular are classified in the Japanese regulatory framework according to their use and supply as Prescription or Non-Prescription Drugs (30) (Non-Prescription Drugs are also referred to as Proprietary Medicine or over the counter "OTC" drugs). Both

prescription and non-prescription drugs as well as other medicinal products regulated by the PAL are further categorized for approval purposes in PFSB Notification No.0331015 revised by PFSB Notification No.0304004 (please refer to Attachment 3). The categories are defined by the amount and content of data required for submission of a marketing approval application.

The correct determination of the category or classification of a medicinal product is critical for the course of the registration procedure and needs to be determined separately for each of the required type of approval procedure and license (see below).

Licenses and approval for marketing medicinal products

In order to place a product on the market in Japan several approvals and licenses are required. The current marketing authorization system in Japan was introduced with enforcement of the revised PAL on April 1, 2005. Prior to the revision of the PAL, each applicant for product approval was required to have its own manufacturing site in Japan.

1) Manufacturing/marketing approval according to Article 14 PAL

2) Marketing authorization license according to Article 12 PAL

3) License for manufacturing a medicinal product according to Article 13 (1) PAL

4) Accreditation as Foreign Manufacturer according to Article 13-3 PAL

1) Marketing approval of drugs according to Article 14 PAL (Seizo-hanbei-Shonin) also referred to as manufacturing/marketing approval or previously as manufacturing (import) approval. A person intending to market a drug (31), a quasi-drug, a cosmetic or a medical device requires for each product for their marketing a marketing approval. Depending on the category of the medicinal product the approval is granted either by the Minister of the Ministry of Health, Labor and Welfare or the Governor of the Prefecture. Medicinal products classified as prescription medicines for sole use in man are invariably approved by the Minister of the MHLW (IDRACT). The marketing approval is not required if the medicinal product complies with the Japanese Pharmacopoeia or if the drug is solely used for manufacturing of other drugs. The marketing approval which requires a review by the PMDA to determine whether or not the product in the application is suitable as a medicinal product to be marketed (Article 14-1 and 14-2 PAL) cannot be granted if the applicant does not obtain a manufacturing license specified in Article 13 (1), accreditation under Article 13(3) if required, a marketing authorization license specified under Article 12(1) for the type of drug concerned and the confirmation that the product has been manufactured in a plant compliant to GMP.

New drugs (i.e. drugs whose active ingredients, quantities, administration and dosage, method of use, indications and effects are distinct from those of drugs which have already been approved for marketing) which obtained approval for marketing are subject to a reexamination by the Government (Article 14-4 (1) PAL). The reexamination periods applicable to different categories of new drugs are further specified in Article 14-4 (1) A-C PAL. The reexamination period, which is intended to reconfirm the clinical usefulness of drugs though collecting information on the efficacy and safety of the drug after approval determines also the period of marketing exclusivity rights for new drugs (please refer to section 5.5.2).

Applications seeking marketing approval for a drug, a quasi-drug, a cosmetic or a medical device must be submitted to the MHLW with results of non-clinical and clinical studies required to show the quality, efficacy and safety of a new drug (Article 14 (3) PAL). It is stipulated in Article 14 (3) that the data submitted must be obtained and compliant to the standards as specified by the Minister of MHLW. These standards are defined in related Ordinances and Standards for the Reliability of Application Data (Article 43, Enforcement Regulations PAL). The acceptance of the data is therefore conditioned on adherence to the standards. The reviews on compliance with these standards are performed by the PMDA at the request of the MHLW (Article 14-2 PAL).

Both foreign applicants and applicants that are domiciled in Japan are permitted to apply directly to the Minister of Health, Labour and Welfare for marketing approval. However, applicants, which are not domiciled in Japan require to designate a holder of the marketing authorization license also referred to as marketer (see above) which is domiciled in Japan. The appointed marketer handles the marketing of the approved drug and takes measures required to prevent the onset of health and hygiene related hazards caused by the approved drug in Japan.

2) License for Marketing Approval **Holders** according to Article 12 PAL also referred to as "marketing authorization license" or "marketing business license" (Seizo-hanbai-gyo Kyoka) represents a permit to market medicinal products. Depending on the classification of the medicinal product a license for marketing business of drugs has to be obtained from the Minister. The type of required marketing business license depends on the classification of the medicinal product e.g. a type 1 license for marketing of prescription drugs (article 12 and 49 (1) PAL).

Granting of the marketing authorization license allows the holder of the license also to conduct importing business of medicinal products. One license per entity (juridical person) is sufficient to conduct marketing business in Japan.

3) License for manufacturing a medicinal product according to Article 13 Paragraph 1 PAL (Seizou-gyou Kyoka) also referred to manufacturing (import) license. In general the manufacturing license is granted by the Minister and is valid for a period not exceeding 3 years. The granting of the license depends on compliance of the buildings and facilities with standards specified by the MHLW Ministerial Ordinance (PAL Article 13 Paragraph 4(1) and on an examination in writing or an on-site examination by the Minister or the PMDA (PAL Article 13 Paragraph 5 and Article 13-2). For products with manufacturing processes involving recombinant DNA technology the manufacturing license is granted by the director of the regional bureau of Health and Welfare (PAAB/ERD Notification No.243 and PAAB/ERD-1 Notification No.10). The holder of the license is responsible for the application for accreditation as foreign manufacturer in case the manufacturing site for the approved drug is located outside Japan (see below).

4) Accreditation as Foreign Manufacturer according to Article 13-3 PAL (Nintei). A person intending to manufacture in foreign countries drugs, quasi-drugs, cosmetics or medical devices, which are imported to Japan from overseas needs accreditation by the Minister as an foreign manufacturer. The application should be submitted by the time of the marketing

approval application. For the accreditation of a foreign manufacturer the provisions for a license application for manufacturing a medicinal product according to Article 13 apply.

A detailed team review of applications for manufacturing and marketing approval (Article 14-2 PAL) is performed by PMDA after the confirmation of reliability of the submitted data in the preceding compliance review. In 2005 two notifications were issued on the handling of applications for manufacturing/marketing approval of medicinal products:

- Notification No. **0331015** "Applications for Approval of Medicinal Products" issued on March 31, 2005 by the Director-General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (PFSB). This Notification specifies categories of manufacturing/marketing approval applications by the range of data to be submitted for a specific product category (see section 4.2.2)
- Notification No. **0331009** "Items to note when submitting applications for approval of manufacturing/marketing of medicinal products" of the PFSB/ELD dated 31 March 2005. This Notification provides more details of the handling of data and refers further to specific guidelines, which should be considered.
- In the Notice entitled "Items to Note when Submitting Applications for Approval of Manufacturing/Marketing of Medicinal Products" issued by PFSB/ELD on 31 March 2005, detailed information is given regarding the correct presentation of the data in the CTD structure as required by Notification No 0331015.

Marketing approval applications for all categories of medicinal products submitted as of April 01, 2005 are handled in accordance with the above mentioned Notifications.

Approval Applications for Biosimilars

In order to serve as a legal basis for approval of Biosimilar Products, the existing regulatory framework, in particular Notifications, for medicinal products had been adapted in 2009.

The introduction of the biosimilar concept comprised basically of the implementation of a new category of manufacturing/marketing approval application for prescription drugs (i.e. Biosimilar Products). In particular two above mentioned Notifications have been amended as follows:

- PFSB Notification No 0331015 has been amended in order to reflect changes in relation to the extent of data to be provided for an approval application for a biosimilar product by **PFSB Notification No. 0304004** entitled "Applications for Approval of Biosimilar Products" dated 04 March 2009). The revision became effective as from 01 April 2009. With this amendment the definition of Biosimilar Products as medicinal products, which are comparable to biotechnological medicinal products, which have been approved for marketing, were introduced.
- PFSB/ELD Notification No 0331009 dated 31 March 2005 has been amended by **PFSB/ELD Notification No. 0304015** dated 04 March 2009 and entitled "Items to Note when Submitting Approval Applications for Biosimilar Products", in order to reflect changes in the detailed guidance on the generation of data to be submitted with

an manufacturing/marketing approval application due to the implementation of the approval category biosimilar medicinal product

With the implementation of Notification No. 0304004 which came into effect on 01 April 2009, the term "biosimilar" was introduced into the Japanese jurisdiction as a separate category of a prescription medicinal product by establishing a new category of manufacturing/marketing approval applications. The new category of approval application is defined by a specific set of data, which is required to be attached to a manufacturing/marketing approval application (please refer to Table 2(-1) of Notification No 0304004 presented in Attachment 1).

As far as the manufacturing/marketing approval is concerned relevant Notifications were either amended or newly generated with the implementation of "Biosimilar Products" into the Japanese jurisdiction (see above). As outlined above additional licenses, in particular a Type 1 marketing authorization license according to Article 12 PAL as well as a license for manufacturing a medicinal product according to Article 13 PAL and/or an accreditation as Foreign Manufacturer according to Article 13-3 PAL are a prerequisite for granting a manufacturing/marketing approval. No changes to the Notifications related to these licenses were required when the category of "Biosimilar Products" was introduced.

As Biosimilar Products are usually manufactured by means of a biotechnological manufacturing process, the requirements for getting a license for manufacturing a medicinal product according to Article 13 PAL or the accreditation as Foreign Manufacturer according to Article 13-3 PAL, are identical as for other manufacturing processes involving recombinant DNA technology products.

Simultaneously with the implementation of the new category of manufacturing/marketing approvals " (7) Biosimilar Product", new guidance documents were implemented providing detailed guidance on the data which need to be provided when applying for manufacturing/marketing approval and on the naming (see section 4.2.2).

The implementation of a new regulatory pathway for biosimilar products in Japan, didn't require a review of the current legislation as far as norms with legal forces are concerned such as the Pharmaceutical Affairs Law or enforcement ordinance and regulations. No changes to the PAL were necessary as the corresponding Article concerning the requirement of manufacturing/marketing approval for the marketing of medicinal products, refers to the general categories: drugs, quasi-drugs, cosmetics, medical devices and controlled medical devices (Article 14(1) PAL). The current PAL remains therefore the legal base for Biosimilar Products without any adaptations. The implementation of the new regulatory pathway was accomplished by amending or generating new notifications issued by the Director General of the Bureau or the Directors of the Division in charge in the MHLW. The notifications provide comprehensive administrative directions and operation statements for the application for manufacturing and marketing approval of biosimilar products.

4.2.2 Guidance documents

In recent years, various standards and guidelines have been established and implemented in Japan according to ICH harmonization and the reliability and amount of data has been

internationally harmonized. To meet demands for more efficient and less costly development of new drugs, international utilization of data is on the increase. Japan has taken various measures in keeping with this change in the international environment, and data from non-clinical and clinical studies performed in foreign countries are accepted, in principle if the study design and performance comply with the Japanese guidelines (please refer to section 5.8.3).

Further to the implementation of a manufacturing/marketing approval category for Biosimilar Products few Notifications were either amended or newly generated:

- PFSB/ELD Notice dated July 21, 2009 entitled "Q&A on the Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products".
- PFSB/ELD Notification No. 0304015 dated 04 March 2009 entitled "Items to Note when Submitting Approval Applications for Biosimilar Products".
- PFSB Notification No. 0304004 dated 04 March 2009 entitled "Applications for Approval of Biosimilar Products" amending PFSB Notification No. 0331015 (32). With this Notification the definition of biosimilar products and the data requirements on a broad level for marketing authorization applications of a biosimilar product are stipulated and compared to manufacturing/marketing approval applications of other prescription drugs. In Table 2-(1) of Notification No. 0331015, which specifies the extent of data to be submitted, Biosimilar products have been included as number 7 (please refer to section 4.2.1 and Attachment 1).
- PFSB/ELD Notification No. 0304011 dated 04 March 2009 entitled "Handling of Non-proprietary Names and Trade Names of Biosimilar Products" With this Notification the Director of the Evaluation and Licensing Division/PFSB provided a detailed guidance document on the selection of the non-proprietary and trade name for biosimilar products is provided (33).
- PFSB/ELD Notification No. 0304007 dated 04 March 2009 entitled "Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products" (34) With this Notification the Director of the Evaluation and Licensing Division/PFSB provided a detailed guidance document on the creation of required data for a manufacturing/marketing approval application for a biosimilar product. This guideline covers all aspects of the development of a Biosimilar Product from establishment of production process to non-clinical/clinical studies. The guideline is also indicating the data requirements for the approval application. Although the definition of a Biosimilar Product is rather broad as it refers to medicinal products which are comparable to biotechnological medicinal products all kinds of follow-on biologics can be developed. The guideline deals however with recombinant protein products for which the approach for characterization is considered easy.

4.3 Canada

4.3.1 Legislation and regulatory framework

National standards i.e. Acts such as the Canada Health Act or the Food and Drugs Act are a part of the law in Canada. They are passed by Parliament and are legally binding.

Regulations such as Food and Drug Regulations, are passed by an order in Council of the Government, and are also a part of the law in Canada and legally binding. Regulations shall carry the purposes and provisions of the Food and Drug Act into effect (Article 30 of the Food and Drug Act)

Health Canada is the federal regulatory authority that evaluates the safety, efficacy, and quality of health products in Canada.

Drug products, containing drugs as defined in the Food and Drug Act section 2, are divided into "New Drugs" and "Old Drugs". As defined in section C.08.001 of the Food and Drugs Regulation, the term new drug refers for example to a drug that contains a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug.

A list of drugs regulated as "New Drugs" is maintained by the Therapeutic Products Directorate (TPD)/ Biologics and Genetic Therapies Directorate (BGTD) (35).

Those drugs which are not listed as a new drug or drug products which have been on the market for 7 years without significant change are considered "Old Drugs". However, the "sufficient time" policy applies only to specific drug product (i.e. a certain strength of a drug product) (36).

Some drugs which are classified as old dugs may be re-classified by Health Canada in case of newly identified safety concerns.

All drugs (37), regardless of classification of "new" or "old" drug, require marketing authorization i.e. requirement of a Drug Identification Number (DIN) (38). The DIN, which must appear on the label of the drug, identifies the manufacturer, brand name, medicinal ingredient(s), strength, pharmaceutical form, and route of administration.

- The submission of a New Drug Submission (NDS) or Abbreviated NDS (ANDS) is required for a "new drug" i.e. drugs which are already listed or re-classified as "new drugs" or new chemical entities. A Notice of Compliance (NOC) is issued by Health Canada which signifies that the NDS or ANDS application has been approved.
- Drugs which are regarded as "old drugs" i.e. drugs for which their safety and efficacy has been considered as being proven require a DIN submission (39).
- In either case, NDS or DIN submission the products cannot be sold before a DIN number is issued. In case of a NDS/ANDS the DIN number accompanies the NOC.

- Prior to issuing a DIN number the Drug Directorate requires to evaluate the data provided with the NDS/ANDS or DIN submission, according to subsection 9(1) of the Food and Drugs Act (40).

In Canada, any person or company may apply for a NDS of DIN without the necessity of to be a Canadian based company. However, the company who is distributing the product in Canada needs to hold a valid Establishment License has to be identified in the application form (41).

Regulation of Subsequent Entry Biologics (SEB)

SEBs are regulated under the Food and Drug Act and Regulations. They are also regulated under the Patent Act and Regulations (please refer to section 5.5.3).

In Canada, the existing legislation and regulatory framework for pharmaceuticals and biologics serves as the legal basis for approval of subsequent entry biologics, as SEBs are not considered a new class of biologics but second versions of biologics (52). Neither the revision of the Food and Drug Act or the Food and Drug Regulation is necessary to enable the implementation of an abbreviated licensing pathway for new drugs, which qualify as SEBs. Part C, Division 8 of the Food and Drug Regulation sets out the requirements for the marketing of new drugs in Canada, including SEB and prohibits the marketing of new drugs unless the following requirements are complied with.

- According the Food and Drug Regulations C.08.002(1)(a) No person shall sell or advertise a new drug unless the manufacturer of the new drug has filed with the Minister a **new drug submission** (NDS) or an **abbreviated new drug submission** (ANDS) relating to **the new drug** that is satisfactory to the Minister.
- A NDS shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of a new drug according to Food and Drug Regulations C.08.002(2). C.08.002(2) (a –n) provides a list of all required terms and information to be provided with a NDS.

SEBs, which describes biologic products that are similar to and would enter the market subsequent to an approved innovator biologic, are subject to all of the current regulatory requirements for biologics. The term biologics refer to drugs, which are listed on Schedule D (= Section 12) to the Food and Drugs Act. Schedule D comprises a list of individual or classified biological products. They have in common, that they are either manufactured from or through the use of animals and micro-organisms:

- Individual biological products e.g. Insulin, Interferon, Glucagon, Urokinase
- Product class: e.g. allergenic substances, Monoclonal antibodies, immunizing agents
- Classified according to the manufacturing process e.g. Drugs obtained by recombinant DNA procedures, human plasma collected by plasmapheresis
- Drugs obtained from certain sources: Blood and blood derivatives, prepared from micro-organisms other than antibiotics.

The above mentioned regulations, in particular C.08.002(1)(a) and C.08.002(2) shall apply to SEBs as stipulated in section 2.1.1 "Applicable Regulations" of the draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) released by Health Canada on March 27, 2009. Therefore, an application for an SEB must fulfill all requirements as a NDS although the extent of the clinical data required may be different than that required for the innovator's reference product. An ANDS (42) is not applicable as the draft Guidance for Sponsors; Information and Submission Requirements for Subsequent Entry Biologics does not refer to C.08.002.1(1).

As SEBs are subject to all of the current regulatory requirements for biologics, a NDS for an SEB requires as other biologic submission required the submission of:

- Samples of the drug substance, drug product and reference material during the review.
- Detailed facility information and a pre-approval inspection
- Post authorization: a yearly biologic product report (YBPR)

The Biologics and Genetic Therapies Directorate (BGT) within the Health Products and Food Branch (HPFB) of Health Canada is the regulator of biologic drugs. BGTD provides regulatory oversight for biologics with its comprehensive reviews of biologic submissions including SEBs.

Once a Notice of Compliance (NOC) is granted for a SEB, the SEB is regulated like any other new biologic drug (43). This has great impact on post-approval changes, as any changes to the manufacturing process that warrant a demonstration of comparability, the products to be compared will be the pre-change and post-change versions of the SEB and not the reference product. The draft guideline is silent on other post-approval changes than changes to the manufacturing process (44 section 2.3.1.6).

In a proposed guideline on the Information and Submission Requirements for Subsequent Entry Biologics (SEBs) (see below) guidance is given to sponsors on the data and submission requirements required to comply with the marketing authorization requirements for a new drug submission (NDS) i.e. to enable the Authority to evaluate the safety and effectiveness of the product.

As a SEB application is based on direct or indirect comparison to and reliance on an originator product already authorized in Canada, the current laws, patent and intellectual property principles are also applicable to SEBs as they apply for generic applications (please refer to section 5.5.3).

4.3.2 Guidance documents

In Canada draft guidance for sponsors: "Information and Submission Requirements for Subsequent Entry Biologics (SEBs)" has been released by Health Canada. This master thesis refers to the revised version of the draft guidance dated March 27, 2009 (44). Guidance documents have no law force and allow for flexibility in approach.

The concept of an SEB and therefore the scope of the draft guidance apply to all biologic drug submissions where the sponsor seeks authorization for marketing in Canada, based on

demonstrated similarity to an authorized reference biological drug for sale in Canada. Due to proven similarity the applicant may rely, in part on information provided by the marketing authorization holder of the reference "originator" products in order to present a reduced non-clinical and clinical data package.

In this context biologic drugs are specified as drugs, which contain as an active substance, well characterized proteins derived by modern biotechnological methods such as recombinant DNA and/or cell culture.

With revision of the draft guidance in response to written comments following the release of the previous draft guidance document dated January 30, 2008, a Question&Answer document has been published by Health Canada (45).

As outlined in section 1.3 "Policy Statement" of the said guideline, the requested data and submission requirements should permit the applicant to satisfy the requirements for a NDS as stipulated in Food and Drug Regulation C.08.002(2) i.e. sufficient information and material to enable the Minister to assess the safety and effectiveness of a New Drug.

The Food and Drug Regulation does not define application format requirements. The wording provides the Minister the flexibility to accept other formats than the CTD. Detailed guidance regarding the CTD format requirements as developed by ICH, for NDS is provided in draft guidance for industry "Preparation of New Drug Submissions in the CTD Format" (50).

4.4 WHO

Regulatory capacity and knowledge is in most developing countries considered as weak (46) and applying rules of developed country regulatory authorities such as the FDA or the EMEA may not necessarily be the most appropriate approach in less developed countries. The judgment on market approval should appropriately reflect local circumstances. Besides the scientific assessment based on the factual analysis of the data provided the judgment should also take the risks and benefits for the local health needs into account (46). The World Health Organization was mandated to set up a guideline document pertaining to globally accepted norms and standards for the evaluation of biosimilar products, in order to provide at least guidance on the evaluation of similar biotherapeutic products destined primarily for third countries. Under guidance by the WHO, it is up to the developing countries to implement the recommendations and principles of scientific evaluation into their own legislation.

The World Health Organization (WHO) is the directing and coordinating authority for health within the United Nations system. One of the core functions of the WHO as set out in the 11th General Program of Work (2006 to 2015) is the setting norms health guidelines and standards and promoting and monitoring their implementation.

4.4.1 Mandate for the development of guidance for biological therapeutics

As part of its constitutional responsibilities and mandate the WHO to assure global quality, safety and efficacy of biotherapeutics, the WHO by its expert committees shall provide globally accepted norms and standards for the evaluation of biotherapeutics.

The written standards established by the Expert Committee on Biological Standardization (ECBS) serve as a basis for setting national requirements for the production, quality control and overall regulation of biological medicines. WHO provided for example guidelines on biological products derived from recombinant DNA technology.

Besides written standards, the WHO provides also global/international measurement standards as essential tools for the establishment of potency for biological medicines worldwide. Used as primary standards they are often used to calibrate secondary standards for biological standards.

During the first WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products held in Geneva, 19-20 April 2007, the scientific basis for the evaluation and regulation of similar biotherapeutic products was discussed among the WHO, international drug regulatory authorities and industry associations (47). It has been acknowledged that the existence of divergent approaches to the regulatory oversight of biosimilars in different countries requires the definition of regulatory expectations for these products at the global level. The WHO was mandated to develop a guidance document providing scientific principles for the development and evaluation of similar biotherapeutic products (SBPs) in order to promote and improve patient's access, particularly from developing countries, to biotherapeutics. At the same time, the standards provided should ensure that the SBPs meet acceptable levels of quality, safety and efficacy to ensure public health (48). Access was limited for theses patients as the costs of the originator products have often been too high and the expiration of patent protection would provide the opportunity for licensing biopharmaceuticals as SBPs. SBPs refers to products that are designed to be similar to a licensed originator product and which rely, in part, for their licensing on prior information regarding safety and efficacy obtained with the originator biotherapeutic produces.

Following the drafting group meeting in March 2008 the first draft was developed by the members of the WHO drafting group on similar biotherapeutic products.

The second draft (BS/08.2101) was prepared after a WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products held in Seoul, May 27-29, 2008.

In October 2008 the WHO ECBS declined the approval of draft 2 and requested improvements. The draft comprised two separate approaches by which similarity between a biotherapeutic product and a reference product is supposed to be demonstrated:

- A pathway similar to the EU approach, where comparability on the physico-chemical level is a prerequisite to allow for data reduction at the non-clinical/clinical level
- A "clinical comparability pathway" without comparability exercise at the molecular level. The approach would therefore allow different quality standards for biosimilar and reference product. This approach was abandoned in the following drafts.

The third draft (BS/08.2101) was prepared by the drafting group members after a meeting in Tokyo on Feb 06 and 18, 2009.

The forth draft (BS/09.2110) was prepared after a WHO/HC Consultation on Regulatory Consideration in Evaluating Similar Biotherapeutic Products in Ottawa, July 15-17, 2009. Comments from the ECBS, regulatory agencies, industry and academia were considered during the development period

This master thesis refers to the forth draft (BS/09.2110) dated Oct 19 – 23, 2009 (48).

Following a public consultations on the forth draft, the fifth draft originated

The WHO ECBS discussed the fifth draft and if the draft guideline is ratified by the ECBS, the guideline may be officially approved by WHO executive committee in January 2010.

4.4.2 Proposed draft guideline document

The WHO draft guideline "Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) (48), intends to provide guidance on the globally acceptable scientific principles which should be employed by the national authorities for the evaluation and licensing of SBPs. It has been acknowledged that the amount of data required by different National Regulatory Authorities (NRAs) may vary.

The guideline therefore serves as basis for:

- A global set of standards and key principles for the evaluation and licensing of SBPs, with room for national authorities to include national requirement, as a basis for setting national requirements, which are legally not binding,
- Partial or complete implementation into national legislation (WHO will support implementation by means of educational workshops with national regulators) or
- Establishing national regulatory frameworks for licensure for SBPs.

5 Similarities and differences in the abbreviated licensing pathways for biosimilars

5.1 Basic concepts of the approaches for abbreviated licensing pathways

5.1.1 European Union: Similar Biological Medicinal Products

The standard for comparability between a biosimilar and it's reference product is the similar nature of the concerned products (49).

The amount of information required for essentially similar products (i.e. demonstration of bioequivalence for standard generics) does not permit the demonstration of the comparable nature of two biological medicinal products due to the broad spectrum of molecular complexity inherent to biological products as well as due to the manufacturing process characteristics, the raw material used for the manufacture and the therapeutic mode of action(s) of biotherapeutic medicines.

For the demonstration of the similar nature of the two biological products in terms of quality, safety and efficacy, comprehensive/extensive comparability studies are needed instead. The comparability exercise includes the quality, safety and efficacy part of the development.

Systematic proof of similarity of the reference medicinal product in terms of quality, safety and efficacy, which is a prerequisite for the approval of all medicinal products in Europe, is required.

Similar biological medicinal products are manufactured and controlled according to their own development, taking relevant up-to-date information into account (25). As a consequence a complete product and process development is required for biosimilar medicinal products.

Additional toxicological and other pre-clinical as well as clinical data are to be supplied.

The demonstration and prove of comparability of the similar biological medicinal product and the reference product is a sequential/step-wise process starting with the molecular level followed by the demonstration of comparable safety and efficacy at non-clinical and clinical level:

Level 1:	Physico-Chemical Comparability: Comprehensive analysis by means of state-of-the-art analytical methods
Level 2:	Biological Comparability: *in-vitro/in-vivo* bioassays
Level 3:	Non-clinical Comparability: Tox Studies, Repeated Dose, PK/PD, Immunogenicity
Level 4:	Clinical Comparability - Bioequivalence: Phase I Single Dose / multiple Dose, PK/PD, Immunogenicity
Level 5:	Clinical Comparability – Safety and Efficacy: Phase III clinical studies in most sensitive indication as defined in product-class specific non-clinical and clinical guidelines
Level 6:	Risk-Management Plan and Pharmacovigilance (not comparative) as for Biopharmaceuticals in general)

Provided comparability could be demonstrated at the quality level by means of sufficiently sensitive analytical systems, a reduction of the non-clinical and clinical data requirements compared to a complete dossier may be possible (25).

The dossier requirements can be summarized as follows:

Module 1	full dossier according to Annex I Part I of Directive 2001/83/EC
Module 2	full dossier according to Annex I Part I of Directive 2001/83/EC
Module 3	Quality: • full dossier according to Annex I Part I of Directive 2001/83/EC

- compliance with technical requirements of the monographs of the European Pharmacopoeia
- including results from the comparability exercise

Module 4 Non-clinical reduced dossier according to Annex I Part II (4) of Directive 2001/83/EC = comparability exercise

Module 5 Clinical reduced dossier according to Annex I Part II (4) of Directive 2001/83/EC = comparability exercise

5.1.2 Japan: Biosimilar Products

According PFSB Notification No. 0331015 as amended by Notification No. 0304004 Biosimilar products are defined as *"medicinal products which are comparable to biotechnological medicinal products which have been approved for marketing"*. In the Guideline for Quality/Safety/Efficacy Assurance of Biosimilar Products (PFSB/ELD Notification No. 0304007) a consistent definition of a biosimilar product is given: *a "medicinal product which has comparable quality, safety and efficacy to a biotechnology-applied medicinal product"*.

An application for marketing authorization of a biosimilar product is possible with a reduced data package based on proven comparability of the biosimilar product with a reference product in terms of quality, safety and efficacy while the reference product is a biotechnological medicinal product approved in Japan.

The underlying assumption is that a biosimilar product may not be identical to a reference product due to the complexity of the structure of the active substance (e.g. multiple functional sites) and its quality attributes (e.g. biological activity, instability and immunogenicity). By means of a comparability evaluation it needs to be demonstrated that the biosimilar product is highly similar to the reference product in terms of quality attributes and that quality differences, if any have no adverse impact on the safety and efficacy of the biosimilar product. The extent of the non-clinical and clinical data requirements depends on the extent of comparability in quality attributes (34).

- Similar biological medicinal products are manufactured and controlled according to their own development, taking relevant up-to-date information (e.g. production methods, analytical technologies) into account.
- A comprehensive characterization of the quality attributes by means of state of the art technologies is required, whereas the level of data should be the same as the level for a new recombinant protein products.
- In addition, the similarity of the quality attributes between the biosimilar and the reference product needs to be demonstrated whereas for some products, it may be even possible to refer to literature information.
- Comparability with regards to non-clinical and clinical data needs to be demonstrated by means of non-clinical and clinical data, whereas the amount of the data depends on the extent of demonstrated comparability of the quality attributes. Non-clinical studies

should be conducted after full characterization of the biosimilar product. Comparability evaluation in clinical studies should be carried out step-by-step, designing the next study based on the data obtained (34).

The approach takes into account that at the time of approval of a biosimilar product (i.e. after expiry of the re-examination period of the reference product) a certain period of marketing and clinical use of the reference product has been established.

5.1.3 Canada: Subsequent Entry Biologics (SEBs)

The expression "*Subsequent Entry Biologics*" refers to biologic drug submissions which are based on established similarity with an innovator biologic drug that is authorized for sale in Canada (i.e. reference product) and listed on the patent register (please refer to sections 4.3 and 5.5.3).

SEB submissions rely in part on information regarding the reference innovator drug in order to present a reduced non-clinical and clinical data package. Within the submission, the demonstration of similarity is based on comparative data including analytical and biological characterization, comparative pharmacokinetic and pharmacodynamic studies and comparative clinical trials.

As in other jurisdictions, the principles and procedures applicable to generic pharmaceutical drugs, are not applicable to subsequent entry biologic drugs as biologic drugs are considered more variable and structurally complex than pharmaceutical drugs due to their different manufacturing processes.

Authorization of an SEB depends on the demonstrated similarity with regards to quality, safety and efficacy, based on direct or indirect comparison of the SEB with an authorized innovative biologic drug, whereas the use of a reference biologic drug that is not authorized for sale in Canada could be accepted, provided that a link can be established between the reference product used and the product authorized for sale in Canada. In this case the required demonstration of similarity between the SEB and the Canadian reference product is indirect (please refer to section 5.3.3).

The demonstration of similarity depends on a detailed and comprehensive side-by-side product characterization. Similarity should be demonstrated for both the active substance and drug product. Characterization is considered easier for biological products manufactured by modern biotechnological methods (use of recombinant DNA and/or cell culture techniques), whereas the proposed guideline for SEBs applies in particular to this type of biological products.

The demonstration of similarity of the quality level is considered

- sufficient to predict that any differences in quality attributes should have no adverse impact on safety and efficacy of the SEB
- to establish the relevance of non-clinical and clinical data previously generated with the reference biologic drug to the SEB

In fact, for consideration as an SEB, similarity should be primarily deduced from comprehensive quality studies (i.e. extensive side-by-side characterization) (section 2.3.1 of reference 44).

Demonstrated similarity of the SEB to the reference product based on the comparability exercise on the quality level is a prerequisite to consider a reduced non-clinical and clinical data package. If similarity on the quality level cannot be established, complete non-clinical and clinical data are required (section 2.3.2.1 of reference 44). The extend of non-clinical and clinical data to be generated is determined by:

- The existing knowledge of the reference product (section 1.5 of reference 44). The reference product should have significant safety and efficacy data accumulated whereas the term "significant data" has not been defined.
- Nature of the indication being claimed (section 1.5 of reference 44) The SEB shall be granted clinical indications within those granted to the reference product and for which supporting data are provided. Additional indications may be granted without own clinical data provided the same mode of action. Still, any claims made by the SEB sponsor should be supported by suitable scientific data.
- Complexity of the product and the suitability of the analytical methods to demonstrate comparability.

A final determination of similarity will be based on a combination of the multi-level comparability exercise (i.e. analytical testing, biological assay and non-clinical and clinical data) whereas the weight of evidence should be provided by the analytical and biological characterization (section 2.3.1.4 of reference 44).

Products employing clearly different manufacturing approaches than the reference product are not considered eligible for authorization as SEB (44).

SEBs are regulated as New Drugs in Canada. The requirements for a New Drug Submission (NDS) according to section C.08.002 of the Food and Drug Regulations apply. In addition, if an applicant is able to provide the information and submission requirements as outlined in the draft SEB guideline, the expectation of "sufficient information" according to C.08.002(2) of the Food and Drug Regulations should be satisfied. The dossier requirements can be summarized as follows:

Module 1 full dossier in the CTD Format as for a NDS (50)

Module 2 full dossier in the CTD Format as for a NDS (51)

Module 3 Quality:

- full dossier with full chemistry and manufacturing data package for a new biologic drug
- Including results from the comparability exercise (i.e. side-by-side characterization of the SEB and the chosen reference biologic drug) as a distinct collection of data with an associated section in the Quality Overall Summary in Module 2.

Module 4 Non-clinical reduced dossier in the CTD Format as for a NDS

Module 5 Clinical reduced dossier in the CTD Format as for a NDS

5.1.4 WHO: Similar Biotherapeutic Products

The WHO draft guideline provides globally acceptable principles for the licensing of biotherapeutic products that are claimed to be similar to biotherapeutic products that have been licensed based on a full licensing dossier. A full registration dossier of the reference biotherapeutic product (RBP) denotes that all approved indications were granted on the basis of full quality, safety and clinical data (48)

The standard generic approach (the demonstration of therapeutic equivalence by means of bioequivalence of the generic medicines with a reference product) is not applicable for SBPs due to their size and complexity, which render their characterization difficult.

The clinical performance (i.e. pharmacokinetics, pharmacodynamics, efficacy and/or safety) of biotherapeutics might be influenced by the manufacturing process.

Therefore, SBPs are manufactured and controlled according to their own development. Full understanding of the product and a consistent and robust manufacturing process is a requirement. A full quality dossier (Module 3) should be submitted.

The dosage form and route of administration of the SBP should be same as for the RBP.

Biotherapeutic products with proven "similarity" to the reference product demonstrated by means of comprehensive comparability exercise may then rely for their approval as SBP, in part, on non-clinical and clinical data generated by the originator with the reference product with substantial evidence of safety and efficacy.

The similarity should be demonstrated in a step-wise approach. If at any step relevant differences between SBP and reference product are detected, they should be evaluated with regards to their potential impact on safety and efficacy. If the differences can not be explored and justified, the product under development may not qualify as SBP (48):

- Starting with characterization and evaluation of quality attributes of the product (to be included in Module 3).
- Followed by a comprehensive comparability head-to-head exercise between the SBP and RBP. This comparability exercise is considered an integrated set of comparative data:
    - In the quality part (= additional and separate element to the traditional full quality dossier). Besides the SBP the active substance of the SBP and the RBP must be shown to be similar as well.
    - Followed by non-clinical and clinical studies, which should be comparative in nature. The "main clinical" studies should use the final formulation and the material use should be derived from the final manufacturing process
- The amount of required non-clinical and clinical data depends on :

- The extend of the comprehensive characterization and comparison on the quality level
- Observed differences at any stage of development should be investigated for underlying reasons and can give rise to the requirement for further data
- Product/Product class concerned and clinical experience with the product class (i.e. safety concerns in a specific indication or immunogenicity).

5.2 Scope of products eligible for abbreviated licensing

5.2.1 European Union

According to Article 10(4) of Directive 2001/83/EC, the licensing route of "*similar biological medicinal products*" applies to any biological medicine. Therefore even complex biologics such as blood-derived products, vaccines, gene/cell therapy products are eligible for this application type. However, the CHMP stated, that the ability to characterize the product as a basis to demonstrate the similar nature of the concerned products determines the success of the Article 10(4) application (24). The required comparability exercise is more likely to be applied to highly purified product which can be thoroughly characterized (e.g. biotechnology-derived medicinal products). Except for Low Molecular Weight Heparin (LMWH), all of the product-classes covered by the Annex guidelines (please refer to section 5.6.1.1) are manufactured by means of biotechnology techniques (Somatropin, Epoetin, G-CSF, Insulin, Interferon alfa).

Whether a biological medicinal product is acceptable for an Article 10(4) application depends therefore:

- On the state of the art of analytical procedures
- The manufacturing process (biotechnology rather than extraction from biological sources)
- Clinical and regulatory experience

Heparin is usually sourced from domestic animals (porcine intestinal mucosa) by extraction and LMWH is obtained from unfractionated Heparin by subsequent chemical or enzymatic depolymerisation processes (22). LMWH is a complex product, with multiple different polysaccharides. It is currently not known to which extent the multiple different polysaccharides contribute to the clinical effects and heparin possesses numerous plasmatic and cellular interactions with uncertain clinical relevance and insufficiently investigated. Still, several state of the art analytical methods for physico-chemical characterization of LMWH are available. On the other side LMWH are difficult to detect while conventional pharmacokinetic (PK) studies cannot be performed. Absorption and elimination of LMWH can be therefore only be studied by it pharmacodynamic (PD) effects (22). Due to heterogeneity of LMWH, the poor understood mode of action and uncertainty or the relevance of PD markers for clinical effects, the demonstration of biosimilarity of LMWH is mainly based on comparative clinical trials (22).

5.2.2 Japan

According PFSB Notification No. 0331015 as amended by Notification No. 0304004 Biosimilar products are defined as *"medicinal products which are comparable to biotechnological medicinal products which have been approved for marketing"*. A consistent definition is given in the Guideline for Quality/Safety/Efficacy Assurance of Biosimilar Products (PFSB/ELD Notification No. 0304007) a biosimilar product is defined as *"a medicinal product which has comparable quality, safety and efficacy to a biotechnology-applied medicinal product"*.

The scope of the guideline and therefore the scope of products which are eligible for the new marketing approval application category (1-(7) biosimilar products) are stipulated as follows:

- *Recombinant proteins including simple proteins and glycoproteins, manufactured using microorganisms or cultured cells, which are highly purified and which can be characterized using a set of appropriate analytical methods,*
- *Polypeptides, their derivatives and medicinal products which are composed of them (conjugates)*
- The principles of the guideline could also be applied to medicinal products which are outside the above mentioned scope but can be *highly purified and characterized in terms of quality* (e.g. non-recombinant proteins manufactured using cell-culture technology or isolated from tissues/body fluids). However, applicants are advised to consult the regulatory authority to determine applicability:
    - Non-recombinant protein manufactured by cell-culture technology
    - Proteins or polypeptides isolated from tissues or body fluids
    - Product where the active ingredient is manufactured by chemical synthesis whereas the reference product is manufactured biopharmaceutically using recombinant DNA technology is not per se excluded from the scope of the guideline (Notification No. 0304007) as the agency stated in PFSB/ELD Notice dated July 21, 2009 entitled "Q&A on the Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products".

The following products are clearly excluded from the guideline:

- Antibiotics
- Synthesized peptides and polypeptides
- Polysaccharides,
- Vitamins,
- Cell metabolites
- Nucleic acids as active substance

- Allergen extracts
- Conventional vaccines using attenuated or inactivated pathogenic microorganisms or their extracts
- Cells
- Whole blood or cellular blood components

5.2.3 Canada

The concept of SEBs and therefore the data requirements for approval as proposed in the daft guideline "Information and Submission Requirements for *Subsequent Entry Biologics* (SEBs)" (44), applies to all biologic drug submissions where the sponsor seeks authorization for sale based on demonstrated similarity to a biologic drug that was authorized for sale in Canada and relies, in part, on prior information regarding the authorized innovative biologic drug in order to present a reduced clinical and non-clinical package (44). Please refer to section 4.3.1 for the definition of biologic or Schedule D drugs. As the approval of an SEB requires the demonstrated similarity based on a direct or indirect comparison to a biologic reference product, Health Canada limited the eligibility of the SEB approach to *drugs that contain, as their active substance, well characterized proteins derived through modern biotechnological methods such as use of recombinant DNA and/or cell culture* (44, section 1.2 Scope and application). Products such as insulin and human growth hormone were mentioned by Health Canada as examples for products eligible for approval as SEB (52).

According to the draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) released by Health Canada on March 27, 2009, a number of additional criteria are listed to determine the scope of eligible products:

- Existence of a suitable reference product that was originally authorized for sale base on a complete data package
- Has significant safety and efficacy data accumulated
- Product can be well characterized by a set of modern analytical methods
- A judgment of similarity to the reference product should be possible by extensive characterization and analysis which meet pre-determined criteria
- Products which follow a different approach to manufacture than the reference product are not eligible products (e.g. use of transgenic organisms versus cell culture) (44 and please refer to section 5.6.1.3.1).

5.2.4 WHO

The draft guideline on evaluation of similar biotherapeutic products (SBPs) applies to well-established and well-characterized biotherapeutic products (e.g. recombinant DNA-derived therapeutic proteins).

The term well-established biotherapeutic product is further defined as a product which has been marketed for a *suitable period of time with a proven quality, efficacy and safety.*

Vaccines and plasma derived products are excluded from the scope of the guideline as requested by the ECBS. Guidance on these products is provided by the WHO elsewhere.

5.3 Choice of the reference product

5.3.1 Europe

In Directive 2001/83/EC as amended the term reference product is defined in Article 10(2) of the before mentioned Directive as a medicinal product authorized under Article 6, in accordance to the provisions of Article 8 of the said Directive i.e. the reference product must be approved, based on a complete dossier in accordance with Article 8, in the European Union either by a national competent authority or by the European Commission. However, it is not legally required that the reference product is still authorized at the time the biosimilar application is filed (12).

Data generated from comparability studies with a medicinal product authorized outside the EU may only provide supportive information.

Requirements with regards to the similarity of the active substance contained in the reference product and the medicinal products are given in the "overarching" Guideline on Similar Biological Medicinal Products (CHMP/437/04) (14):

- Active substance must be similar in molecular and biological terms (e.g. interferon alfa)
- Pharmaceutical form, strength and route of administration should be the same, otherwise additional data in the context of the comparability exercise are to be provided

5.3.2 Japan

According to the Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products (53), the reference product needs to be a medicinal product approved in Japan as a drug with a new active ingredient. Further to the definition of a biosimilar product outlined in section 5.2.2, the reference product is expected to be a "*biotechnological medicinal product*". In general a biological drug, which has been approved on an abbreviated application (e.g. a biosimilar medicinal product), may not qualify as reference product. A biosimilar product may be chosen as reference product under certain circumstances (54):

- No biopharmaceutical product approved as drug with a new active substance (full dossier) is available due to abolition of the approval
- The biosimilar product has an adequate post-marketing clinical track record

The same reference products must be used during the duration of development and in case the drug substance of the reference product is not available the comparability should be performed with the formulated product.

5.3.3 Canada

A reference product used in the comparability studies to demonstrate similarity between the SEB and the chosen reference product, is defined as a biologic drug already approved on the basis of a complete dossier (section 1.2 of reference 44).

The dosage form, strength and route of administration of the SEB should be the same as the reference product. In addition, the reference biologic drug should also serve as a basis for the design of additional clinical trials with the SEB.

In general, the reference biologic drug must be authorized for sale and should be marketed in Canada (section 2.1.3 of reference 44). Unlike in other jurisdictions a non-Canadian reference biologic product may be used for the demonstration of similarity of the SEB and the reference biologic product. However, a link must be established in the new drug submission between the non-Canadian or foreign reference product and the drug authorized in Canada. Criteria for the acceptance of a foreign reference product include (44,52):

- Widely use and accumulation of significant information on its safety and efficacy data such that the establishment of similarity will bring into relevance a substantial body of reliable data
- Approval in a jurisdiction that has similar processes and procedures for drug approval as Health Canada (e.g. established relationship with Health Product and Food Branch of Health Canada and formally adopted ICH guidelines)
- The foreign reference product can be tied to a product authorized in Canada:
    - Same innovator company or corporate entity for the Canadian and foreign reference products (same dosage) – to be documented in the submission
    - Foreign reference product is marketed in Canada through a licensing arrangement with the innovator company/corporate entity
- This link between the foreign reference product and the Canadian reference product used in any comparative studies needs to be shown
- The sponsors are encouraged to consult Health Canada when considering a foreign reference product early in the development

By allowing the use of a foreign reference product, Health Canada addressed the fact, that biosimilars are currently developed outside Canada. By providing the flexibility in terms of the selection of the reference product, Health Canada intents to encourage companies to submit applications for SEBs in Canada (52).

5.3.4 WHO

As stipulated in the draft WHO guideline on Evaluation of Similar Biotherapeutic Products (SBPs) (48), a reference biotherapeutic product (RBP) is defined as follows:

- To be used as the comparator for head-to-head comparability studies in order to show similarity in terms of quality, safety and efficacy

- Licensed on basis of a full dossier
- Substantial evidence of safety and efficacy of the RBP is a precondition.
- The term does not refer to measurement standards (e.g. international, pharmacopoeia or national standards of reference standards)
- The dosage form and route of administration of the SBP should be same as for the RBP

The RBP should be used throughout the entire comparability exercise between the SBP and the RBP and is therefore considered central to the licensing of a SBP. The rationale for the choice of the RBP should be provided in the marketing approval application.

The WHO guideline does not stipulate the use of a nationally authorized RBP but summons the national authorities to consider the following issues when establishing their policies on RBPs:

- The nature of the biologics industry in their country
- Availability of nationally licensed RBPs
- The laws or regulations for patents, intellectual property and/or data protection as appropriate
- Establishing additional criteria in case of acceptability for RBP registered in other countries

The applicant is requested to take the following issues into account when selecting the RBP:

- Should be marketed for a suitable duration with a volume of marketed use providing a substantial body of acceptable data regarding safety and efficacy
- In case the RBP is marketed in another jurisdiction, the RBP should be taken from country with a well-established regulatory framework and considerable experience of evaluation of biotherapeutics and post-marketing surveillance activities
- Patents and intellectual property rights should not be infringed, neither in the country of origin nor in the country where the SBP is supposed to be marketed.

The suitability of the RBP to support the application of the SBP should be provided, whereas the parameters to be assessed are not further elaborated.

Whereas the term RBP does not require per definition the licensure by the national regulatory authorities, the definition of an originator product does:

- A medicine which has been licensed by the national regulatory authorities on the basis of a full dossier (i.e. the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data.

5.4 Naming convention

5.4.1 Brand name

5.4.1.1 Europe

In the European Union, the marketing authorization application for a medicinal product shall contain a single name of the medicinal product (Article 6 Regulation No 726/2004/EC), which may be either a single invented name not liable to confusion with the common name, or a common or scientific name (when available, the recommended INN of the active substance accompanied by a trade mark or the name of the marketing authorization holder (Articles 1(20) and 1(21) of Directive 2001/83/EC) 55.

In case an applicant chooses to use an invented or brand name, it should be clarified at an early stage whether an invented name is considered valid throughout the Community when using the centralised procedure. The applicant is requested to submit to the EMEA the proposed invented name at the earliest 12 months and at the latest 4-6 months prior to the planned MA for the assessment of the acceptability of the proposed invented name.

The Guideline on the acceptability of invented name for human medicinal products processed through centralised procedure should be taken into account 56. The assessment whether the proposed invented name may constitute an infringement of another entity's intellectual property rights is the responsibility of the applicant and is not taken into account by the EMEA during the assessment of the acceptability of the proposed invented name.

5.4.1.2 Japan

Handling of non-proprietary names as well as trade names of biosimilar products, which fall under PFSB/ELD Notification No. 0304007, is stipulated in PFSB/ELD Notification No. 0304011 dated 04 March 2009 entitled "Handling of Non-proprietary Names and Trade Names of Biosimilar Products".

The Evaluation and Licensing Division/PFSB intended to allow a clearly distinction of a biosimilar product, the reference product and other biosimilar products.

With this Notification detailed guidance is provided on the selection of the non-proprietary and trade name for biosimilar products is provided (57).

The trade name consists of

- the non-proprietary name of the reference biologic product (without the term "recombinant") followed by
- BS
- the dosage form
- the content
- The company name.

5.4.1.3 Canada

The draft guidance for sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) has been released by Health Canada (44) is silent on the naming. As the draft guidance refers in general to the requirements for NDS, C.08.002.(2) (a and b) applies to SEBs:

(a) a description of the new drug and a statement of its proper name or its common name if there is no proper name

(b) *a statement of the brand name of the new drug or the identifying name or code proposed for the new drug,*

should be contained in a new drug submission.

5.4.2 International Nonproprietary Name (INN)

The INN system was initiated in 1950 by the World Health Assembly. The basis for INN system is the constitutional responsibility to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products". The unique names of pharmaceutical substances or active pharmaceutical ingredients, that are provided by the INN system serve globally to designate, in an unequivocal manner, the composition of medicinal products and are also widely used as drug names for generic medicinal products. Once adopted, an INN applies to the pharmaceutical substance globally and does not change over the life cycle of any given product. INNs therefore facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. INNs are intended for use in pharmacopoeias, labeling, product information, advertising and scientific literature. INNs form an essential part of the regulatory process in many countries where a nonproprietary name is required for licensing and serve as basis for product names. Generics usually have the same INN as the reference product and healthcare professional prescribe by INN as a generic medicinal product is considered therapeutic equivalent provided bioequivalence has been shown. The same INN for a biosimilar can therefore be seen as a signal for substitution.

National names such as Japanese Accepted Names (JAN) or British Approved Names (BAN) are mainly identical to the INN. Names created under the INN program should also indicate a specific therapeutic activity or a specific mode of action of the substance in question.

A request for an INN is submitted either by manufacturers or in countries where national nomenclature commission exist by the corresponding national nomenclature authority (e.g. Japanese Accepted Name (JAN)) to the WHO/INN secretariat.

INNs are selected by INN Expert Group (members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations) in close collaboration with national nomenclature commissions. Each name proposed by the originator of a request for an INN is examined in accordance with the procedures for the selection of recommended INNs for pharmaceutical substances as adopted by the WHO Executive Board 58. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary59. The INN which all INN Experts agreed upon is then first published as a proposed INN in *WHO Drug Information*. The

consultations of the INN Exert Group take place twice a year during meetings of the Expert Group convened by the Secretariat. During a four-month period any person can comment on the proposed name or file a formal objection to a name. According to the WHO procedure for the selection of recommended INNs, a name shall not be selected by HWO while there exists a formal objection thereto. If no objection is raised the "proposed name" will be published as a "recommended name". The proposed or recommended INN are not published individually but grouped in lists which are published twice a year.

The time needed for completion of the selection and publication of a recommended INN has been examined and published by WHO. For example, only 41% or the cases examined during year 200 and 2004 received acceptance of the name proposed by the applicant. In 59% of the cases modifications were necessary thereby lengthening the process. The average duration of the process, from receipt of a request by the INN secretariat to publication of the recommended INN was 26.4 months- 24.2 months (names that were accepted as originally proposed) and 28 months (names which required modification).

On 4-5 September 2006 the WHO convened an informal consultation on the INN policy for biosimilar products. In the context of the broad WHO discussion on regulatory approaches of biosimilar products, the policy on the naming of biosimilars was discussed among regulators from Europe, USA, Japan, Canada, Korea and Australia. Difficulties in developing INNs for biological products are seen due to their complexity. For generics the same INN is given as the innovator product since they are considered to be equivalent, even if synthesized by different routes. By definition, biological products cannot be fully characterized by physical and chemical means alone. Differences in glycosylation for example would require a new INN. General policies for assigning INNs to biologicals are in place for many years. Differences in glycosylation for example, are handled by adding a Greek letter in full as a second word. Some stand alone biologicals even if they were slightly different in terms of glycosylation had the same INN. Different INNs were assigned in cases where significant differences in glycosylation were known. Other post-translational effects contribute to the complexity and variability of biologics as well.

In the biological field, different sources or production processes give potentially rise to different product profiles. If differences occur this may raise concerns about interchangeability/substitution, tracing and pharmacovigilance, in particular in countries where physicians prescribe according to the INN. The regulatory authority in Korea considers the current INN scheme to be less of a problem with regards to interchangeability and traceability of biological products as the Korean physicians prescribe according to the brand names. Concerns exist on the other side, that the use of the same INN for a biosimilar and it's reference product implies product interchangeability in the absence of credible scientific evidence. Likewise, however, INNs should not be used to differentiate biological products with the same active ingredient when credible scientific data demonstrate that no pharmacologically relevant differences exist.

It was however acknowledged by attendees that the assurance of adequate pharmacovigilance and traceability and the prevention of inappropriate substitution of the biologics are issues for the regulatory authorities. It was agreed that the concept of a biosimilar product is regulatory

in nature, whereas assignment of an INN is a nomenclature process based on scientific molecular characterization and the pharmacological class of the pharmaceutical substance. Both areas should be independent and it was recommended no distinctive designation to indicate the regulatory term biosimilar be built into the INN.

- Decisions on interchangeability should be the responsibility of a national regulatory authority and based on appropriate scientific and clinical data and not simply on the basis of INN. The INN should not be the sole indicator of product interchangeability.
- The INN is a useful tool in worldwide pharmacovgilance. However, for this purposes, identification should include in addition to the INN additional indicators (e.g. trade name, manufacturer's name and lot number).
- Other biological product identifiers than INN can be included in the labeling which indicate the biosimilar nature of the product

Limitations of the INN systems for biologicals still exist due to the difficulties in defining differences in post translational modifications such as glycosylation or phosphorylation and the fact of batch to batch variation. This does not only apply to biosimilars but to biologics in general.

With regards to a global biosimilar development process problems would arise, if the INN of a biosimilar which is the same as the INN of the reference product is accepted for regulatory purposes by one regulatory authority but not by another. A separate INN would have to be applied for. As a result several INNs would have to be assigned to a single biological substance or the INN would have to be changed with worldwide implications on already existing marketing authorizations and pharmacovigilance reporting. However, the issuance of multiple INNs for an active ingredient nor the change of INNs once issued is not stipulated in the WHO INN procedures. So far no instance has been published in which the same product containing the same active ingredient and manufactured by the same manufacturer has different INN in different jurisdictions. A different approach to avoid discussions with health authorities on the INN during global development would be to apply for a distinct INN prior to application for marketing authorization. Although the data set generated claims similarity and comparability of the biosimilar with it's reference product, the two different INNs indicate clearly different pharmaceutical ingredient (Epoitin zeta in Silapo/Retacrit). Taking into consideration that several epoetin alpha containing branded products from different sponsors share the same INN although theses products have not been compared with each other in terms of molecular structure or biological activity (Eprex, Erypo, Epogen, Procrit) and that a biosimilar product which has demonstrated similarity to a reference product has an INN which is different from INN of the reference product bears the risk of undermining the INN system.

5.4.2.1 Japan

Please refer to section 5.4.1.2 for the legal basis of the naming convention of biosimilar products as well as to PFSB Notification No. 0331001 "Administration Procedures for Handling Non-Proprietary Names for Medicinal Products".

If the biosimilar product and in particular the nature of the active substance including its primary structure is judged during the assessment of the application to be identical to the active substance of the reference product, the biosimilar product is given the same non-proprietary name as the reference product. This rule would apply to "simple" products such as Insulin and Growth Hormone:

- The non-proprietary name of the reference product, followed by
- [follow-on 1 (2, 3 ...)]

For more complex biosimilar products a separate non-proprietary name is given according to Notification No. 0331001 "". The whole non-proprietary name shall be a compound name consisting of:

- A non-proprietary name (as specified in Notification No. 0331001) followed by
- The non-proprietary name of the reference product, followed by
- [follow-on 1 (2, 3 ...)]

During the WHO Informal Consultation on International Nonproprietary Names (INN) Policy for Biosimilar Products in Geneva on Sep 4-5, 2006, representatives from the national institute of Health Science of Japan already stated, that due to the heterogeneity of glycosylation, follow-on protein products modified post-translational should be better discriminated from the innovative products in the INN. For pharmacovigilance and traceability reasons Japan considered that biosimilar products should be distinguished from the innovator product during prescribing (60). With PFSB Notification No. 0331001 a system has been devised to identify biologicals with the same INN which additionally indicates the biosimilar nature of the product.

5.4.2.2 CANADA

Canada uses the INNs when they exist.

5.4.2.3 European Union

Although the EMEA/EU commission is responsible for decisions on marketing authorization of biosimilars, prescribing policy is strictly a national responsibility. Regarding the INN policy, the EU considers the INN as a classification system based on molecular structure and mechanism of action and the assignment should be based on scientific criteria. There should be no specific process for the naming of biosimilar substances in terms of assignment of an INN. The policy for the assignment of INNs should apply to biologics in general.

Brand names are not mandatory in the EU for any type of medicine (see chapter 5.4.1.1) and the INN may be used as part of the common or scientific name for a medicinal product.

Further to the naming of a medicinal product, the INN appears to be an important criterion for the selection of the reference product. According to CHMP Guideline on Similar Biological Medicinal Products (CHMP/437/04), the active substance of a similar biological medicinal product must be similar, in molecular and biological terms to the active substance of the

reference medicinal product. As an example the product with the INN interferon alpha-2b is considered not an appropriate reference medicinal product for interferon alpha-2a. Assigning a different INN to the biosimilar and the reference product would contradict the biosimilar concept.

5.5 Intellectual Property Rights (Patent protection and exclusivity provisions)

The pharmaceutical industry and in particular the innovator companies rely upon legitimate intellectual property (IP) rights including patents, copyrights and trade marks as well as other forms of protection such as national exclusivity provisions. With regards to abbreviated applications for generic and biosimilar products, which may be brought to market immediately upon expiration of any patents and/or other exclusivity periods, IP rights provide the innovator with a time-limited, exclusive right to market a particular medicine once it has been approved by a health authority, in order to recoup their investment for research and development. These incentives for investment are considered a prerequisite to research and development investments, necessary to promote the development of innovative medicinal products, new treatments and cures (2, 64).

Periods of exclusivity for new drugs originating either from patents or complementary forms such as data exclusivity, exist in most developed countries which have mechanisms for abbreviated applications for generic and biosimilar products in place. They are intended to provide a balance between innovation and public health. This balance is in part determined by the length of the market exclusivity period for new drugs. During the market exclusivity period the originator pharmaceutical company may sufficiently compensate for research and development costs by selling their products with higher prices. By providing this monopoly for research based pharmaceutical companies, healthcare quality and the growth of this high-tech industry are supposed to improve. By limiting the marketing exclusivity period and the monopoly power of the research based companies on the other hand, national healthcare costs should be reduced and access to essential drugs for all patients should be made possible by accelerating the entry of generic or biosimilar drugs.

Patents on biologics and the periods of marketing exclusivity which are complementary forms of IP rights, play a key role in determining the time point when biosimilar products emerge on the market. Taking the nature of biologic patents (61) and the extended development times for biologics compared to generics, into account, data and marketing exclusivity provisions may be even more significant than patents, in this respect (62).

The systems and measures that countries have introduced in their national law in order to supply their population with affordable drugs as needed while protecting the research based pharmaceutical industry include data and market exclusivity, patent term extensions , experimental use exceptions and patent restoration.

A patent is a government grant that gives the applicant sole permission to make, sell, and import or use an invention. Patents are rewards for innovation based on the criteria of novelty, utility and non-obviousness (see below). Patent laws are territorial in nature and their operation reflects national needs and circumstances. In most countries patents are enforced by

court proceedings. In the pharmaceutical industry patents give exclusive rights to a particular new drug product or compound, a specific molecule or particular methods to use such a product, compound or molecule. Patents also serve to protect manufacturing processes and apparatuses. A prerequisite for granting a patent is that the invention, which must have a practical purpose (industrial applicability", is not obvious in light of what has been done before (inventive step), that it is not in the public domain and has not been disclosed anywhere in the world at the time of the application (novelty). Patents are grantable nationally and provide the patentee the right to protect the innovation for 20 years. Under certain circumstances patents for pharmaceuticals can be extended (e.g. the supplementary protection certificate (SPC) in the EU).

Innovators usually apply very early in development for patents (e.g. in the pre-clinical development stage). During the term of the patent complete product development and the marketing authorization application and evaluation takes place. In average ... years of the patent term remains to allow the innovator to earn a positive return. National exclusivity provisions recognize the substantial investment and provide additional incentives to the innovator companies as these provisions delay abbreviated filings.

Exclusivity provisions, which provide the innovator with a time-limited exclusive right to market a particular medicine once it has been approved by a health authority, come in two forms:

Data exclusivity: Data exclusivity prevents the manufacturers from relying on the data generated by their innovator for an abbreviated approval submission. During the regulatory data exclusivity period regulatory authorities are not allowed to refer to the data on file for the assigned reference product in order to assess and process an application for marketing authorization or even to accept this type of application. In other words, a potential biosimilar supplier is prohibited from filing for an abbreviated application making reference to a brand product to substantiate the safety and efficacy of the biosimilar product.

Many countries have established data exclusivity provisions, which provide exclusivity periods of usually 5 to 10 years. The data exclusivity period starts with the date of the first marketing approval of the reference product.

Data exclusivity periods for innovative products are the same in the EU and Japan regardless whether it is a traditional chemical medicines or biosimilar. In the USA however, where chemical medicines have a data exclusivity period of four to five years, innovator companies claim that a data exclusivity period for biosimilars would have to be 14 years, due to differences in the market, the approval process and the medicines themselves. Innovator companies argue that the patent protection and the approval process for biosimilars are not aligned in terms of the scope of protection. Whereas a similar biological product may receive approval due to its proven similarity to the reference product, it may

escape the patent protection due to its still existing differences. The launch of a biosimilar after it has received approval via an abbreviated pathway, before patent expiry of the reference product is not considered an infringement, in the worst case. Therefore a longer data exclusivity period is requested by innovator companies.

Market exclusivity — Market exclusivity (also referred to as approval exclusivity) is a period of time during which a biosimilar supplier can file for marketing approval, but cannot receive approval.

Both data and market (approval) exclusivity constitute marketing exclusivity. The effective period of marketing exclusivity gained by the originator company is the period of data exclusivity extended by the time it takes to register and market the generic/biosimilar product. The clock on the effective period of marketing exclusivity starts with the approval of the brand product. Exclusivity provisions may therefore extend the marketing approval holder's monopoly beyond the term of the patent. When patent protection for a medicinal product is not available, data and market exclusivity may be the sole protection for the innovative drug manufacturer.

The term of data protection, which falls under the intellectual property right category "copyright" should be distinguished from data exclusivity. Commercially sensitive data remain undisclosed to third parties when the data exclusivity period is expired and the regulatory authority relies on the originator's data for regulatory approval. The copyright is as all other intellectual property rights protected and enforced by national legal provisions.

Most developed countries have introduced legal and regulatory systems to protect IP rights in the pharmaceutical industry from early on. On a global level, the minimum international standard for the protection of IP rights in drugs is regulated by the World Trade Organization's (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) coming into effect in 1995. This agreement, which all WTO members had to implement in their national legislation by January 01, 2000, requires all WTO members to create strict intellectual property systems. The TRIPS Agreement specifies in a global framework that a product (e.g. drugs) or processes should be subject to protection by patents while allowing certain exceptions for member states governments. In addition, the core concept of data protection is considered to be also part of the agreement. It should be noted, that the TRIPS agreement does not provide or propose a time limitation to the period, which should apply to data exclusivity provisions, whereas the period of patent protection is recommended to be 20 years from the date the inventor files for the patent application. The obligations under TRIPS apply equally to all member states of the WTO. However the "least developed countries" were allowed a transition period until 2016 to implement the applicable changes into their national law 63 (please refer to section 5.5.4).

Many countries use the provision of research exception or "Bolar" provision admissible under the TRIPS agreement (Article 30). Under this exception researchers are allowed to use a patented invention for research purposes. That includes in some countries the use of patented inventions to obtain the required pre-clinical and clinical data for marketing approval of

generic drugs without the patent owner's permission and prior to patent expiry. The generic products can then be marketed as soon as the patent expires.

Incentives and patent rights are not only provided to the initial product development, but also for sequential development comprising new indications, dosages and changes in formulation, color or markings. Sequential innovation is supposed to lead to product improvements that enhance treatments and cures. Many biologic products are initially developed for a single indication. Due to their pleiotropic effects on the entire human physiology, biologics usually have a therapeutic potential well beyond their initial therapeutic objective. Therefore, these products are subject to further postlauch R&D leading to treatments for additional indications sometimes in entirely different therapeutic areas. Each new approved indication required a distinct development program which together can take three to six years (post marketing commitments excluded) (5). These sequential patents provide additional years of market monopoly to the innovator product.

Generic companies sometime complain that originator companies are seeking to obtain as many patents as possible and to extend them for new uses of established products, thereby delaying market entry of generic/biosimilar products, sometimes referred to as "Evergreening". Often these changes are considered as insignificant changes, providing little therapeutic value to patients. Innovators often claim that 100 or more patents cover their products. Many of them are process patents, which are in general not a barrier to biosimilar competition.

5.5.1 European Union

Patents in the EU are registrable nationally as no EU-wide single patent system in terms of validity of a single patent in all Member States exist to date. An inventor may freely choose to apply for a national patent in one or more Member States. Alternatively, an inventor may file a single patent application at the European Patent Office based on the European Patent Convention (EPC). Once a European patent has been granted, it becomes a single national right in all Member States participating in the EPC and falls under the respective national jurisdiction.

On the international level, the Member States as the Community itself are obliged to adhere to the TIPS Agreement. As in other countries a patent provides the patentee with the right to prevent anyone making, using, selling or importing the invention for 20 years. Before the 20-year patent regime has been introduced in the 1990s product patents expired after 15 years. As the first patent for biotechnology products were granted in 1998, the 20 year patent regimen applies to biosimilars.

In addition to the 20 year period of patent life for pharmaceuticals and plant products, basic patents covering the active ingredient of a new medicinal product can be extended for a maximum of 5 years providing as much as 25 years of patent life for originator medicines. However, the period of the SPC to be granted should not extend the effective patent life (remaining patent life from the date of marketing authorization) of the active substance for more than 15 years. The so called Supplementary Protection Certificate (SPC) was introduced in 1992 to compensate originator companies for the time and costs required for the

development of registration data (64). The legal basis for the SPC is council regulation EEC No 1768/92 of June 18, 1992 (65). The SPC is dependent on a successful marketing authorization and must be lodged within 6 months of the date of granting the marketing authorization. As the patents, the SPC must be applied for at the national patent offices by the original patentee. The SPC is only granted once for the basic patent. An extension of the SPC for additional 6 months is granted if the marketing authorization holder conducted clinical studies in children according to Regulation (EC) No 1901/2006. However, the extension of the SPC is debarred if the applicant received a one-year extension of the period of marketing protection on the ground of an approved new pediatric indication (see below) (66).

In Europe patents are enforced by court proceedings to prevent the sale of products infringing the rights of the patentee. Measures to harmonize rules within Europe are included in Directive 2004/48/EC (67).

With regards to pharmaceutical products, patents may relate to new chemicals or active ingredients, formulations, processes and uses. So called usage patents relate to new indications or modes of administration. These patents are usually applied for products at the end of their basic (i.e. active substance) patent life. In Article 11 of Directive 2001/83/EC provisions related to usage patents are provided for abbreviated marketing authorization applications, including Article 10(4) of Directive 2001/83/EC. Those parts of the summary of product characteristics of the reference product related to indications or dosage forms which are still covered by a usage patent at the time of marketing of the generic or biosimilar product may be omitted from the summary of product characteristic of the generic or biosimilar medicinal products.

Applications for Similar Biologic Medicinal Products according to Article 10(4) of Directive 2001/83/EC are only accepted if the application is submitted after the expiry of the data exclusivity of the reference medicinal product.

Innovative products benefit from a data exclusivity period, which currently varies from 6 to 10 years depending on the member state, which granted marketing approval for the reference product. It should be stressed that the EU data exclusivity covers the initial authorization of the medicinal product but cannot be given for additional indications, strengths or dosages. For reference products for which the initial submission was made prior to 20 November 2005 (centrally authorized) or 30 October 2005 (nationally authorized)(68 69) the following data exclusivity period apply:

10 years for centrally authorized products and for national authorizations granted by the following MS: Belgium, Germany, France, Italy, the Netherlands, Sweden, United Kingdom, Luxemburg

6 years for national authorizations granted by the following MS: Austria, Denmark, Finland, Ireland, Portugal, Spain, Greece, Poland, Czech Republic, Hungary, Lithuania, Latvia, Slovenia, Slovakia, Malta, Estonia, Cyprus as well as Norway, Liechtenstein and Iceland (70).

In 2004, Directive 2004/27/EC, amending Directive 2001/83/EC, and Regulation (EC) No 726/2004 have introduced new rules concerning the data and marketing exclusivity in order to harmonize the periods of data and market exclusivity to the so-called "8+2+1" period (see

below). These periods of protection apply to centrally authorized reference products pursuant to Article 14(11) of Regulation (EC) No 726/2004 as well as to reference products authorized nationally under Article 6 of Directive 2001/83/EC. The new legislation entered into effect in November 2005 and shall not apply to those reference medicinal products for which the initial application for authorization was submitted before 20 November 205 (Article 89 of Regulation (EC) No726/2004. Therefore the first biosimilar application under the "8+2+1" year data exclusivity period will not occur until 2013.

Data exclusivity period:

An authorized product will get a data exclusivity period of eight years, after which a company is allowed to submit a biosimilar application.

Marketing exclusivity period:

The actual placing on the market of the biosimilar will not be permitted until 10 years have elapsed from the initial authorization of the reference product (8+2 years of market exclusivity).

The period of market exclusivity can be extended to a maximum of 11 years (8+2+1 year of market exclusivity) if, during the first eight years of data exclusivity, the holder of the marketing authorization of the reference product obtains an authorization for new therapeutic indication(s) which provide significant clinical benefit in comparison with existing therapies.

Unlike the intellectual property regulation and except for new indications, these periods cannot be prolonged by variations or extensions of the initial marketing authorization in accordance with the "global marketing authorization" concept (e.g. new strengths, pharmaceutical forms, administration routes) (Article 6(1) of Directive 2001/83/EC as amended).

In practical terms an application for marketing authorization of a biosimilar product in accordance with the revised data and market exclusivity periods, can be submitted after the data exclusivity period has been expired. Marketing of the product would be possible after either 2 or 3 years have passed

Table 5-1 Data exclusivity periods in the European Union

Authorization Procedure applicable for Generic/Biosimilar	Submission date of Reference Product	Type and authorization of Reference Product	Reference Product authorized by Member	Period of Exclusivity	Regulatory Basis
Centralised Procedure according Regulation (EC) No 726/2004)	Before Nov 20, 2005 (Article 89 , Regulation (EC) No 726/2004)	National authorization	BE, FR, DE, IT, LU, NL, SE, UK	10 years (data exclusivity)	Article 10(1)(a)(iii) of Directive 2001/83 71
			AT, BG, CY, CZ, DK, EE, FI, GR, HU, IS, IRL, LV, LT, MT, NO, PL (3 years prior to May 05, 2006), PT, RO, SK, SI, ES	6 years (data exclusivity)	

		Centrally authorized products, and ex-concentration products (Article 4 Directive 87/22/EEC)	All MS	10 years (data exclusivity)	Article 13(4) of Regulation (EEC) No 2309/93 72
	After Nov 20, 2005 (Article 89 , Regulation (EC) No 726/2004)	n.a.	n.a.	10 or 11 years (8 years data exclusivity + 2 years market exclusivity +1 year market exclusivity)	Article 14(11) of Regulation (EC) No 726/004 (68)
Products to be authorized by national competent authorities	Before Oct 30, 2005 (Article 2 and 3 of Directive 2004/27/EC) (75)	National authorization	BE, FR, DE, IT, LU, NL, SE, UK	10 years (data exclusivity)	Article 10(1)(a)(iii) of Directive 2001/83 73
			AT, BG, CY, CZ, DK, EE, FI, GR, HU, IS, IRL, LV, LT, MT, NO, PL (3 years prior to May 05, 2006), PT, RO, SK, SI, ES	6 years (data exclusivity)	
		Centrally authorized products, and ex-concentration products (Article 4 Directive 87/22/EEC)	All MS	10 years (data exclusivity)	Article 13(4) of Regulation (EEC) No 2309/93 74
	After Oct 30, 2005 (Article 2 and 3 of Directive 2004/27/EC) (75)	n.a.	n.a.	10 or 11 years (8 years data exclusivity + 2 years market exclusivity +1 year market exclusivity)	Article 1(8) of Directive 2004/27/EC amending 2001/83/EC (75)

An experimental use exception (also referred to as "Bolar type provision") is stipulated in Article 10(6) of Directive 2001/83/EC (75) as amended, providing the permission to conduct studies and trials required for marketing authorization applications including Article 10(4) applications, before patent or SPC expiry. The scope and effective date of the experimental use exception depends on the national implementation into the legislation e.g. into the national legislation related to patents. Article 10(6) of Directive 2001/83/EC has been differently interpreted by the Member States. IDRAC provides a comparative table on the scope of the experimental use exception as implemented in the Member States.

5.5.2 Japan

In Japan several institutional factors exist which affect the market exclusivity for new drugs, which is defined as the period from the approval of a new drug to the moment when the marketing of a generic or biosimilar drug can be initiated:

- Statutory subject matter of patent protection (coming into effect in 1976)
- Patent term extension established in 1988
- Market exclusivity rights introduced in 1967
- Experimental use exception ("Bolar provision")

The market exclusivity period and therefore the restriction of the market entry of generic or biosimilar medicinal products are predominantly determined by relevant patents.

Initially the purpose of the marketing exclusivity right, which was granted the first time in 1967 with establishment of a new review system for new drug approval, was only to reconfirm the clinical usefulness of drugs though collecting information on the efficacy and safety of the drug after approval. The so called re-examination period is therefore statutorily different form the data protection provision established in Europe which was to protect the benefit of originator marketing authorization holder.

The market exclusivity right allows originator manufacturers to have the market exclusivity of a new drug even if the new drug is not protected by any patent of the product.

Although the re-examination period system aims a the reconfirmation of the clinical usefulness of drugs during a period of time after approval, the reexamination period is also that of marketing exclusivity right during which applications for generics based on own bioequivalence data only cannot be filed. However, in the re-examination period of the new drug, a competitor may file an application with its own complete set of safety and efficacy studies (Notification No. 481 dated 08 April, 1999).

The period of re-examination for new drugs (i.e. a drug whose active ingredients, quantities, administration and dosage, method of use, indications and effects, etc. Are distinctly different from those of drugs which have already been approved for marketing) are designated by the MHLW (Article 14-4 (1) PAL). Generally the re-examination period for drugs with new active ingredients has been prolonged from 6 years to 8 years as a rule from 01 April 2007 (Notification of the PFSB No. 0401001 dated 01 April, 2007) (JPMA). In case the Government considers it particularly necessary to perform proper reexaminations of new drugs, the examination period can be extended by the Minister to 10 years (Article 14-4 (2) PAL).

Table 5-2 Overview of re-examination periods in Japan

Re-examination period	The subject drugs
10 years	Orphan drugs Drugs requiring pharmacoepidemiologic methods for evaluation Drugs for which peadiatric clinical studies continue after approval
8 years	Drugs with new active ingredients
6 years	New combination drugs New routes of administration
4-6 years	New Indications New dosages

A patent is a legal, public title granting an intellectual property right to the patent holder, as the information contained in the patent application is made public. The patent holder is rewarded a limited monopoly allowing the holder to prevent others from making profit by manufacturing, using or selling the patented product. The monopoly is limited within the national borders.

Japan is a member of the World Trade Organization (WTO) and a signatory to a number of international agreements including TRIPS. In 1976, the system of product patent for pharmaceuticals was introduced. Neither in the first Japanese Patent Monopoly Act in 1885 nor in the Japanese Patent Act in 1959 the protection of patents for pharmaceuticals was stipulated.

The subject of the protection by the Japanese Patent Act is a statutory invention. Three types of inventions including the invention of a product, of a process or a process for producing a product are defined.

Medical activities, which mean a method for treatment by surgery or therapy, method of dosing, or diagnostic methods practiced on the human body may not be patented.

The patent term is 20 years from the date an application was filed as a rule with no provision for renewal. Patents for medicinal products are eligible for an extension of no more than five years (see below).

Patent term extension was introduced in 1988 as a system which could compensate for a lengthy drug approval process. If the patent cannot be implemented due to necessity of obtaining an approval or other disposition prescribed by Cabinet Order the patent term can be extended for a maximum of 5 years (Article 67, § 2 of the Patent Law). If at least two years have elapsed since the date of granting the patent right and it is not possible to work the patent invention the patent holder is eligible for obtaining an extension of the patent term. The extension is for the period that the patented invention cannot be used, i.e. the period from the date of the start of clinical trials or date of patent registration, whichever is later, until on day prior to the date on which the patentee receives approval for the drug. The period devoted to pre-clinical tests is not included in this period.

Applicants who want an extension of the patent term needs to submit an application to he Patent Office for extension of registration including the required items such as the requested extension period before the patent rights become invalid within 3 months from the date of receipt of drug approval.

Generic drugs will not be approved until the substance (application) patent has expired. Furthermore, MHLW recommends to confirm that no patents are infringed when filing approval applications for generic drugs or to submit a freedom to operate declaration (Office Communication of PAB dated 28 June 1995)

In Japan, there is no legislation concerning the data related to the medicinal product. The patent provides the right to exploit the invention commercially, but does not provide any protection of the underlying data.

In Japan an experimental use exception (Bolar provision) is provided in Section 69(1) of the Japanese Patent Act. This provision allows sponsors to conduct "experimentation or research" including bioequivalence studies with a patented product before the relevant patents on the original branded drug expires. In 19999, the Japanese Supreme Court confirmed that bioequivalence testing for the purpose of gaining approval for the production of drugs falls under "experimentation and research" as stipulated in the Japanese Patent Act.

As shown by Masuda (2008) (76) even though the marketing exclusivity right for new drugs was extended to 8 years, the impact of the marketing exclusivity right on the timing of generic drug applications is rather low, as the effective patent life (period which starts at the date of approval or when the patent was issued, whichever is later, and ends at the date of patent expiration after patent extension) for almost all patented drugs is more than eight years after launch. The overall mean EPL was 11.74 years with the longest period of 19, 31 years and the shortest 5.33 years. The mean extension period was 4.13 years.

According to the Guideline for Quality/Safety/Efficacy Assurance of Biosimilar Products (PFSB/ELD Notification No. 0304007) an approval application for a biosimilar product may become viable mainly when the re-examination period of the reference biologic finishes. As the re-examination period as stipulated in Article 14-4 Paragraph 1 PAL) applies to new products regardless of the nature of the active substance there is no difference in the marketing exclusivity granted by the Government for new drugs with chemical entities or biopharmaceutical active ingredients.

5.5.3 Canada

In Canada, the Canadian Intellectual Property Office is responsible for examining and approving patents. The patent office also maintains a patent database for public use (77).

For applications filed on or after October 01, 1989, a patent is valid for a maximum of 20 years from the filing date (78) which is in agreement with Canada's international treaty obligations under the WTO. Patents based on applications filed before October 01, 1989 were valid for 17 years. Under the Canadian law new compounds, a new use for an old compound, formulations and manufacturing processes, new delivering methods and combination drug products may be patented.

Anyone who makes uses or sells a product on which a patent is in force (20 years) is infringing the patent. The only exception to this provision provides generic manufacturers with the rights to use a patent drug for the purpose of research in order to begin the process of seeking regulatory approval ("Bolar" provision).

In Canada, intellectual property for pharmaceuticals is protected by the Patented Medicines (Notice of Compliance) Regulations (also referred to PM(NOC) Regulations) (patent protection) and by Data Protection under C.08.004.1 of the Food and Drug Regulations.

The PM(NOC) Regulations govern the issuance of the Notice of Compliance. Even though generic companies may proceed to seek regulatory approval prior to patent expiry, Health Canada is prevented from issuing a Notice of Compliance for a generic product as long a relevant patent listed in the patent register (see below) is valid. The applicant is required to address the patents listed on the Patent Register against the innovative drug. In case the applicant agrees to the patents the NOC is issued after expiry of the last patent. Otherwise the applicant may challenge the patent by making an allegation justifying the issuance of the NOC. The innovator may accept that the generic product does not contravene it's patent or the allegation is upheld through a Federal Court decision. Therefore, approval of generic and SEB drugs is linked to the patent status of the corresponding reference product.

In order to obtain the protection according the PM(NOC) Regulations, the patent holder needs to submit a patent form to Health Canada for inclusion in the patent register (79), stating all patents and expiry dates relevant to the product.

With regards to patents, intellectual property and data protection and exclusivity, SEBs shall be subject to existing laws and regulations. An SEB will be therefore only approved based on a submission that makes either a direct or indirect comparison to an innovative biologic product previously authorized for sale in Canada 80. According to PM (NOC) Regulations and C.08.004.1 of the Food and Drug Regulations and related guidance documents entitled „Draft Guidance Document: "Data Protection under C.08.004.1 of the Food and Drug Regulations" dated March 24, 2009, and „Guidance Document: Patented Medicines (Notice of Compliance) Regulations" the following patent protection and data exclusivity periods apply:

Under current regulation (81) patent protection is provided:

- 20 years for patents based on applications filed on or after October 01, 1989
- 17 years for patents based on applications filed before October 01, 1989

Under current regulations (82) data exclusivity is provided:

- Product containing new active ingredients authorized prior to June 17, 2006: 5 years beginning on the date of marketing approval.
- Product containing new active ingredients authorized on or after June 17, 2006:
    - 8 years of data exclusivity for a New Drug Submission (NDS) on a new chemical entity from the date of the Notice of Compliance (NOC). An abbreviated new NDS (generic application) may not be filed for 6 years after the NOC has been granted to the innovator. Approval cannot be granted until 8

years have elapsed since the innovators NOC. It should be noted, that the data exclusivity applies only to the first NOC for a new drug containing a pharmaceutical active ingredient not previously approved in Canada i.e. the data exclusivity is not granted to a second applicant with a full dossier. The data exclusivity does also not apply, if the innovator consents to the reliance on his data by another applicant (83).

- Drugs for which pediatric (84) clinical studies were conducted: 8 years plus 6 months, provided the supplement is submitted within 5 years of the NOC.

It should be noted that the introduction of the revision of the data exclusivity period in October 2006 applied to the implementation of Article 1711 of the North American Free Trade Agreement and to Article 39(3) of the TRIPS agreement (85).

With regards to data exclusivity and patents, two Guidance Documents will be revised to reflect any revisions due to the Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs):

- Guidance Document: "Data Protection under C.08.004.1 of the Food and Drug Regulations" effective date March 24, 2009, which applies to pharmaceutical, biological and radiopharmaceutical drugs that receive NOC, and
- Guidance document: Patented Medicines (Notice of Compliance) Regulations, effective date April 03, 2009.

5.5.4 WHO

The minimum international standard for the protection of IP rights in drugs is regulated by the World Trade Organization's (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which came into effect in 1995. This agreement, which all WTO members had to implement in their national legislation by January 01, 2000, requires all WTO members to create strict intellectual property systems. A transitional period until 2005 was offered under the TRIPS Agreement before the member countries had to introduce product patent protection rules on pharmaceuticals. The TRIPS Agreement specifies in a global framework that a product (e.g. drugs) or processes should be subject to protection by patents while allowing certain exceptions for member states governments (Article 27.1 TRIPS agreement). The minimum obligations for pharmaceuticals are: pharmaceutical products and micro-organisms are patentable for up to twenty years from the date the inventor files for the patent application. Exclusive marketing rights are granted until patent expiry. In addition, the core concept of data protection is considered to be also part of the agreement (Article 39.3). "*Members, when requiring, as a condition of approving the marketing of pharmaceutical ..//.. products that utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use*". Accordingly, regulatory authorities are under the

obligation to protect undisclosed clinical and test data submitted for granting marketing approval against unfair commercial use and against "disclosure.

Some pharmaceutical companies claimed that Article 39.3 also required the introduction of data exclusivity provision, which would provide market protection for pharmaceutical products which are not/no more protected by patents (3). The European Generics Association (EGA) however disagrees that Article 39.3 is meant to obligate member countries to create exclusive rights as it is the case with EU and US data exclusivity laws. The protection of clinical data made for registration purposes against "acts of unfair competition" according to Article 39.3 would rather refer to the prevention of allegations which may mislead the public, discredit the product or enterprise concerned and to acts in respect of unlawful acquisition, disclosure or use of trade secrets 86. It should be noted, that the TRIPS agreement does not provide or propose a time limitation to the period which should apply to provisions resulting form Article 39.3, whereas the period of patent protection is recommended to be 20 years.

Each country that has signed the treaty should adhere with respect to the protection of IP in drugs although a degree of freedom to member states is provided. Patent protection for specific inventions can be denied by member states. In addition, the TRIPS Agreement allows countries a considerable degree of freedom. Developing countries may for example determine in their own ways the definition of an invention, the criteria for judging patentability, the rights conferred on patent owners or exempt from patentability therapeutic methods for the treatment of humans and new indications of known products (46).

Taking concerns of developing and least developed countries into account (e.g. massive exports of IP royalties), the Doha declaration dated Nov 2001 was released in order to reaffirm the flexibility in terms circumventing patent rights for better access to essential medicines (e.g. compulsory licensing, limits on data protection and exceptions to patentability). The obligation under TRIPS applies equally to all member states of the WTO. However the "least developed countries" were allowed a transition period until 2016 to implement the applicable changes into their national law 87.

The TRIPS agreement, by establishing minimum standards of intellectual property rights globally, is one form of incentive for innovative product development and/or marketing in developed a more importantly in developing countries excluding the least developed countries. Although the implementation of the TRIPS agreement among all members of the WTO is supposed to assure patent protection to innovator companies, there has been no documented case of positive impact of the implementation of the TRIPS agreement on innovation in the medicinal field for the time being . If at all, fostering of the development of innovative medicinal products is expected in developing countries that already have a promising science and technology base. Unless a globally acting innovator company applies for marketing authorization in developing countries, certain in particular innovative medicinal products including biotechnological products may not be marketed in less developed countries.

The lack of a reference biotherapeutic product approved by a national regulatory authority may pose a problem for pharmaceutical companies seeking approval for a biosimilar product. In the current version of the Guideline on Evaluation of Similar Biotherapeutic Products (SBPs)

published by the WHO the problem of the non availability of a locally authorized reference product is taken into account (please refer to section 5.3.4).

5.6 Quality Information

5.6.1 Extend of quality data to be provided for abbreviated licensing application

All of the above mentioned implemented or proposed guidance documents require that biosimilar products are manufactured and controlled according to their own development process. In consequence a full quality dossier (Module 3) must be submitted. It has been acknowledged that the manufacturer of biosimilar products normally have no access to all the necessary manufacturing information of the originator product.

In addition to the development and full understanding of a consistent and robust manufacturing process the biosimilar product needs to be characterized in detail by means of state-of-the art technologies similarly to when developing a new biological medicinal product.

The characterization of the biosimilar product is followed by a comprehensive comparability exercise evaluating

Manufacturing process, comprehensive comparative physicochemical and biological characterization (head-to-head studies with the reference medicinal product) including among others the assessment of physicochemical properties, biological activity, immunochemical properties, impurities and stability, specifications, and dossier requirements.

5.6.1.1 European Union

Information regarding the extend of data to be submitted for a biosimilar marketing authorization application, in particular for a product containing recombinant DNA-derived proteins, in terms of quality is provided in the EMEA/CHMP/BWP "Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substances: Quality Issues" (25).

As in other jurisdictions, biosimilars are manufactured and controlled according to their own development, taking into account relevant and state-of-the-art information. Therefore a full quality dossier (CTD module 3) is required supplemented by the demonstration of comparability between the biosimilar and the reference product. Module 3 shall satisfy the technical requirements of monographs of the European Pharmacopoeia and others as defined in relevant CHMP and ICH guidelines (24).

5.6.1.1.1 Manufacturing Process and Quality Characteristics

Quality Characteristics

The pharmaceutical form, strength and route of administration of the biosimilar should be the same as that of the reference product. Other approaches may be considered by the applicant. If differences exist, additional data in the context of the comparability exercise are requested (24).

Even if the manufacturer decides to use the identical formulation as the reference product, own formulation studies should be considered in the course of the development of a suitable dosage form in order to demonstrate the suitability of the proposed formulation (25).

Manufacturing Process

For the biosimilar product its own consistent and robust manufacturing process needs to be established and state-of-the-art technologies should be deployed.

The use of the same host cells for manufacturing of the biosimilar product as the reference product is not considered a requirement. In fact in the European Union two different cell lines may be used for the manufacture of a biosimilar product containing recombinant G-CSF (18). Recombinant G-CSF produced in *E.Coli* (filgrastim) and in CHO cells (lenograstim) are in clinical use. Filgrastim has an additional amino-terminal methionie and lacks any glyocosylation. Somatropin containing biosimilar product Valtropin for example is manufactured in yeast cells (*Saccharomyces cerevisiae*) whereas the somatropin for the designated reference product Humatrope is produced in *E.Coli.*

If changes are introduced into the manufacturing process during the development, a comparability exercise in accordance with ICH Q5E Guideline should be considered.

Stability

Comparative stability studies with the active substances under stress and accelerated conditions are requested as part of the comparability exercise (physicochemical properties – please refer to section 5.6.1.4.2). Otherwise, no specific guidance is provided with regards to stability studies to be performed except for referencing of ICH Q5C Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (24).

Specifications

The specifications for biosimilars should be determined and set in accordance with ICH Q6B. Own analytical data obtained from the reference product should be taken into account, as the specifications for a given test should not be wider than the range of variability observed with the reference product.

5.6.1.1.2 Product Characterisation and Comparability exercise

The evaluation of comparability between the biosimilar with the reference product should be done with both medicinal product and active substance. It is generally necessary to conduct the required comparative quality tests at the level of the active substance although it is acknowledged that the applicant may not have access to the active substance of the reference product (25). The applicant is never the less encouraged to isolate the active substance from the reference product, in order to compare the quality attributes of the active substances from the biosimilar and the reference product directly. The suitability and validity of the isolation process needs to be demonstrated (25).

It is not considered appropriate to demonstrate comparability of the active substance of the biosimilar product with a publicly available standard or reference.

The shelf life of the reference product and potential effects on the quality profile should be taken into account and discussed during the comparability exercise, if appropriate (25).

In general, the applicant is advised to use state-of-the-art methods in order to detect even slight differences in all aspects of the quality. The test methods should be appropriately qualified using publicly available standards and reference substances, if appropriate. Validation is not necessary unless the tests are used for quality control and release testing.

With regards to the quality attributes, which should be evaluated, the CHMP guideline advises to evaluate the following attributes:

- Physicochemical Properties, which comprises the composition, physical properties and the primary and higher order structure (primary, secondary, tertiary and quaternary) of the active substances. Efforts should be made to investigate, identify and quantify post-translational modified forms. The identification of product-related substances and impurities by performing stress and accelerated stability studies is also part of the comparability exercise.
- Biological Activity. The chosen bioassays should reflect the biological properties of the product (e.g. the understood mechanisms of action) and therefore different approaches to measure the biological activity should be considered. If possible, the assays should be calibrated against an international or national reference standard and the results should be expressed in units of activity. The assays should also comply with appropriate European Pharmacopoeia requirements, if applicable. Further information regarding pharmacodynamic *in vitro* studies and product-class relevant PD markers are provided in the product-class specific Annexes to CHMP Guideline "Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (please refer to section 4.1.2 and 5.7.1.1.3),
- Impurities. Product related substances and impurities in the biosimilar product should be identified, quantified and compared between SBP and reference product. Stress and accelerated stability studies could be useful for identification (see above) as the comparison of the purity/impurity profile should not only be based on post-translational modifications but also on degradation pathways. For process-related impurities care should be taken regarding the suitability of the assay (e.g. different host cell proteins host cell DNA due to different host cells used for SBP or reference product, different downstream impurities). Significant differences should be evaluated with regards to their potential impact on safety and efficacy.

5.6.1.1.3 Comparability evaluation

It has been acknowledged by the authority that differences in quality attributes between a biosimilar and a reference product may exist (25). If differences are identified during the comparability exercise with regards to quality attributes, a stepwise approach should be

undertaken to justify any potential implications with regards to the safety and efficacy of the product. Those differences may have consequences with regards to the amount of non-clinical and clinical data required to make satisfactory justification of the safety and efficacy of the biosimilar (25).

5.6.1.2 Japan

Information regarding the extend of data to be submitted for a biosimilar marketing authorization application is provided in Table 2-(1) of PFSB Notification No. 0304004 dated 04 March 2009 entitled "Applications for Approval of Biosimilar Products" amending PFSB Notification No. 0331015 (32). More detailed information regarding the content of the required data is provided with PFSB/ELD Notification No. 0304007 dated 04 March 2009 entitled "Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products" (34).

5.6.1.2.1 Manufacturing Process and Quality Characteristics

Quality Characteristics

The same dosage form and route of administration as the reference product should be considered for the biosimilar product, in principle. A different dosage form (liquid versus lyophilized form) may be chosen, if appropriate (88).

In case the formulation does not impact the safety and efficacy of the biosimilar product, the formulation may be different (e.g. different excipients). If necessary, non-clinical or clinical pharmacokinetic (PK) studies should be considered.

Manufacturing Process

For the biosimilar product its own consistent and robust manufacturing process needs to be established and state-of-the-art technologies should be deployed as not much information may be available concerning the manufacturing process used by the innovator.

If the host cell used for the manufacturing of the reference product is known, it is considered preferable to use the identical host cell for the biosimilar product. For example, the term identical host cell refers to the level of "CHO" but not to further subspecies (88). Never the less, the origin of the host cell needs to be documented in the same way as when developing a medicinal product containing a new active substance.

Manufacturing changes during developments should be evaluated according to ICH Q5E Guideline.

The expression construct used for the manufacture of the biosimilar product should be analyzed according to ICH Q5B Guideline "Quality of Biotechnological Products"

For the preparation of the cell banking system, its characterization and management, ICH Q5A Guideline "Viral Safety Evaluation of Biotechnology products Derived from Cell Lines of Human or Animal Origin", and ICH Q5B and ICH Q5D Guideline "Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological products" should be followed.

Stability

Long-term stability (real time and real storage conditions) needs to be demonstrated and studies under stress or accelerated conditions are desirable but not a requirement. ICHQ5C Guideline "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products" should be taken into account. The expiry date is established based on the results of the long-term stability study. A minimum of 6 months at the time of application is required. A comparison with the reference product is not required or expected.

5.6.1.2.2 Product Characterisation

The level of characterization should be the same as for a new recombinant protein medicinal product. State-of-the-art technology should be deployed to fully clarify:

- Structure/composition
- Physicochemical properties
- Bioactivity
- Immunochemical property
- Impurities (product – and process-related impurities)
- Further not specified parameters

5.6.1.2.3 Comparability evaluation

Studies which are based on the concept of ICH Q5E Guideline "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" should be conducted.

Comparability evaluation of the quality attributes should be performed with drug substance. In case drug substance of the reference product cannot be obtained, formulated product or drug substance extracted and/or purified from the drug product should be used.

Official reference standards which may be available for some products should not be used as a control in structural analysis and comparative studies on physicochemical properties.

The following parameters should be analyzed by means of state-of-the-art technologies in more than one batch, if possible:

- Structural analysis and studies comparing physicochemical properties. A product which claims to be biosimilar requires the same primary structure as the reference product, while heterogeneity due to post-translational processing (N- or C-terminal amino acids) has to be shown to have no adverse impact on safety and efficacy.
- Studies comparing bioactivity to assess comparability in terms of higher order structure. Multiple assays, if available, should be used. In particular in vitro bioactivity assays which are relevant to the clinical effect (e.g. cell proliferation and differentiation, receptor binding and enzyme activity) should be accompanied by in

vivo bioactivity assays in case the in vitro assay is not relevant to the clinical effect (e.g. glycosylated proteins)

- Studies comparing immunogenicity by means of immuno-reactivity assays in animals are considered useful to provide further information regarding quality attributes, in particular product- and process related impurities. Immuno-reactivity studies are designed to test immunological reactions that occur in animals as part of quality characterization (e.g. antibody formation caused by aggregates in transgenic animals that do not recognize the desired protein as a heterologous protein) (88).
- No further quality parameters are specified

The Notification No. 0304007 "Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products" acknowledges that differences in quality attributes may exist. When assessing the acceptable the applicant should take the product's nature and the intended clinical use into account.

5.6.1.2.4 Specifications

The specifications for the biosimilar product including their justification should be established, based on own characterization and batch analysis. When establishing the specifications ICH Q6B Guideline "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" should be taken into account.

If the reference product is listed in a Pharmacopoeia, e.g. Japanese Pharmacopoeia, it is considered preferable to establish the specifications in line with the specifications described in the Pharmacopoeia, whereas additional parameters should be included, based on the outcome of product characterization and non-clinical/clinical testing.

5.6.1.3 Canada

Information regarding the extend and content of data to be submitted for a SEB marketing authorization application is provided in a single draft guidance for sponsors document: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) released by Health Canada on March 27, 2009 (89).

In addition to a full chemistry and manufacturing (CMC) data package (Module 3) as required for a standard new biologic drug, extensive data on the demonstrated similarity with the reference product should be provided

5.6.1.3.1 Manufacturing Process and Quality Characterisation

Quality Characteristics

The proposed guideline does not provide requirements for the SEB with regards to dosage form, formulation and route of administration. However, as outlined by Health Canada in the Q&A Document accompanying the draft guideline, the reference product is mentioned as basis for the sponsor to select the dose and route of administration (45).

Manufacturing Process

The proposed guideline does not provide detailed recommendations regarding the development of the manufacturing process.

However, if a completely different approach as been taken to manufacture the SEB compared to the reference product, the resulting product is not eligible for authorization as an SEB (89). As an example of completely different approaches, the use of transgenic animals versus cell culture is given).

As the proposed guideline allows a great amount of flexibility with regards to the manufacturing process, the applicant is advised to take potential differences into account when setting up analytical methods as in-process controls, release tests or for the side-by-side characterization. If, for example different host cells are used for the manufacturing of the SEB, the manufacturer should determine the suitability of the test for the different host cell proteins.

Stability

Real time and real condition side-by-side stability studies should be conducted with the batches of SEB and reference product, which have been matched with respect to the manufacturing date.

Side-by-side studies at accelerated or stress conditions are considered useful tools to establish the degradation profiles of SEB and reference product.

The ICH Guidance documents ICH Q5C and Q1A should be taken into consideration when designing the stability studies.

Specifications

No detailed recommendations are given in this respect.

5.6.1.3.2 Product Characterisation and Comparability exercise

The demonstration of similarity depends upon detailed and comprehensive side-by-side characterization of the SEB and the reference product. Although SEBs are outside the scope of ICH Q5E Guidance, many of the principles and approaches are considered as applicable for the comparison of an SEB with it's reference product.

The characterization should be in general performed with the reference drug substance and drug product, as the product should be evaluated at process steps most appropriate to detect differences in the quality attributes between SEB and reference product. If the reference drug substance is isolated from the formulated drug product, additional studies are required to demonstrate, that the drug substance is not changed by the isolation process.

With regards to the quality attributes, which should be evaluated, the proposed guidance for sponsor document refers to the ICH Q6B Guidance, which includes the following attributes:

- Physicochemical properties. The manufacturer should attempt to determine higher order structure (secondary, tertiary and quaternary) is comparable. If information on

higher order structure cannot be obtained, relevant biological assays should be deployed to assess comparability in the conformational structure.

- *In vitro* Biological activity. Biological assays may complement the physicochemical methods for the assessment of comparability in terms of higher order structure (see above). In case both physicochemical and biological assays may not be considered appropriate to confirm comparability of the higher order structure, data from non-clinical and clinical studies may be warranted. However, if comparability of the higher order structure could only be confirmed by means of non-clinical and clinical studies, the product may not be considered as an SEB. If the product in development possesses multiple biological activities, multiple biological assays should be deployed to evaluate all relevant functional activities.
- Immunochemical properties – relates for example the immunological activity of antibodies or antibody-based products.
- Purity, Impurities and Contaminants. If differences in the purity and impurity profile exist between SEB and reference product, the differences should be evaluated and further actions should be considered (characterization of specific impurities, non-clinical and clinical studies).
- Quantity
- If necessary, additional characterization may be warranted.

5.6.1.3.3 Comparability evaluation

For consideration as an SEB, similarity should be primarily deduced from comprehensive quality studies in particular the side-by-side characterization of the SEB and the reference product (89).

In addition to the physicochemical and biological characterization data of drug substance and drug product, the applicant should also take the following points into account when assessing the similarity:

- Stability data including those from accelerated or stress conditions which could reveal potential differences in the degradation pathways.
- Multiple batches of SEB and reference product should be analyzed.

5.6.1.4 WHO

A full quality dossier for both drug substance and drug product will always be required, which complies with the standards as required by National Regulatory Authorities. In addition, the manufacturer should carry out a comprehensive physicochemical and biological characterization of the SBP in side-by-side comparison with the reference product in order to evaluate comparability.

5.6.1.4.1 Manufacturing Process and Quality Characterization

Quality Characteristics

Manufacturing Process

For an SBP an independent, consistent and robust manufacturing process needs to be established and state-of-the-art technologies should be deployed, as not much information may be available concerning the manufacturing process used by the innovator. The manufacturing process should be optimized so that SBP as similar as possible is achieved. The manufacturing process should meet the same standards as requested by National Regulatory Authorities for originator products.

With regards to the type of host cell, formulation, container closure system, the manufacturer of the SBP is encouraged to be as close to reference product as possible in order to minimize the differences resulting from this factors. In particular the same host cell type (e.g. *E.coli* or CHO cells) should be used otherwise it has to be demonstrated, that the structure is not affected by the different host cell (48).

General guidelines such as ICH Guidance documents should be taken into account.

Stability

Real time and real condition side-by-side stability studies of drug substance, drug product and intermediates should be conducted in compliance with relevant guidelines recommended by the National Regulatory Authority. Unlike studies under accelerated and stress conditions, a side-by-side real time and real condition stability study is not required.

Real time and real condition stability studies will determine the licensed storage conditions and expiration date of the SBP independently from the reference product.

Side-by-side studies at accelerated or stress conditions are considered useful tools to establish the degradation profiles of SBP and reference product.

Specifications

The specifications for SBBs should be determined and set in accordance with established guidelines (e.g. ICH Q6B) and monographs, where they exist. Additional specification parameters may be required.

Specifications, analytical methods and limits should be justified, analytical methods should be validated.

Although the specifications set for the SBP should be based upon the manufacturer's experience with the SBP (own manufacturing process) the limits set for a given specification should not be significantly wider than the range of variability of the reference product over the shelf life (48).

5.6.1.4.2 Product Characterization and Comparability exercise

The characterization should be in general performed with the reference drug product in its final formulation. It should be verified, that the excipients do not interfere with the analytical methods employed. If otherwise, the reference drug substance needs to be isolated from the formulated drug product, additional studies are required to demonstrate, that the drug substance is not changed by the isolation process.

When conducting the comparability exercise, side-by-side characterization studies are required to demonstrate comparability of the SPB and reference product.

With regards to the quality attributes, which should be evaluated, the proposed guideline document proposes to evaluate the following attributes:

- Physicochemical Properties. The manufacturer should characterize higher order structure (secondary, tertiary and quaternary) as well as other biophysical properties. Efforts should be made to investigate, identify and quantify variants. The determination of the structure is complemented by an appropriate biological assay
- Biological Activity. The chosen bioassay should reflect the understood mechanism of action and will therefore serve as a link to clinical activity. If the product in development possesses multiple mechanisms of action, the whole range of functions should be characterized by appropriate assays. If possible, the assays should be calibrated against an international or national reference standard and the results should be expressed in units of activity or if possible as specific activity.
- Impurities. Process – and product related impurities should be identified, quantified and compared between SBP and reference product. In particular for process-related impurities care should be taken regarding the suitability of the assay (e.g. different host cell proteins due to different host cells used for SBP or reference product). Significant differences should be evaluated with regards to their potential impact on safety (incl. immunogenicity) and efficacy.
- Immunochemical Properties - relates for example the immunological activity of antibodies or antibody-based products.

5.6.1.4.3 Comparability evaluation

A high degree of similarity between the SBP and the reference product is a requirement for the reduction of the non-clinical and clinical data package. Never the less, the occurrence of differences in quality attributes, e.g. impurities or excipients, and their potential impact on clinical safety and efficacy is acknowledged by the WHO. If the clinical impact remains unknown after a comprehensive assessment of the difference, may warrant additional non-clinical or clinical studies.

The draft WHO guideline states, that differences in quality attributes with potential impact on clinical activity (e.g. glycosylation pattern with an altered biodistribution requiring a different dosing scheme) will influence the decision whether the product is considered a SBP (48). Other differences such as lower levels of aggregates or known heterogeneity in the terminal

amino acids of the reference product may be acceptable without additional clinical or non-clinical studies, provided the differences do not affect bioactivity, distribution or immunogenicity.

Factors which should be taken into account when determining the acceptable limits of the differences include:

- Knowledge of the relationship between product quality attributes and clinical activity of the reference product/related products. Composition, glycosylation profile and the biological activity are known to be related to the clinical activity.
- Clinical history of the reference product
- Lot-to-lot differences for commercial lots of the reference product
- Limitations of analytical techniques

5.7 Extend of safety data to be provided for abbreviated licensing application - non-clinical evaluation

5.7.1 General design of required non-clinical studies

5.7.1.1 European Union

As outlined in section 4.1.2, CHMP has developed a separate guidance document addressing the non-clinical and clinical aspect for the development of biosimilars. The CHMP Guideline on non-clinical and clinical issues (15) lays down the non-clinical and clinical requirements in particular the exercise to demonstrate comparable clinical efficacy and safety for a biological product claiming to be similar to a reference product. The guideline is progressively supplemented by product-class specific guidance documents on non-clinical and clinical studies to be conducted (please refer to section 4.1.2).

The non-clinical studies should be comparative in nature and conducted prior to the clinical development. Consideration should be given to the use of emerging technologies/assays. Studies should be designed to detect differences in response between biosimilar and reference product.

Non-clinical animal studies should be performed in a species known to be relevant and employ state-of-art technology

5.7.1.1.1 Toxicity Studies

At least one repeated-dose toxicity study, ideally including toxicokinetic measurement, should be conducted in a relevant species. The study should also include the evaluation of antibodies (i.e. titer, cross reactivity and neutralizing capacity). The duration should be sufficient to detect potential differences between biosimilar and reference product. In case of safety concerns, other relevant tests (i.e. local tolerance) should be included.

Other non-clinical safety studies including safety pharmacology, reproductive toxicity, and mutagenicity and carcinogenicity tests are not required unless findings from the repeated dose toxicity studies make the tests necessary.

In the product-class specific Annexes to CHMP Guideline "Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (please refer to section 4.1.2), details regarding the design of the toxicity studies are provided:

- The relevant species and the duration of the repeated-dose toxicity study (e.g. a (at least) 4 week repeated-dose toxicity in a relevant species (e.g. rats) for somatropin, epoetin, Insulin and LMWH containing products, and 28 days for G-CSF containing products; at least 4 weeks for IFN-alfa in Syrian golden hamster)
- As toxicokinetic measurement is not possible for LMWH, appropriate PD markers should be measured (22).
- PD measurements should be included for G-CSF containing products (18).
- Reference to CHMP guidance documents e.g. "Note for guidance on repeated dose toxicity (CHMP/SWP/1042/99) and "Note for guidance on toxicokinetics: guidance for assessing systemic exposure in toxicological studies (CHMP/SWP/2145/00) is made.
- Requirement for local tolerance testing is further specified (e.g. at least in one species possibly as part of the repeated-toxicity testing for somatropin, epoetin, LMWH, G-CSF and Insulin containing products)
- Non-human primate species or even chimpanzees are in most cases the relevant animal species for monoclonal therapeutic antibodies. In the concept paper regarding the development of a guideline on similar biological medicinal products containing monoclonal antibodies, EMEA acknowledges that comparative toxicity studies for mAbs may no be feasible or ethically acceptable. Based on experiences gained with mAbs over the past decades a differential discussion on the need/requirement for non-clinical toxicity and PD studies with mAbs should be considered, instead (23).

5.7.1.1.2 Pharmacokinetic Studies

As no information is provided it can be assumed that Pharmacokinetic and metabolic studies are not required.

5.7.1.1.3 Pharmacology Studies

Pharmacodynamic studies relevant to the clinical application should be conducted.

In the product-class specific Annexes to CHMP Guideline "Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (please refer to section 4.1.2), details regarding the number and type of comparative *in vitro* bioassays to be deployed including appropriate PD markers are given.

With regards to *in vivo* PD studies information regarding the appropriate species and accepted/appropriate animal models including PD markers are provided also by referring to the European Pharmacopoeia, if applicable.

In particular for LMWH, detailed information regarding the conduct of in vivo PD studies are given due to the fact, that conventional PK studies cannot be performed for LMWH as it is difficult to be physically detected. Absorption and elimination of LMWH can be therefore only be studied by it PD effects (22).

In particular for Insulin, comparative in vivo PD studies are not required as part of the comparability exercise, as in vitro bioassays are considered sufficiently sensitive to detect any non-equivalence between biosimilar and reference product (16).

5.7.1.2 Japan

Information regarding the extend of data to be submitted for a biosimilar marketing authorization application is provided in Table 2-(1) of PFSB Notification No. 0304004 dated 04 March 2009 amending PFSB Notification No. 0331015 (32). More detailed guidance regarding the content and scope of non-clinical studies to be performed during development of a biosimilar product is provided in PFSB/ELD Notification No. 0304007 dated 04 March 2009 entitled "Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products" (34). This guidance does not refer to specific products or product classes but is applicable to all biosimilar products falling under scope of the above mentioned guideline.

Non-clinical studies should only be conducted after completion of the full quality characterization. ICH Guideline ICHS6 "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" should be taken into account, when necessary.

In general the non-clinical studies do not need to be comparative:

- Studies confirming the safety of the biosimilar product could be conducted without comparison to the reference product, if the impurity profile differs from the reference product
- Comparative studies with the reference product would be appropriate
    - if the equivalence of the pharmacological activity should be confirmed or
    - if differences in the pharmacokinetic are expected due to heterogeneity in glycosylation

Drug product should be used for non-clinical studies, except for cases where high doses need to be administered (88). GLP standards must be met by testing facilities for non-clinical safety tests on drugs from the viewpoint of the structure/equipment and the operation/management of the facilities.

5.7.1.2.1 Toxicicity Studies

Single dose and repeated dose toxicity studies including the assessment of the local tolerance and toxicokinetic in an appropriate animal species are recommended. Whereas the repeated

dose toxicity study is mandatory, the requirement for a single dose and local tolerance study will be assessed for each individual product (32; please refer to Attachment 1).

The conduct of toxicity studies directly comparing the biosimilar and the reference product should be considered in case of large differences in the impurity profile. Non-comparative studies should be considered in particular if large differences exist in the product- or process related impurity profile.

Other non-clinical safety studies such as secondary pharmacology, safety pharmacology, reproduction toxicity, genotoxicity and carcinogenicity tests are not required unless findings from the repeated dose toxicity studies or product class specific information make the tests necessary (32, 34).

5.7.1.2.2 Pharmacokinetic Studies

Pharmacokinetic and metabolic studies are not mandatory. The requirement for studies to assess absorption, distribution, metabolism and excretion, will be assessed for each individual product (32).

5.7.1.2.3 Pharmacology Studies

Pharmacology studies should be designed as comparative studies, in order to demonstrate comparability of the pharmacological activity. In vivo pharmacology studies to confirm comparability in pharmacodynamics or efficacy should be conducted in particular, if the in vitro bioactivity assay used during the comparability assessment of the quality attributes is not related to the clinical effect e.g. in case of glycosylated proteins (please refer to section 5.6.1.2.3).

5.7.1.3 Canada

Information regarding the extend and content of data to be submitted for a SEB marketing authorization application is provided in a single draft guidance for sponsors document: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) released by Health Canada on March 27, 2009 (90).

The proposed guidance document is not product or product-class specific. Non-clinical studies should be conducted prior to the initiation of clinical studies. The non-clinical studies should be comparative in nature.

5.7.1.3.1 Toxicity Studies

One repeated-dose toxicity study including the characterization of toxicokinetic parameters should be conducted. The duration of the study should be sufficient to detect differences between SEB and reference product. The observation of local tolerance is recommended.

Other non-clinical safety studies including safety pharmacology, reproduction toxicity, and mutagenicity and carcinogenicity tests are not required unless findings from the repeated dose toxicity studies make the tests necessary.

5.7.1.3.2 Pharmacokinetic

As no information is provided it can be assumed that Pharmacokinetic and metabolic studies are not required.

5.7.1.3.3 Pharmacology Studies

Pharmacodynamic studies relevant to the clinical application should be conducted.

5.7.1.4 WHO

In general, the assessment of the pharmaco-toxicological comparability between SBP and reference product should be conducted with the final formulation of the SBP. As the non-clinical studies are an integral part of the overall comparability exercise, they should be comparative in nature and designed to detect differences between SBP and reference product.

With regards to the animal species to be used, the relevance of the species could be deduced from the species used by the manufacturer of the reference product.

The proposed guideline acknowledges that the amount of non-clinical data required for an SBP largely depends on product - and substance-class related factors and that the spectrum of studies required to establish comparability with regards to safety and efficacy may vary considerably. In consequence, only general considerations are provided which should be taken into account when non-clinical studies are set up on a case-by-case basis.

When setting up a non-clinical programme, the results from the physico-chemical and biological characterization as well existing guidelines such as ICH S6 "Note for preclinical safety evaluation of biotechnology-derived pharmaceuticals" should be taken into account.

5.7.1.4.1 Toxicity Studies

As a minimum requirement for the non-clinical evaluation of all SBPs under development, a side-by-side repeated-dose toxicity study including toxicokinetic measurements should be conducted.

The determination and characterization of antibody responses (titer, cross reactivity, neutralizing activity) should also be included.

The evaluation of the local tolerance of the SBP may be part of the repeated-dose toxicity study as well.

The duration of the study should be sufficiently long to detect potential differences in the toxicity profile (incl. antibody formation) of SBP and reference product.

Other non-clinical safety studies including safety pharmacology, reproductive toxicity, genotoxicity, and carcinogenicity tests are not required unless findings from the repeated dose toxicity studies or known properties from the reference product make the tests necessary.

5.7.1.4.2 Pharmacokinetic

As no information is provided it can be assumed that Pharmacokinetic and metabolic studies are not required.

5.7.1.4.3 Pharmacology Studies

If the *in vitro* assays, which have been deployed in the quality comparability exercise (please refer to section 5.6.1.4.2) have been validated to reliably reflect the clinically relevant pharmacodynamic activity of the reference product, *in vivo* pharmacological studies may be dispensable.

Otherwise the evaluation of the pharmacodynamic activity may be evaluated as part of the repeated-dose toxicity study.

5.8 Extend of efficacy data to be provided for abbreviated licensing application – clinical evaluation

5.8.1 General design of required clinical studies

5.8.1.1 Pharmacodynamic and pharmacokinetic studies

5.8.1.1.1 Japan

Comparability of the biosimilar product with its reference product in pharmacokinetics must be confirmed in cross-over studies in general.

The same route of administration as the reference product should be used for the biosimilar product and if multiple administration routs apply to the reference product, all of them should be investigate.

The recommended dose for the reference product should be used in the investigation. In case of a dose range for the reference product, a dose within the range could be chosen, based on scientific reasons.

The area under blood-concentration curve (AUC) and the maximum blood concentration (Cmax) are considered the principle pharmacokinetic parameter to assess.

If possible, it is necessary to select a pharmacodynamic (PD) marker which reflects clinical efficacy of the product. If possible, comparability should be demonstrated by using a PD marker. Preferably, comparability should be investigated through analysis of the PK/PD relationship.

The comparability acceptance range needs to be specified and justified prior to the conduct of the study.

If comparability at the targeted clinical endpoint is obtained from clinical PK studies, PD studies and pharmacokinetic/pharmacodynamic (PK/PD) studies, it may be possible to omit efficacy but not safety clinical studies.

5.8.1.1.2 Canada

Pharmacokinetic Studies

Comparative pharmacokinetic studies should be conducted as part of the comparability evaluation of the pharmacokinetic characteristics.

The general design of the PK study i.e. cross-over versus parallel, single-dose versus multiple should be determined by the sponsor, taking multiple factors such as half-life, linearity of PK parameters, conditions and diseases to be treated and the endogenous level of the protein under study, into account.

PK parameters, not only reflecting absorption should be selected. Differences in elimination (clearance and terminal half-life) should also be compared.

In general, the comparative PK study should be preferably conducted in the relevant patient population as the results from healthy volunteers may not adequately reflect the PK parameters in the patient population concerned.

The dose applied in the PK study should be within the therapeutic dose range of the reference product as specified in the Product Monograph.

With regards to the determination of similarity of PK parameters in comparative PK studies, the sponsor is advised to pre-define the equivalence range prior to the initiation of the study, based on the criteria for comparative bioavailability studies for generic pharmaceuticals i.e. both, the 90% confidence interval of the relative mean AUC_T and the relative mean measured C_{max} of the SEB to reference product should be within 80% - 125%.

Pharmacodynamic Studies

The PD studies should be comparative in nature and could be combined with PK studies.

The sponsor is advised to investigate PD markers, which are clinically relevant and in case surrogate markers are used, they should be validated.

5.8.1.1.3 WHO

For the main/pivotal clinical studies, the product intended to be marketed (final manufacturing process) should be used. Any changes to the manufacturing process may entail the conduct of comparative PK bridging studies (bridging product from the previous and final formulation).

Pharmacokinetic Studies

Comparative pharmacokinetic studies should be conducted as part of the comparability evaluation of the pharmacokinetic characteristics.

In general all routes of administration applied for should be analyzed.

The dose applied in the PK study should be within the therapeutic dose range of the reference product.

The general design of the PK study i.e. cross-over versus parallel, single-dose versus multiple dose, healthy volunteers versus patient population, should be determined by the sponsor, taking multiple factors into account:

- A single dose PK study is considered to be sufficient. An additional comparative multiple dose PK study is recommended, in case of dose or time-dependent PK with a higher concentration at steady state than expected from single dose data. The difference in the absorption may be higher at steady state level.
- Cross-over design, although limiting inter-subject variability may not be appropriate for product with long half-life or likelihood to induce an antibody response.
- Healthy volunteers are preferred unless potential adverse effects or risks due to the pharmacological effect demand to perform the study in the relevant patient population.

Not only PK parameters, reflecting absorption/bioavailability should be selected but also parameters suitable to detect differences in elimination (clearance and elimination half-life) should be applied.

Acceptance criteria should be pre-defined and justified. Although acceptance criteria used in standard PK comparability studies (bioequivalence studies) man not be applicable to biopharmaceuticals, the use of the traditional 80% - 125% range is acknowledged due to the lack of appropriate established criteria for biologics. However, if the SBP fails the acceptance criteria, it may be still considered a SBP provided that similarity is sufficiently demonstrated by quality, non-clinical and clinical efficacy and safety data (48).

Other PK studies e.g. interaction studies and studies in special populations are usually not required.

Pharmacodynamic Studies

The investigation of PD parameters in the context of a combined PK/PD study is considered as a useful tool to gain information about the relationship between dose/exposure and effect, in particular if different dose levels are investigated. The PD markers should be clinical relevant.

Under certain circumstances comparative PK/PD studies are considered appropriate to demonstrate similar efficacy between the SBD and the reference product. In order to be considered a confirmatory PK/PD study the following requirements should be fulfilled:

- Well characterized PK and PD properties of the reference product
- Use of an accepted surrogate marker for efficacy as PD marker (91)
- Established relationship between dose/exposure – relevant PD marker and response/efficacy of the reference product
- The selection of the study population and dose should ensure sufficient sensitivity to detect potential differences between SBP and reference product in terms of PD (92)

However, no clear criteria are given under which circumstances it may be possible to omit clinical efficacy studies. Never the less the WHO proposed guideline requests additional safety studies in the relevant target population in case comparability in efficacy has been demonstrated in confirmatory PK/PD studies (please refer to sections 5.8.1.3.3 and 5.8.1.4.3)

5.8.1.1.4 European Union

As outlined in section 4.1.2, CHMP has developed a separate guidance document addressing the non-clinical and clinical aspect for the development of biosimilars. The CHMP Guideline on non-clinical and clinical issues (15) lays down the non-clinical and clinical requirements in particular the exercise to demonstrate comparable clinical efficacy and safety for a biological product claiming to be similar to a reference product. The guideline is progressively supplemented by product-class specific guidance documents on non-clinical and clinical studies to be conducted (please refer to section 4.1.2).

The clinical comparability exercise is a stepwise procedure, beginning with PK and PD studies followed by clinical efficacy and safety trials. In certain cases PK/PD studies could be considered to demonstrate clinical comparability.

For the required clinical data for the comparability studies, product manufactured with the final manufacturing process should be used (25).

Pharmacokinetic Studies

Comparative pharmacokinetic studies should be conducted as part of the comparability evaluation of the pharmacokinetic characteristics.

Reference is made to EMEA Guideline on clinical investigation of the pharmacokinetics of therapeutic proteins (93).

Not only PK parameters, reflecting absorption/bioavailability should be selected but also parameters suitable to detect differences in elimination (clearance and elimination half-life) should be explored.

The general design of the PK study i.e. cross-over versus parallel, single-dose versus multiple should be determined by the sponsor, taking multiple factors such as half-life, potential formation of antibodies into account.

The acceptance range to conclude clinical comparability should be pre-defined and based on clinical judgment. Criteria used in standard clinical comparability studies, developed for chemically derived products, may not be appropriate.

In the product-class specific Annexes to CHMP Guideline "Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (please refer to section 4.1.2), product class specific details regarding the design of the PK study:

- General design (e.g. crossover, route of administration, single versus multiple dose)

- Suitable population (e.g. healthy volunteers) and if necessary pretreatment for suppression of endogenous protein expression.
    - Somatropin: single dose, crossover, subcutaneous, healthy volunteers (suppression of endogenous growth hormone)
    - Epoetin: single dose, crossover, subcutaneous and intravenous, healthy volunteers
    - G-CSF: single dose, crossover, subcutaneous and intravenous, healthy volunteers (18).
    - IFN-alfa: single dose, crossover, subcutaneous and intravenous, healthy volunteers (23).
    - Insulin: single dose, crossover, subcutaneous, preferably in patients with type1 diabetes (16).
- Primary and secondary PK parameters to be use
    - Somatropin: AUC as primary and Cmax, $T_{1/2}$ as secondary PK parameter
    - Epoetin: AUC as primary and Cmax and $T_{1/2}$ or CL/F as secondary PK parameter
    - G-CSF: AUC as primary and Cmax, $T_{1/2}$ as secondary PK parameter
    - IFN-alfa: AUC as primary and Cmax and $T_{1/2}$ or CL/F as secondary PK parameter
    - Insulin: AUC as primary and Cmax, $T_{1/2}$ and T_{max} as secondary PK parameter

Due to the heterogeneity of LMWHs and difficulties to detect it physically, conventional PK studies cannot be performed. As a surrogate marker for the circulating concentration of LMWH, PD markers should be compared (22).

Pharmacodynamic Studies

In general, PD studies should be comparative and performed in a population in which potential differences may best be observed. The PD marker selected should be relevant to the therapeutic efficacy.

For PK/PD studies, the dose should be selected from the steep part of the dose-response curve and more than one dose level should be tested.

Under certain circumstances as in the case of Insulin and G-CSF containing products (please refer to section 5.8.1.2.4) comparative PK/PD studies are considered appropriate to demonstrate clinical comparability of the biosimilar and the reference product. In order to be considered a confirmatory PK/PD study the following requirements should be fulfilled:

- Well characterized PK and PD properties of the reference product
- Use of an accepted surrogate marker for efficacy as PD marker and the relationship of PD marker and dose/exposure is known (94)

- Established relationship between dose/exposure and response/efficacy of the reference product

In the product-class specific Annexes to CHMP Guideline "Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (please refer to section 4.1.2), product class specific details regarding the design of PD studies are provided:

- General design (e.g. evaluation of PD marker as part of the comparative PK study (i.e. healthy volunteers) for Somatropin, Epoetin, G-CSF but not for LMWH or Insulin, not specified for IFN-alfa)
    - General design for LMWH: randomized, single dose two way crossover study in healthy volunteers using subcutaneous and if other routes of administration if approved for the reference product.
    - General design for Insulin: double-blind, crossover hyperinsulineaemic euglycaemic clamp study for demonstration of comparability (16). Study population is not specified
- Dose selection (e.g. linear ascending part of the dose response curve for Somatropin, Epoetin, G-CSF, IFN-alfa and LMWH
- Preferred PD marker and their assessment of suitability as surrogate marker for the evaluation of efficacy in clinical trials
    - Somatropin: IGF-1, not an established surrogate marker
    - Epoetin: reticulocyte count, not an established surrogate marker
    - LMWH: anti Fxa and anti-FIIa activity, Tissue Factor Pathway Inhibitor (TFPI) acitivity, not established surrogate markers
    - G-CSF: absolute neutrophil count (ANC) as primary and the CD34+ cell count as secondary PD parameter,
    - IFN-alfa: β2 microglobulin, neopterin and serum 2´, 5´-oligoadenylade synthetase activity, not established surrogate markers
    - Insulin: the clinical activity is determined by its time-effect profile of hypoglycaemic response which incorporates PD and PK components (glucose infusion rate and serum insulin concentration). PD data are considered as of primary importance to demonstrate comparability.

5.8.1.2 Efficacy studies

5.8.1.2.1 Japan

Clinical studies confirming comparability in efficacy of the biosimilar and the reference product are required, in case a conclusion on comparability in clinical efficacy could not be drawn from PK, PD or PK/PD studies (see section 5.8.1.1.1).

The efficacy study should be conducted in the claimed indication. The study design should be comparative in nature:

- Appropriate number of subjects
- Use of a clinically established endpoint
- Pre-specified comparability acceptance range (equivalence margin)
- An appropriate surrogate endpoint can be considered, if available and justifiable (e.g. increase in hemoglobin concentration for erythropiesis-stimulating agents (88))

Although the possibility to extrapolate indications i.e. to claim further indication which are approved for the reference product based on a clinical efficacy study in only one of the approved indications, exist in Japan, no advice is given with regards to the most appropriate indication for the comparative efficacy trial.

5.8.1.2.2 Canada

Comparative clinical studies confirming comparability in efficacy of the biosimilar and the reference product are required.

Careful consideration should be given to the design and the clinical comparability margin. No further requirements or recommendations with regards to the clinical efficacy trials are provided.

5.8.1.2.3 WHO

Comparative clinical studies are usually required to confirm comparability in efficacy of the biosimilar and the reference product.

The study should be adequately powered, randomized and consist of parallel groups. Preferably, the study should be double-blind or at a minimum observer-blind.

In case the reference product is approved in multiple indications, the investigation of the differences between the SBP and the reference product should be done in a well-established and sensitive model (95).

For the purpose of demonstration of comparable efficacy of the SBP and the reference product both equivalence or non-inferiority study designs may be acceptable.

Equivalence studies

In principle equivalence trials are preferred. When used at the same dosage, this design is suitable to demonstrate, that the SBP is not less nor more effective than the references product. Sample size tends to be higher than for non-inferiority studies

Non-inferiority studies

Non-inferiority trials may be accepted if appropriately justified. This trial design may be suitable for product with a flat dose response curve and a wide safety margin. Although comparability in efficacy between an SBP and its reference product can be demonstrated, it

cannot be excluded that the SBD has a superior efficacy than the reference product. Sample size tends to be lower than for non-inferiority studies. In case of confirmed superior efficacy, it needs to be verified, that it is not associated with an increase in adverse events or whether the superiority is clinically meaningful. Otherwise the product may not be considered as a SBP (48).

A comparability margin should be pre-defined and justified scientifically and clinically. The effect size available from historical trials performed with the reference product, if available, should also be taken into account for justification of the proposed comparability margin. For equivalence trials both the lower and upper equivalence margin should be defined.

5.8.1.2.4 European Union

Comparative clinical studies are usually required to confirm comparability in efficacy of the biosimilar and the reference product.

In the product-class specific Annexes to CHMP Guideline "Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (please refer to section 4.1.2), product class specific details regarding the design clinical efficacy studies are provided:

- General design (e.g. randomized, parallel group trail, double-blind, if possible)
- Most sensitive model / study population including recommended route of administration
- Recommended primary, secondary endpoints, surrogate markers and diagnostic procedures if applicable
- Duration of treatment period
    - Epoetin: two (correction phase and maintenance phase studies) adequately powered, randomized, parallel group trials, preferably double blind in patients with renal anaemia (erythropoietin-defcient condition with high sensitivity); subcutaneous and intravenous administration. Comparative phase at least 6 months to establish comparable clinical efficacy. Doses should be titrated to achieve/maintain target haemoglobin concentrations in accordance with current clinical practice.
    - Somatropin: one adequately powered, randomized, parallel group trials, preferably double blind in treatment-naïve children with GH deficiency for somatropin containing products. Comparative phase at least 6 months and maybe up to 12 months.
    - LMWH: one adequately powered, randomized, double-blind, parallel group clinical trial in the setting of prevention of venous thromboembolism (VTE) in patients undergoing surgery with high VTE risk. Posology and administration in accordance with current European recommendations (22). The use of a surrogate composite endpoint is possible to assess comparative safety and

efficacy. A strict equivalence design with pre-defined equivalence margins is mandatory (22).

- IFN-alfa: a randomized, parallel group over at least 48 weeks, double-blind in treatment-naïve patients with chronic hepatitis C preferably a single genotype, or other patient populations depending on the indications desired. The posology (i.e. dose, route and method of administraion) according to the reference product.
- Insulin: provided that clinical comparability can be concluded from PK and PD data, a clinical efficacy study can be omitted (please refer to section 5.8.1.1.4)
- G-CSF:
  - a two-arm comparability study in a chemotherapy-induced neutropenia model (prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous (tumour) patient group with known frequency and duration of severe neutropenia. A three arm (incl. placebo arm) study is needed if other chemotherapy regimens are used). Primary and secondary endpoints are proposed.
  - Alternatively, a confirmatory PD study in healthy volunteers may be performed for the demonstration of comparability. Applicants are advised to request scientific advice for study design, duration, dose, efficacy PD endpoints and comparability margins (18).

5.8.1.3 Safety studies

5.8.1.3.1 Japan

Studies to confirm clinical safety are required even if comparability in efficacy has been demonstrated (see section 5.8.1.2). Depending of the clinical studies conducted in order to demonstrate comparability in efficacy the clinical program to show clinical safety could be as follows:

- A separate clinical safety study in case comparability in efficacy has been demonstrated by PD, PK and PK/PD studies
- The assessment of clinical safety could be combined with the comparability of the efficacy in a single clinical trial

5.8.1.3.2 Canada

Comparative clinical studies confirming comparability in safety of the biosimilar and the reference product are required.

Careful consideration should be given to the design and the clinical comparability margin.

In particular a sufficient statistical power of the clinical safety study should be assured in order to detect significant differences in the safety profile of the SEB and the reference product.

No further requirements with regards to the clinical safety trials are provided.

5.8.1.3.3 WHO

Clinical studies to generate preferably comparative safety data in particular type frequency and severity of adverse events and reactions are required. The assessment of the safety profile may be included in the clinical efficacy studies, if possible.

In case, comparability between SBP and reference product in terms of efficacy has been demonstrated in confirmatory PK/PD studies, a separate study to gain safety data in the relevant target population my be warranted.

5.8.1.3.4 EU

Clinical studies to generate comparative safety data in particular type, frequency and severity of the adverse reactions are required pre-licensing.

In the product-class specific Annexes to CHMP Guideline "Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (please refer to section 4.1.2), product class specific details regarding the design clinical safety studies are provided:

- Recommendation regarding adequacy of pre-marketing data base (e.g. data from efficacy trial(s) sufficient in case of somatropin, epoetin containing products)
- Safety testing parameters
- For Insulin, the main safety concern relates to the potential for immunogenicity (16).

As safety data from pre-authorisaton clinical studies are usually insufficient to identify rare adverse reactions or potential differences, clinical safety should be continuously monitored post-marketing. In particular, the risk specification of the biosimilar (i.e. potential safety issues identified) should be presented in the application dossier as part of the risk management plan.

5.8.1.4 Immunogenicity

It is well know and considered in all biosimilar guidance documents considered in this thesis, that many patients develop clinically relevant anti-drug antibodies in particular against protein and peptide based therapeutics. The immunogenic potential is influenced by many factors, such as the nature of active substance (e.g. extend of glycosylation), product-and process-related impurities, excipients used, route of administration and target population (e.g. genetic background, immunocompromised status). The consequences of immunogenicity may have serious impact to safety and efficacy of the treatment ranging from irrelevant for therapy to serious and life-threatening. Therefore, the generation of data regarding immunogenicity is requested by each health authority considered in this thesis.

5.8.1.4.1 Japan

The investigation of immunogenicity could be included in the clinical safety study. The design of the study should allow making a scientifically sound judgment regarding the generation of antibodies.

- In case antibodies are detected in response to the treatment with the biosimilar product, it should be investigated:
- The neutralizing activity of the antibodies
- The class of antibodies, affinity and specificity
- Impact on the efficacy and safety of the biosimilar product

5.8.1.4.2 Canada

The investigation of immunogenicity of the SEB should be performed in clinical studies in which state-of-the-art methods to assess efficacy and safety are used. The inclusion of the investigation of immunogenicity in the clinical efficacy/safety trials is neither explicitly recommended nor excluded.

Validated methods should be used to characterize potential antibody development in terms of titer, type, cross-reactivity and neutralizing activity.

If neutralizing antibodies have been detected, the impact on PK/PD parameters should be analyzed.

Should there be any cause of concern with regards to immunogenicity of the SEB; clinical trials should be prolonged in order to obtain sufficiently long-term safety and efficacy data prior to authorization.

5.8.1.4.3 WHO

Immunogenicity and in particular the frequency, type of antibodies induced and possible clinical consequences should be compared for the SBP and reference product. The amount of immunogenicity data obtained from clinical efficacy trials is in general considered sufficient pre-licensing. In case of chronic administration for example, 1 year data are considered appropriate pre-licensing.

Validated methods should be used to characterize potential antibody development in terms of titer, iso-type, cross-reactivity and neutralizing activity. The potential clinical implications regarding safety, efficacy and PK should be evaluated.

In case, comparability between SBP and reference product in terms of efficacy has been demonstrated in confirmatory PK/PD studies, a separate study to gain immunogenicity data in the relevant target population my be requested.

With regards to the target population the WHO advises the applicant to investigate immunogenicity in the patient population with the highest risk, in case the applicant intends to extrapolate efficacy and safety data from one to other indications.

In general, further characterization of the immunogenicity profile of SBPs is requested post-marketing in particular to detect rare antibody-related serious adverse events. Risks of serious antibody related events which are already known from the reference product should be addressed in a post-marketing risk-management plan for the SBP.

5.8.1.4.4 European Union

Immunogenicity must always be investigated and long-term data should be collected from a sufficient number of patients. Antibody testing should be considered as part of all clinical trial protocols. It is also considered important to consider the risk of immunogenicity in the different therapeutic indications separately (15).

In case of chronic administration for example, 1 year data are considered appropriate pre-licensing (15).

Validated methods should be used to characterize potential antibody development in terms of titer, iso-type, cross-reactivity and neutralizing activity. The potential clinical implications regarding safety, efficacy and PK should be evaluated in case of different immune response to the biosimilar and the reference product (15).

In the product-class specific Annexes to CHMP Guideline "Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (please refer to section 4.1.2), product class specific details regarding the assessment of immunogenicity are provided:

- Duration of observation period pre-marketing (e.g. 12 month comparative immunogenicity data in case of somatropin, epoetin containing products, and 6 months comparative data pre-marketing for Insulin and 12 months post-marketing) and testing intervals
- Reference is made to EMEA guidance documents "Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins" EMEA7CHMP/BMWP/14327/2006) and "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" EMEA/CHMP/42832/05/).

5.8.2 Extrapolation of clinical data to other indications

5.8.2.1.1 Efficacy data

WHO

If similarity between the SBP and the RBP as a result of the comparability exercise has been demonstrated, the SBP may be approved for use in other clinical indications of the RBP that have not directly been tested in clinical trials if appropriate scientific justification is provided (48).

The justification may be based on:

- Same "Mechanism of action"
- Same "Pathophysiological mechanism of the disease or conditions involved"
- Sufficient "Clinical experience of the reference biologic drug"

The basic conditions which have to be fulfilled in order to render extrapolation possible include:

- A sensitive clinical test model has been used which is suitable to detect potential differences between SBP and RBP
- The relevant clinical mechanism of action and/or involved receptors are the same. Examples for human Growth Hormone and Epoetins are provided by the WHO.
- The absence of unique safety issues expected for the indications concerned and the safety and immunogenicity have been sufficiently characterized.
- If for the efficacy trial a non-inferiority study design has been chosen and acceptable safety and efficacy has been demonstrated, convincing arguments should be provided by the applicant justifying the requested extrapolation

Japan

If the comparability of the biosimilar product and the reference product has been demonstrated in one, not further specified, indication, it may be possible to extrapolate the other approved indications of the reference product to the biosimilar product und the following condition:

Same "Mechanism of action" in the other indications

Canada

The proposed clinical indications for an SEB should be identical to/or within the scope of indications granted to the reference product and clinical studies should be provided for each indication claimed.

However, it may be possible in some cases to bridge two or more indications by comparative PK/PD data. Under the following circumstances which are identical to the proposed WHO provisions, extrapolation of results from clinical studies conducted in one indication to another indication may be possible:

- Same "Mechanism of action
- Same "Pathophysiological mechanism of the disease or condition involved"
- Sufficient "Clinical experience of the reference biologic drug"

European Union

The CHMP guideline on non-clinical and clinical aspects for the development of biosimilar (15) states that in general, the efficacy and safety of the biosimilar product has to be justified

or, if necessary, demonstrated separately for each of the claimed indications, provided that the reference product has more than one indication approved.

The applicant may however extrapolate the therapeutic similarity shown in one indication to other indications of the reference product. The justification will depend on the following criteria:

- Clinical experience and available literature data
- Same Mechanism of action or the same receptor(s) involved in the claimed indications

In the product-class specific Annexes to CHMP Guideline "Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (please refer to section 4.1.2), product class specific details regarding the extrapolation of indications are provided:

- Extrapolation may be allowed in case of somatropin containing products in case of demonstrated comparable efficacy and safety in GH-deficient children.
- Extrapolation may be allowed in case of epoetin containing products in case of demonstrated comparable efficacy and safety in renal anaemia.
- Extrapolation may be allowed in case of LMWH containing products in case of demonstrated comparable efficacy and safety in surgical patients at high risk for VTE.
- Extrapolation may be allowed in case of G-CSF containing products in case of demonstrated clinical comparability in the chemotherapy-induced neutropenia model (18).
- For IFN-alfa containing products extrapolation from one therapeutic indication to another may be allowed in case of demonstrated comparable efficacy where the mechanism of action and/or the receptor are known to be the same

5.8.2.1.2 Safety data

WHO

Extrapolation of safety data is in general possible. The same requirement as for the efficacy (see section 5.8.2.1.1) have to be fulfilled otherwise own clinical data need to be submitted to support the desired indication(s).

Japan

The PFSB/ELD Notification No. 0304007 dated 04 March 2009 entitled "Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products" (34), is silent on the extrapolation of safety data.

5.8.3 Acceptance of foreign clinical data

In general, the clinical studies conducted during the development of a biosimilar product have to meet the regulatory standards and clinical trial practices (i.e. study design and conduct,

nature and quality of data, requirements for evidence of bioequivalence, safety and efficacy) applicable in the regions where an application for registration is considered (please refer to section 5.8). When setting up a clinical strategy for a globally acceptable development of a biosimilar product the applicant should take into consideration that clinical data obtained in one region is considered as foreign clinical data in another region. The acceptance of foreign clinical data by health authorities may depend on the impact, which ethnic differences of the populations concerned may have on the safety and efficacy of the biosimilar product. Potential effects of ethnic factors on the efficacy, safety, dosage and dose regimen of the medicinal product under development may necessitate the conduct of a bridging study to allow extrapolation of the clinical data obtained in one region to another region or in the worst case the duplication of the clinical data in the new region.

According to ICH E5 (R1) "Ethnic Factors in the Acceptability of Foreign Clinical Data" ethnic factors are defined a factors relating to intrinsic (i.e. the genetic and physiologic) characteristics and extrinsic (i.e. cultural and environmental) characteristics of a population (96).

Regardless of the potential impact of ethnic factors on the safety and efficacy of the product in development, the clinical data should per se comply with the regulatory requirements in the new region (see section 5.8).

In case the regulatory requirements cannot be met additional clinical studies specific for the new region may be requested by the regulatory authority concerned. For biosimilar products, this may apply for all comparative clinical trials, as most regulatory authorities require comparative studies with reference product authorized in their own territory. Comparative clinical studies conducted with reference product authorized in one region may not be accepted in another region. Another aspect which may require the duplication of clinical studies could be that the dosage and dose regimen may be different in the regions concerned.

For clinical data, which meet the new region's regulatory requirements, the evaluation of the suitability of clinical data for extrapolation to the population of the new region should be evaluated according to ICH E5 (R1). Extrapolation of clinical data depends largely on the products sensitivity to ethnic factors as well as clinical experience with other members of the drug class in the new region. A number of properties of the product such as clearance by an enzyme showing genetic polymorphism or the gradient of the dose-response curve may have major impact on the product's sensitivity or insensitivity to ethnic factors. A comprehensive list of product properties which should be considered for the evaluation of its sensitivity to ethnic factors is provided in Appendix D of ICH E5 (R1). The need and the type of bridging study are determined by the results of the evaluation of the product's ethnical sensitivity:

In case of ethnically insensitive products with similar extrinsic factors in the regions concerned (e.g. similar medical practice), extrapolation of clinical data may be feasible without a bridging study.

In case an impact of ethnic differences on the safety and efficacy is expected a bridging study performed in the new region may be required to allow the extrapolation of the foreign data to the population in the new region. The type of required bridging study (i.e. PK, PD, or a full

clinical efficacy of safety trial) is determined by the relative sensitivity. and should be discussed with the regional regulatory authority during development. As the possibility and decision about the acceptance is left up to the authorities concerned, this topic should be discussed early during development with the national regulatory authority, which provides consultations on clinical studies. The bridging study would then allow extrapolation of an adequate data base to the new region.

Japan has formally implemented ICH E5 with PMSF/ELC Notification No.672 ICH Guideline (E5, Step4): Ethnic Factors in the Acceptability of Foreign Clinical Data, 11-Aug-1998. In conjunction with PMSB Notification No.739 "The Handling of Clinical Data on Pharmaceuticals Generated in Foreign Countries" in 1998, clinical trial data generated in foreign countries and used for approval applications are generally accepted as review documents provided that the data comply with legal requirements in Japan. Dependent on the assessment of the impact of the ethnic factors on safety and efficacy of the product and the results of the bridging study, it is concluded that the study outcome in a foreign population can be extrapolated to the Japanese population.

In Japan clinical data should be collected and processed in compliance with guidelines issued and recommended by MHLW whereas most of the guidelines are implementation of the corresponding ICH guidelines. The remaining guidelines were developed to reflect more closely Japanese medical practice and cover specific therapeutic categories or classes of medicinal products. All currently effective guidelines concerning clinical trials are compliant to GCP principles. Most importantly, guidelines for clinical trials serve as a standard for the assessment of clinical data packages originated from outside Japan.

Canada has formally adopted ICH E5 in February, 2003 and has thereby endorsed the principles and practices described in ICH E5.

ICH E5 has been implemented in the EU in September 1998 with CPMP/ICH/289/95 Note For Guidance. In June 2006 a concomitant Question & Answer document has been published by the EMEA (CPMP/ICH/5746/03). To reinforce the ICH E5 guideline, in particular aspects of extrinsic factors, the EMEA published a reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU-population (EMEA/CHMP/EWP/692702/2008). According to EMEA's experience, extrinsic factors such as medical practice (e.g. co-medications and invasive procedures), disease definition and study population affects the adequacy of foreign data for extrapolation. The adherence to relevant regional treatment guidelines for example may in turn result in clinical study data which are not adequate for extrapolation to another region.

6 Conclusion

The ability to access global markets is an important factor for the success of a biosimilar development program for a globally acting pharmaceutical company. As most of the currently established or proposed regulatory pathways for biosimilar applications constitute abbreviated licensing applications, regional differences in the regulatory requirements for a marketing

authorization application should be taken into account early during development in order to avoid unethical replication non-clinical and clinical studies.

In the context of considerations concerning a global biosimilar development program, the principles and regulatory requirements for abbreviated licensing procedures for biosimilar products in the EU, Canada and Japan as well as proposed by the WHO are compared in this thesis.

In 2003 the EU has taken the lead amongst regulated markets in creating a regulatory framework for the marketing authorization of biosimilar products by amending Directive 2001/83/EC: Article 10(4) of the said Directive introduced the regulatory approval pathway or licensing route for similar biological medicinal products and Annex I to the said Directive lays down the requirements for the presentation and the content of the marketing authorization application dossier for a biosimilar product. The scope of eligible products, but not type and amount of quality, non-clinical and clinical data required for marketing authorization are pre-defined in the legislation. Detailed guidance is continuously provided on the basis of general and product-class specific guidance documents thereby accounting for the wide spectrum of molecular complexity of biological products. Although EMEA develops continuously specific guidance for new product-classes, only limited guidance for the non-clinical and clinical biosimilar development, is available for those product candidates, which are not covered by the current guidelines.

In March 2009 the Japan Minister of Health issued a biosimilar guidance providing instructions on the development and registration of biosimilar products. Unlike in the EU however, the implementation of a new approval application category for biosimilars did not require an update of the current legislation. Biosimilar products are regulated in Japan as "prescription drugs". Only administrative directions and detailed explanations in form of "Notifications" were amended or newly issued, laying down the requirements for marketing authorization applications for biosimilar products.

In Canada, a regulatory framework for biosimilars is currently under discussion. The existing legislation will serve as legal base for the intended introduction of an abbreviated licensing pathway for subsequent entry biologics (SEB). In March 2009 Health Canada issued draft guidance for sponsors pertaining to the amount of data required for submission of a SEBs. Adherence to the guideline should permit the applicant to satisfy the requirements for approval of the SEB as "New Drug".

In 2007 the World Health Organization (WHO) was mandated to develop a guidance document providing globally acceptable scientific principles for the development and evaluation of biosimilar products in order to promote the access to innovative medicines, in particular for developing countries. In October 2009 the forth draft of the guideline on the evaluation of similar biotherapeutic products (SBPs) has been released. Less developed countries, which don't have the knowledge and resources to develop their own guidelines, may implement and employ the principles provided by the WHO for the evaluation and licensing of biosimilar products.

Unlike the EU, the PMDA, Health Canada and the WHO published single guidance documents covering the quality, safety and efficacy development of biosimilar products. This guidance related to the non-clinical and clinical development provided in these documents is thereby less specific and detailed as in the European product-class specific guidance documents (see below).

As it is the case for generic products, biosimilar products may be brought to market immediately upon expiration of any patents and data or market exclusivity periods. This marketing monopoly is made possible to innovator companies for their new drugs in most developed countries, which have mechanisms in place for abbreviated application pathways. These measures are supposed to stimulate price competition with innovator drugs and to keep the balance between the continuous development of better innovative medicines and the reduction of public health care costs due to price competition. Unlike the 20 year patent term as recommended by the WTO (TRIPS Agreement) and implemented in national patent laws, the periods of patent extension and data and/or market exclusivity differ between the EU, Canada and Japan. Whereas no provisions with regards to patent extension is in place in Canada, the periods of data exclusivity range from currently 5 in Canada (filing date of the reference product before June 2006) to 10 years (for certain drugs in Japan).

In general even complex biologics are eligible for biosimilar applications in the EU as the licensing route of biosimilar products applies to any biological medicines. However, as the biosimilar concept denotes the ability to characterize the product in development, the required comparability exercise is more likely to be applied to highly purified products, which can be thoroughly characterized (i.e. biotechnological products). In fact all currently approved biosimilar products in the EU are manufactured by recombinant DNA technology. Still, a product-class specific guideline for Low Molecular Weight Heparin, which is extracted from tissue, has been issued by the EMEA.

In Japan, the scope of product eligible for the biosimilar application pathway is limited to biotechnological products, whereas the principles could also be applied to other non-recombinant biological product, provided the product can be highly purified and characterized in terms of quality. Even chemically synthesized products are not per se excluded from the guideline e.g. where the reference product is manufactured biopharmaceutically. Other products which might fall under the scope of the EU biosimilar regulation are however clearly excluded in Japan (e.g. nucleic acids as active ingredients). The WHO draft guideline follows the proposed guideline from Health Canada, which limits the eligibility of the biosimilar approach to well characterized proteins derived through modern biotechnological methods (e.g. recombinant DNA technology).

Unlike the terms chosen by the regulatory authorities or the WHO for biosimilar products, the underlying concept and principles, which apply to the marketing authorization of follow-on biological products, are highly similar in the EU, Canada, Japan and in the WHO guideline. It has been emphasized by all authorities, that the requirements which apply to the marketing authorization applications of "generic" products, in particular the demonstration of therapeutic equivalence by means of a single bioequivalence study, is considered insufficient for a biosimilar product. This is mainly due to the diversity of biological medicinal products in

terms of raw materials used for the manufacturing of the biosimilar product, differences in the manufacturing processes (use of living cells/mico-organisms) and the complexity of the products (e.g. glycosylation, higher order structure, post-translational modifications). In addition to a stand alone development of the manufacturing process of the biosimilar, the marketing authorization application should be based on the demonstration of the similar nature of the biosimilar and the chosen reference product. The similarity is demonstrated in a systematic approach by a comprehensive comparability exercise, comprising a sequential head-to-head comparison of the biosimilar and the reference product in the order of 1) physico-chemical comparability 2) biological comparability 3) non-clinical comparability 4) clinical comparability – bioequivalence 5) clinical comparability – safety and efficacy.

Provided comparability could be demonstrated at the quality level a reduction of the non-clinical and clinical data requirements compared to a complete dossier for a new innovative product may be possible after the expiration of patent and other exclusivity periods in the respective jurisdiction.

With regards to the comparability exercise in terms of quality, only minor differences exist between the respective guidance documents in EU, Canada, Japan and the WHO.

In general state-of-the art technologies should be applied to compare the biosimilar with the reference product in terms of physicochemical properties including higher order structure, related substances and impurities as well as biological attributes such as pharmacological activity. Ideally the pharmaceutical form, strength and route of administration of the biosimilar should be the same as that of the reference products whereas other approaches may be considered by applicant. Differences exist with regards to the selection of the host cell. While the Japanese and WHO guideline proposes to use, if possible, the same host cell (e.g. CHO or *E.Coli*) for the manufacturing of the biosimilar as the one the originator uses, neither the Canadian nor the EU guidelines require to use the same host cell. In the EU for example the somatropin containing biosimilar product Valtropin is synthesized in *S. cerevisiae*, the originator uses *E.Coli*. Significant differences exist in the required design of the stability studies. Whereas in the EU and Canada the real time, stress and accelerated studies should be comparative in nature, the reference product can be omitted in Japan and as suggested by the WHO guideline. In case of specifications and bioassay the respective guidelines in Japan and the EU refer to relevant national Phamacopeias. The manufacturer should evaluated potential discrepancies between different national Pharmacopeias and/or guidelines and may consider to apply both, if possible.

In all jurisdictions similarity should be primarily deduced from comprehensive quality studies. If similarity on the quality level cannot be established, complete non-clinical and clinical data are required. A final determination of similarity will be based on a combination of the multi-level comparability exercise.

With regards to the non-clinical comparability the implemented and proposed guidance documents are consistent in terms of required repeated-toxicity study and comparative nature of the studies. The only exception is the conduct of a single dose toxicity study, which should be decided on a case-by-case basis according to the Japanese guidance document. A single dose toxicity study is not required in the EU, Canada or in the WHO guideline. Differences

exist with regards to the level of detail on the relevant species, PD parameters, accepted animal models and study duration. The most detailed information on the non-clinical study design is provided in the EU product-class specific guidance documents. As no major discrepancies exist between the other rather general recommendations from the Japanese, Canadian and WHO guidelines, the applicant is advised to follow the product-specific EU guidance. In all jurisdictions it is generally accepted that safety pharmacology, reproductive toxicity, mutagenicity and carcinogenicity test are not required, unless findings from the toxicity studies make the tests necessary.

With regards to clinical comparability, the Japanese guideline appears as the least detailed guidance document. As for the non-clinical comparability, the most detailed information on the clinical requirements can be found in the EU product-class specific guidance documents. Product-class specific recommendations regarding study design [single versus multiple dose, crossover, route of administration, test population (healthy volunteers versus patients)], PK and PD parameters are given. No major discrepancies exist between the unspecific general recommendations from the Japanese, Canadian, WHO guidelines and the product-class specific guidelines. In all cases a comparative PK and PD study is required. Except for the less detailed Japanese guideline, all other guidance documents allow the combination of the comparative PD study with the PK study. However, except for the Canadian guideline, the concept of and the criteria for a confirmatory PK/PD study is provided in the European, the Japanese and the WHO guidance document. The concept would allow omitting a Phase III efficacy trial to confirm comparability provided comparability in efficacy has been demonstrated in such a confirmatory PK/PD study. In the EU, this concept has been specifically suggested for the development of Insulin and G-CSF in the product-class specific guidance. One of the pre-requisites is the acceptance of the PD marker as surrogate marker for efficacy. For Insulin and G-CSF the recommended PD markers are provided in the product-class specific guidance documents. With regards to the determination of similarity of PK parameters in comparative PK studies, the sponsor is advised to pre-define the equivalence range prior to the initiation of the study. While the Canadian guideline proposes to base the equivalence range on the criteria for comparative bioavailability studies for generic pharmaceuticals i.e. both, the 90% confidence interval of the relative mean AUC_T and the relative mean measured C_{max} of the biosimilar to reference product to be within 80% - 125%, the European and the WHO guidelines emphasize, that this approach could be accepted but may not be appropriate. No further guidance is given by the European and WHO guidance on the determination of the equivalence range. Except for the requirement to pre-specify the acceptance range the Japanese guidance is silent on the issue.

Unless the clinical efficacy has been shown in confirmatory PK/PD studies (EU: Insulin, optional G-CSF, Japan, WHO: G-CSF) Phase III comparative clinical trials to demonstrate comparability in efficacy are required in all regions. The least detailed guidance with regards to the conduct of phase III clinical trials is provided in the Canadian guideline. Consistent in all regions is the requirement, that the phase III studies should be comparative in nature. In case the chosen reference product is approved for the use in multiple indications, only the WHO and the EU guidelines provide criteria for the selection. In both guidelines, the sensitivity of the indication for the treatment is the key criteria. While the EU guideline

recommends to select the most sensitive indication, the WHO guideline requires that the indication is sensitive per se and a well-established model. However, if a product-class specific guidance exists in the EU for a product candidate, recommendations with regards to the indication for the phase III efficacy trial is given as well as for other aspects of the trial (e.g. endpoint, surrogate marker and general design) are given. The applicant is advised to consult other agencies with regards to the acceptability of the study design.

All guidance documents are consistent with regards to the requirement to conduct a phase III safety trial to confirm comparability. The option to combine the phase III safety trial with the phase III efficacy trial is given in all guidance documents as well. Immunogenicity, which is a concern of all regulatory agencies, should be evaluated in any case and might be included in the required clinical safety study. Content, class, affinity, specificity of antibody, neutralizing activity and impact on efficacy and safety should also be investigated. Only the EU guidance document even recommends to consider the risk of immunogenicity in different indications separately.

Biopharmaceutical products are usually approved for multiple indications (see above). The spectrum of approved indications for a specific reference product may however, differ from region to region. A different spectrum of approved indications may have impact on the selection of the indication to be tested in the phase III efficacy and safety trials, as the claimed indications in one region have to comply with the indications approved for the reference product.

Extrapolation of indications i.e. in case where the originally authorized medicinal product has more than one indication approved the comparability of efficacy and safety of biosimilar product demonstrated in one indication may be extrapolated to other indications, if scientifically justified. The possibility for extrapolation of indications is stipulated in all regions provided the claimed indications share the same Mode of action and same pathophysiological mechanism with the indication investigated in the comparative phase III efficacy and safety trial.

As a major obstacle to the global biosimilar development appears the requirement that the reference product, which should be used during the whole development i.e. in the comparability exercise, should be approved in the individual territory. This applies to biosimilar applications in the EU and Japan. Data generated from comparability studies with a medicinal product authorized outside the EU for example may only provide supportive information. As the same reference product is supposed to be used during the whole comparability exercise, repetition of comparative phase III efficacy trials might even be necessary for filing of biosimilar applications in other territories (see below). In Canada, the reference product to use should be approved in Canada. However a non-Canadian reference product may be used provided a link can be established between the non-Canadian used in the comparability study and the reference product approved in Canada. The WHO is addressing the fact, that biosimilars are currently developed in high regulated markets. The guideline does not stipulate the use of a nationally authorized reference product but encourages the national authorities to accept foreign reference products.

With regards to the clinical data package the goal should be to set up the clinical program in such a way, that the resulting clinical data meet all of the concerned regional regulatory authorities' requirements. This "Complete" clinical data package should be further assessed with regards to ability to extrapolate the data to the populations of the all regions where an application is intended. Potential regional differences resulting from intrinsic and extrinsic ethic factors should be addressed already during development. Provided, the regulatory requirements in all intended regions are satisfied, potential differences in intrinsic or extrinsic factors should be assessed according to ICH E5. In case, the product in development appears sensitive to ethnic factors a bridging studies may be required in order to extrapolate the data to the other regions. It may also be possible, to generate the data necessary for the extrapolation simultaneously by conducting multi-regional trials under a common protocol. If these trials have a sufficient number of trial subjects from the individual regions concerned it may be possible to assess the impact of the ethnic factors on the safety and efficacy in those studies. These trials could be conducted in the context of a global biosimilar development program intended for simultaneous registration in multiple regions world-wide.

Although the potential impact of ethnic factors needs to be evaluated for each biosimilar product separately, the existing safety and efficacy data base of the reference product in the new region may be helpful for the assessment of the impact of ethic factors. Publicly available data indicating that the chosen reference product, which has been demonstrated to be pharmacological similar to the biosimilar product, has similar effects in the population of the different regions, may be sufficient to allow the extrapolation of the own data base to the population of the other regions.

When setting up multi-regional comparability trials several aspects of regional requirements should be considered and included in the design of the study to ensure adequacy of the clinical for the other regions. In particular, the definition/diagnosis and treatment of the disease condition/indication, the choice of the control group, choice of efficacy variable/primary and secondary endpoints, treatment effect size, methods for the assessment of safety, medical practice, duration of the trial, regional concomitant medications and regional reference product, similarity of dose and dose regimen. These regulatory requirements would have to be considered not only for multi-regional trials but also for comparability trials conducted in one region in case the sponsor whishes to use the data from these trials to support marketing authorization applications in other regions. Further, if comparative studies using reference product authorized in the respective country are required, foreign clinical studies with a reference product authorized in only one region could mean that the new regions regulatory requirements are not met and that an additional clinical trial using a different reference product at the new region's approved dosage and dose regimen becomes necessary even if the product is considered ethnically insensitive and extrinsic factors in the regions are generally similar.

In conclusion, the regulatory requirements for biosimilar products appear to be very similar in the high regulated markets of the EU, Canada and Japan. Also the proposed WHO guideline, which is intended to provide guidance to less developed countries demonstrates a high scientific level which is comparable to other high regulated markets. All regulatory pathways share the same scientific and regulatory principles. Thereby most of the regulatory

requirements are similar in all jurisdictions and would allow the submission of single reduced data package to all regions. Never the less, early consultation with the regulatory authorities in the regions concerned is recommended in order to determine whether the data are compliant with the requirements of the specific regions. The impact of ethnic differences on the required clinical data package should be evaluated on a case by case basis. However, the requirement that the reference product, which should be used during the whole development, should be approved in the individual territory has been identified as a major obstacle to a global biosimilar development. Whereas the Canadian and the WHO guideline do not strictly require the use of a reference product approved in the individual territory, it is strictly required in the EU and Japan.

7 Appendices

Attachment 1: Table 1 and details from Table 2-(1) of Notification No 0304004

Attachment 2: Overview regulatory framework for biosimilar products in EU, Canada, Japan and as proposed by the WHO

Attachment 3: Overview of Medicinal Product Classification and Approval/License Requirements in Japan

8 References

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2 White Paper on the intersection of intellectual property and antitrust law in the pharmaceutical industry "Delivering on the Promise of Pharmaceutical Innovation: The Need to Maintain Strong and Predictable Intellectual Property Rights" by the Pharmaceutical Research and Manufacturers of America, April 22, 2002

3 A review of existing data exclusivity legislation in selected countries – Third revised version – January 2004 by IFPMA, available on http://www.who.int/intellectualproperty/topics/ip/data_confidentiality/en/index.html, last accessed on 10 October 2009.

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5 White paper "Continued Development of Approved Biological Drugs" by Boston Consulting Group, December 2007, available on http://www.bcg.com/documents/file15138.pdf, last accessed 03 October 2009

6 EGA Handbook on Biosimilar Medicines, available at http://www.egagenerics.com/bio-handbook.htm, last accessed on 07 December 2009

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8 Directive 2001/83/EC Article 10(1)(a)(iii): The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he can demonstrate: ... that the medicinal product is essentially similar to medicinal products which have been authorized within the Community,..." Directive 2001/83/EC dated Nov 06, 2001.

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10 Article 10(2)(a) of Directive 2001/83/EC defines a generic medicinal product:... which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference product and whose bioequivalence with the reference product ahs been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regards to safety and/or efficacy.

11 Recital 15 of Directive 2001/83/EC as amended by Directive 2004/27/EC states, that biological medicinal products similar to a reference medicinal product do not usually meet the conditions to be considered as a generic medicinal product...

12 Testimony by Nicolas Rossignol given to the members of the US Senate HELP Committee dated March 2007, available at http://www.safeinnovativemedicine.com/resources/statement-of-nicolas-rossignol-european-commission/, last accessed onOct 27, 2009.

13 These processes include: recombinant DNA technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells and Hybidoma and monoclonal antibody methods, according to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf, last accessed on Oct 27, 2009.

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15 CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (CHMP/42832/05) dated 22 February 2006

16 Annex to Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Non-Clinical and Clinical Isues – Guidance on Similar Medicinal Products Containing Recombinant Human Soluble Insulin. EMEA/CHMP/BMWP/32775/2005; Dated 22 February 2006

17 Annex to 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. EMEA/CHMP/BMWP/94528/2005; Dated 22 February 2006

18 Annex to 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 Granulocyte-Colony Stimulating Factor. EMEA/CHMP/BMWP/31329/2005; Dated 22 February 2006

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20 Concept Paper On Similar Biological Medicinal Products Containing Recombinant Alpha-Interferon; Annex to Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance (Non) Clinical Issues. CHMP/BMWP/7241/2006; Dated 26 April 2006

21 Reflection Paper Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing Recombinant Interferon Alfa. EMEA/CHMP/BMWP/102046/2006; Dated 23 April 2009

22 Annex to Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Non-Clinical and Clinical Issues – Guidance on Similar Medicinal Products Containing Low-Molecular-Weight-Heparins. EMEA/CHMP/BMWP/118264/2007; Dated 19 March 2009

23 Concept Paper On The Development Of A Guideline On Similar Biological Medicinal Products Containing Monoclonal Antibodies, EMEA/CHMP/BMWP/632613/2009, Dated 22 October 2009.

24 CHMP Guideline On Similar Biological Medicinal Products (CHMP/437/04) dated 20 October 2005.

25 Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Quality Issues" EMEA/CHMP/BWP/49348/2005), dated 22 February 2006.

26 JPMA- Pharmaceutical Administration and Regulations in Japan, http://www.jpma.or.jp/english/parj/0903.html, last accessed 11 September 2009.

27 Presentation "Module International Registration Procedures Japan" dated January 2007 by Dr Bettina Fiedler at DGRA Masterstudiengang

28 The term "drug" refers to substances, which are

- Listed in the Japanese Pharmacopoeia
- (other than quasi-drugs), including dental materials, medical supplies, and sanitary materials, which are intended for use in the diagnosis, treatment, or prevention of disease in humans or animals, and which are not equipment or instruments
- (other than quasi-drugs), which are intended to affect the structure of functions of the body of humans or animals, and which are not equipment or instruments

29 Pharmaceutical Affairs Law (Law No.145 of August 10, 1960, last revision: Law No.73, June 11, 2003)

30Proprietary medicines (synonymous with the term "non-prescription medicines). The categories are stipulated by PFSB Notification No. 0331015 "Applications for Approval of Medicinal Products, dated 31 March 2005.

- Category 1 "New ingredient" proprietary medicines
- Category 2 "New proprietary ingredient" proprietary medicines
- Category 3 "New combination ingredient" proprietary medicines
- Category 4 "Miscellaneous" proprietary medicines

31 Exempt from the requirement for marketing approval are medicinal products compliant to Japanese Pharmacopoeia and drugs solely for manufacturing other drugs (Article 14 (1) PAL.

32 PFSB Notification No.0331015 dated March 31, 2005 "Applications for Approval of Medicinal Products"

33 PFSB/ELD Notification No.0304011, March 4th, 2009 "Handling of Non-proprietary Names and Trade Names of Biosimilar Products

34 PFSB/ELD Notification No. 0304007 dated 04 March 2009 entitled "Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products"

35 Listing of Drugs Currently Regulated as New Drugs. This list represents substances and formulations which have been assessed by the Therapeutic Products Directorate on the basis of an application to market or further to promotion of products for medicinal purposes where safety and efficacy for such purposes have not been established. The listing will be updated periodically. The list should be used as a guide in determining the status of subsequent market entry drug products.

36 The "sufficient time" policy from the Drugs Directorate stipulates that "sufficient time" for new drug is interpreted as a minimum of 7 years from the initial date of marketing in Canada. However, the status "new product" remains, if 7 years is not regarded as sufficient time to establish its safety or when significant changes occurred i.e. the sufficient time policy applies only to specific drug product (i.e. a certain strength of a drug product).

37 Several products such as Category IV Monographs or labeling standards, both are low-risk nonprescription drugs, Special Access Programme (emergency situations or drugs for personal use are exempt from these requirements. Other requirements apply. Please refer to IDRAC exploratory text "legal framework (Canada) IDRAC 91648.

38 Under the provisions of section C.01.014 of the Food and Drug Regulations, no manufacturer shall sell a drug in dosage form unless a drug identification number (DIN) has been assigned for that drug. In case of a new drug, a new drug submission (NDS) filed pursuant to Part C Drugs, Division 8 (ref. to New Drugs) of the Food and Drug Regulation is regarded as an application for a DIN. When a product is not subject to Part C Drugs, Division 8, the application is called a DIN submission. Drugs Directorate Guidelines – Preparation of Drug Identification Number Submissions issued by Health Protection Branch Health Canada, February 22, 1995.

39 Drugs Directorate Guidelines – Preparation of Drug Identification Number Submissions issued by Health Protection Branch Health Canada, February 22, 1995.

40 "No person shall label, package, treat, process, sell or advertise any drug in any manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety." It is therefore in the interest of public health that the Drugs Directorate determines that a drug product is of sufficient quality not to be injurious to the Canadian public.

41 IDRAC Document 91648 "Legal Framework (Canada)

42 An abbreviated new drug submission (ANDS) applies to new drugs where the new drug is a) pharmaceutical equivalent of a Canadian reference product, b) the new drug is bioequivalent with the Canadian reference product, based on the pharmaceutical and where the Minister considers it necessary, bioavailability characteristics, C) the route of administration of the new drug is the same as that of the Canadian reference products and D) the condition of use for the new drug fall within the conditions of use for the Canadian reference products. C.08.002.1.(1) of the Food and Drug Acts Regulation

43 Article 1.3.6 of Draft Guidance For Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs). Published by the authority of the Minister of Health. Draft Date March 27, 2009

44 Draft Guidance For Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs). Published by the authority of the Minister of Health. Draft Date March 27, 2009. File number 09-108207-966

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49 Guideline on "Similar Biological Medicinal Product" (CHMP/437/04) available at http://www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf, last accessed 29 September 2009.

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52 Question and Answer to Accompany the Release of the Subsequent Entry Biologics Guidance Document available at http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/2009-03-seb-pbu_qa-qr-eng.php, last accessed on 02 November 2009.

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54 PFSB/ELD Notice dated July 21, 2009 entitled "Q&A on the Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products".

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57 PFSB/ELD Notification No.0304011, March 4th, 2009 "Handling of Non-proprietary Names and Trade Names of Biosimilar Products

58 WorldHealth Organization Executive Board 115th Session 09 December 2004 (EB115/11): "International Nonproprietary Names: revised procedure – Report by the Secretariat"

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73 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, Official Journal L – 311, 28/11/2004, p. 67 – 128, available under http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_83/dir_2001_83_en.pdf, last accessed on October 10, 2009

74 Regulation (EEC) No 2309/93 of 22 July 1993 (OJ No L 214 of 24.8.1993, p.1) available under http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_1993_2309/reg_1993_2309_en.pdf, last accessed on October 10, 2009

75 Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC (OJ L 136, 30/4/2004, p. 34-57) available under http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf, last accessed on Oct 10, 2009

76 Sachiko Masuda "The maret exclusivity period for new drugs in japan: Overview of intellectual property protection and related regulations" Journal of Generic Medicines (2008) Vol 5, No 2, 121-s130

77 A Guide to Patents, Canadian Intellectual Property Office, available under http://www.cipo.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/wr00102.html, last accessed on 02 October 2009.

78 1987 Amendment to the Patent Act

79 The patent register is available under http://www.patentregister.ca/; last accessed on Nov 22, 2009.

80 Draft Guidance For Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs), Health Canada, Draft Date March 27, 2009

81 Patented Medicines (Notice of Compliance) Regulations as amended (also referred to as "PM(NOC) Regulations")

82 Food and Drug Regulation C.08.004.1(3) as amended on October 05, 2006

83 Food and Drug Regulation C.08.004.1(8) as amended on October 05, 2006

84 According the Food and Drug Regulation C.08.004.1 as amended on Oct 05, 2006, pediatric population means the following groups: premature babies born before the 37th week of gestation; full-term babies from 0-27 days of age, and all children from 28 days to 2 years of age, +1 day to 11 years of age, +1 day to 18 years of age.

85 Food and Drug Regulation C.08.004.1(2) as amended on October 05, 2006

86 , EGA Position Paper "TRIPS Article 39.3 does not require Data Exclusivity Provisions: A critical issue for access to medicines", available at http://www.egagenerics.com/doc/ega_trips39.3_2000.pdf, last accessed on 10 October 2009.

87 "The Doha Declaration explained" by WTO, available at http://www.wto.org/english/tratop_e/dda_e/dohaexplained_e.htm, last accessed on 10 October 2009-

88 PFSB/ELD Notice dated July 21, 2009 entitled "Q&A on the Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products".

89 Draft Guidance For Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs). Published by the authority of the Minister of Health. Draft Date March 27, 2009. File number 09-108207-966

90 Draft Guidance For Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs). Published by the authority of the Minister of Health. Draft Date March 27, 2009. File number 09-108207-966

91 WHO is accepting "absolute neutrophile count" and "CD34+ cell count" as relevant PD markers for the Granulocyte colony stimulating factor (G-CSF) which could be used in PK/PD studies to demonstrate similar efficacy

92 In case of Insulin, WHO proposes a study population consisting of on-obese healthy volunteers or patients with type 1 diabetes rather than insulin-resistant obese patients with type 2 diabetes?

93 EMEA Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins – draft. EMEA/CHMP/89249/2004. Dated 27 July 2005.

94 Consistent with the WHO draft guideline, the absolute neutrophil count is a considered an acceptable surrogate marker for granulocyte-colony stimulating factor (G-CSF).

95 For human growth hormone, the WHO proposes the investigation in growth hormone treatment naïve children with GH-deficiency instead of non-GH-deficient children with short stature which are less sensitive to GH treatment.

96 ICH E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data, available at http://www.ich.org/cache/compo/276-254-1.html, last accessed on 07 December 2009.

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

Oberaudorf den 15 Januar 2010

Dr. Uwe Goßlar 

Attachment 1

Detail from Table 2-(1) of Notification No 0304004 Applications for Approval of Biosimilar Products March 04, 2009

Attached Table 2-(1) Prescription Medicinal Products

Left Column	Right Column						
	A 1 2 3	B 1 2 3	C 1 2 3	D 1 2 3	E 1 2 3 4 5 6	F 1 2 3 4 5 6 7	G
(1) Medicinal products with new active ingredients	OOO	OOO	OOO	OO△	OOOOx△	OOO△O△△	O
(2) New prescription combination medicinal products	OOO	xOO	OOO	O△△	OOOOx△	OOxxx△x	O
(3) Medicinal products with new routes of administration	OOO	xOO	OOO	O△△	OOOOx△	OOx△O△△	O
(4) Medicinal products with new indications	OOO	xOx	xxx	Oxx	△△△△x△	xxxxxxx	O
(5) Medicinal products with new formulations	OOO	xOO	OOO	xxx	OOOOx△	xxxxxxx	O
(6) Medicinal products with new dosages	OOO	xOx	xxx	Oxx	OOOOx△	xxxxxxx	O
(7) Biosimilar products	OOO	OOO	O△△	Oxx	△△△△x△	△Oxxx△△	O

The symbols and numbers in the right-hand columns refer to the data stipulated in Attached Table 1 (see next page). O signifies cases where data is required, x cases where data is not required, and Δ cases where requirements will be assessed for each individual product.

Table 1 of Notification No 0304004 Applications for Approval of Biosimilar Products March 04, 2009

Attached Table 1

Left Column	Right Column
Data relating to:	Data relating to:
A. The origin or background of findings and conditions of use overseas	1 Origin or background of findings 2 Conditions of use overseas 3 Properties and comparative studies with other medicinal products
B. Manufacturing methods and specifications and testing methods	1 Structural determination and physicochemical properties 2 Manufacturing methods 3 Specifications and testing methods
C. Stability	1 Long-term storage tests 2 Severe tests 3 Accelerated tests
D. Pharmacological actions	1 Tests supporting efficacy 2 Secondary pharmacological/safety pharmacological 3 Other pharmacological
E. Absorption, distribution, metabolism and excretion	1 Absorption 2 Distribution 3 Metabolism 4 Excretion 5 Bioequivalence 6 Other pharmacokinetic
F. Acute toxicity, sub-acute toxicity, chronic toxicity, teratogenicity and other types of toxicity	1 Single dose toxicity 2 Repeated dose toxicity 3 Genotoxicity 4 Carcinogenicity 5 Reproductive and developmental toxicity 6 Local irritation 7 Other toxicity
G. Clinical trial results	Clinical trial results

Attachment 2

Overview regulatory framework for biosimilar products in EU, Canada, Japan and as proposed by the WHO

	Europe	Japan	Canada	WHO guideline
Terminology	Similar biological medicinal product (also referred to a biosimilars)	Biosimilar Product	Susequent entry biologic (SEB)	Similar biotherapeutic product (SBP)
Legal Basis	Legal Framework for licensing: Article 10(4) of Directive 2001/83/EC and Section 4, Part II Annex I (content of application dossier) to the said Directive. Marketing authorisation procedure: Regulation EC 726/2004 (biotechnological processes[1])	Biosimilars were introduced to the Japanese jurisdiction as a separate category of Art14(1) PAL manufacturing /marketing approval applications for prescription medicinal products[2]. No adaptation of the PAL was required.	Defined as a Schedule D biologic product and regulated as a „New Drug"; Part C, Division 8 of the Food and Drug Regulation sets out the requirements for the marketing of new drugs in Canada, including SEBs.	It is the constitutional responsibility and mandate of the WHO to assure global quality, safety and efficacy of biotherapeutics, by providing globally accepted norms and standards for their evaluation. To be implement into legislation by national authorities (primarily third countries).
Definition of a biosimilar products	Biological medicinal products which are similar to a reference biological product but which do not meet the conditions in the definition of a generic medicinal product; Results of appropriate pre-clinical or clinical tests relating to these conditions, should be provided when applying for marketing authorization application[3]	Medicinal products which are comparable to biotechnological medicinal products which have been approved for marketing[4] in Japan. A medicinal product which has comparable quality, safety and efficacy to a biotechnology-applied medicinal product[5]	A SEB is a biologic drug that would enter the market subsequent to, and similar to an innovtor product authorised for sale in Canada. A SEB relies in part on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to the reference product.	A SBP is a well-established (marketed for a suitable period of time) and well-characterized (with a proven quality, efficacy and safety) biotherapeutic products (e.g. recombinant DNA-derived therapeutic proteins)

[1] Annex (1) of Regulation EC No 726/2004
[2] PFSB Notification No. 0331015 as amended by Notification No. 0304004
[3] (Article 10(4) of EC Directive 2001/83/EC as amended)
[4] PFSB Notification No. 0331015 as amended by Notification No. 0304004
[5] PFSB/ELD Notification No. 0304007

	Europe	Japan	Canada	WHO guideline
Scope	Article 10(4) applies to any biological medicinal products However, scope of current guidelines focuses on products which can be sufficiently characterised e.g. recombinant DNA-derived proteins. LMWH is manufactured by extraction from biological sources	• Recombinant proteins (highly purified and characterised by state-of-art analytical methods) manufactured using MOs or cell-culture technology, • non-recombinant protein products on case-by-case basis • List of excluded products[6]	• Proposed guideline for SEBs applies in particular to biotechnologically manufactured products (use of rec.DNA and/or cell cuture techniques)	• Proposed guideline for SBPs applies in particular to biotechnologically manufactured products (use of rec.DANN)
Naming conventions	• invented or non-proprietary as for other centrally authorised products. No distinction from brand product • same INN as the reference product accepted	• clear distinction of biosimilar product and brand product required: trade name contains non-proprietary name and BS (for biosimilar) • same INN as the reference product accepted	• Draft guideline is silent on naming • same INN as the reference product accepted	• Draft guideline is silent on naming
IP rights	• 20 years patent term (nationally granted) • Bolar provision • supplementary protection certificate max 5 years • currently 6-10 years data exclusivity • 8+2+1 rule for biosimilar applications at the earliest 2013	• 20 years patent term • patent term extension max 5 years • 8-10 years re-examination period (= data exclusivity) • Bolar provision	• 20 years patent term • Bolar provision • 5 years data protection (reference product filing date before June 2006) • 8(+6months) years data protection (reference product filing date after June 2006)	• 20 years patent term in WTO countries (TRIPS) • Bolar provision (TRIPS) • transition period until 2016 for least developed countries (Doha declaration)

[6] PFSB/ELD Notification No. 030407

	Europe	Japan	Canada	WHO guideline
Reference Product	• Reference product must be authorised in the Community on the basis of a full dossier. • Data from comparability studies with foreign reference product may only be supportive information.	• Biotechnological medicinal product approved in Japan for marketing based on a full dossier • Reference products based on abbreviated applications may be accepted und certain conditions	• Refreference product should be authorized for sale in Canada • Foreign reference product could be accepted, provided a link (indirect) with the Canadian Reference product can be established • Reference products based on abbreviated applications are not accepted	• Guideline does not stipulate the use of a nationally authorized reference product • Reference product based on abbreviated application/dossier is not accepted
Product Attributes	• Pharmaceutical form, route of administration and strength should be the same as that of the reference product • Formulation may differ	• Pharmaceutical form, route of administration and strength should be the same as that of the reference product • Formulation may differ	• The guideline is silent on the pharmaceutical form, route of administration formulation and strength	• Formulation and container closure system should be the same as that of the reference product
Manufacturing process (used host cell)	• The use of the same host cell as the originator is not required	• The same host cell as the originator should preferably be use, if known to the manufacturer	• Guideline is less detailed • No completely different approach should be used for manufacturing (cell culture versus transgenic animal)	• The same host cell type as the reference product (e.g. *E.coli* or CHO cells) should be used if possible
Product Characterization	• Compliance of assays with European Pharmacopoeia, if applicable		• Similarity should be demonstrated for both the active substance and drug product.	Analytical methods scientificly sound and qualified
	• Physicochemical Properties (higher order structure and related substances) • Biological activity • Impurities	• Physicochemical Properties (higher order structure + composition) • Biological activity • Impurities • Immunochemical Properties (Immunoreactivity)	• Physicochemical Properties (higher order structure) • Biological activity • Impurities • Immunochemical Properties • Quantity	• Physicochemical Properties (higher order structure) • Biological activity • Impurities • Immunochemical Properties

	Europe	Japan	Canada	WHO guideline
Stability	• Comparative real time and real condition • Comparative Stress and accelerated conditions are required • Comarison to reference product not required • ICHQ5C taken into account	• 6 Months real time and real condition at the time of submission (not comparative) • Stress and accelerated conditions desirable but not required • Comarison to reference product not required • ICHQ5C taken into account	• Real time and real condition side-by-side stability required • Stress and accelerated conditions (comparative) is considered useful • ICHQ5C taken into account	• Real time and real condition stability study (not comparative) • Stress and accelerated conditions (comparative) is considered useful
Shelf life	• Guideline is silent on shelf life	• Based on own long-term studies (real time, real condition)	• Guideline is silent on shelf life	• Guideline is silent on shelf life
Specifications	• To be established based on own findings from characterisation, batch analysis • Range not wider than variability observed with reference product • ICH Q6B should be taken into account	• To be established based on own findings from characterisation, batch analysis • ICH Q6B and information from a Pharmacopeia (e.g. JPh) if available, should be taken into account	• No specific guidance	• To be established in accordance with established guidelines (ICH Q6B) and based on the manufacturer's experience (multiple batches) • Limits not significantly wider than variability of reference substance
Non-clinical studies	• Studies should be comparative in nature	• Comparative studies not necessary but appropriate in case of expected differences in PK due to heterogeneity or if equivalence in PD shold be confirmed	• Studies should be comparative in nature	• Studies should be comparative in nature
		• Drug product should be used, except for cases where high doses need to be administered		• Studies should be conducted with final formulation
	Relevant species = clearly defined in product-class specific annexes	• Relevant species not further defined		• Relevant species = used be manufacturer of reference product

	Europe	Japan	Canada	WHO guideline
Non-clinical studies cont.	• Repeated-dose toxicity is minimum requirement and should include:toxicokinetic and antibody formation in general. • Relevant species, local tolerance, toxikokinetic, PD parameters, study duration are clearly specified in product-class annexes. • Safety pharmacology, reproductive tox., mutagenicity and carcinogenicity tests are not required • Pharmacology (comparative) relevant to the clinical application only if not shown in vitro. • Silent on Pharmacokinetic • Pharmacology (comparative) relevant to the clinical application required. Details with regards to in vivo PD studies (species, accepted models, requirement on comparative design) are provided in product-class specific annexes.	• Repeated dose toxicitiy is mandatory • Single dose toxicity, toxicokinetic and local tolerance t.b. decided case by case • Secondary pharmacology, safety pharmacology, reproduction tox., genotoxicity are not required • Pharmacokinetic and metabolic studies t.b. deciced case by case • Pharmacology (comparative) if in vitro bioactivity assay is not related to clinical effect	• Repeated-dose toxicity incl. toxicokinetic is mandatory and local tolerance is recommendet. Duration as required to detect differences • Safety pharmacology, reproduction tox., mutagenicity and carcinogenicity tests are not required • Pharmacology (comparative) relevant to the clinical application required • Silent on Pharmacokinetic	• Repeated-dose toxicity is minimum requirement and should include:toxicokinetic, local tolerance, antibody formation and if necessary PD parameters. Duration as required to detect differences • Safety pharmacology, repro. tox., geno. tox and carcinogenicity tests are not required • Pharmacology (comparative) relevant to the clinical application only if not shown in vitro. • Silent on Pharmacokinetic

	Europe	Japan	Canada	WHO guideline
Clinical Studies	• Product manufactured with the final manufacturing process should be used for the comparability studies	• -	• -	• For main/pivotal studies, the final product to be marketed should be used. Any changes require comparative PK bridging studies
	• Design Phase I PK (single vs multiple dose, crossover, route of administration, test population) are clearly defined in product-class specific annexes • Primary and secondary PK parameters are clearly defined in product-class specific annexes • PK parameters should include: absorption, clearance, elimination half life • Equivalence range (standard PK comparbility 80-125% range) may not be appropriate • Design Phase I PD (dose, crossover, route of administration, test population and PD marker) are clearly defined in product-class specific annexes • Comparative PD study can be combined with Phase I PK study (product-class specific)	• Phase I PK, PD and PK/PD (comparative, cross over design) • AUC and Cmax = principle parameters	• Phase I PK (comparative in nature) design (cross-over, single-multiple dose is flexible) • PK parameters should include: absorption, clearance, terminal half life • Equivalence range is provided • Comparative PD study can be combined with Phase I PK study (validated surrogate marker if possible)	• All routes of administration applied for should be tested • Phase I PK usually single dose (comparative in nature); Design (cross-over, population is flexible) • PK parameters should include: absorption, clearance, elimination half life • Equivalence range (standard PK comparbility 80-125% range) could be accepted but may not be appropriate. • Concept of and criteria for confirmatory PK/PD studies provided

	Europe	Japan	Canada	WHO guideline
Clinical Studies cont.	• Concept of and criteria for confirmatory PK/PD studies provided for Insulin	•	•	•
	• Phase III comparative trial(s) to confirm comparability in efficacy required unless comparability in efficacy has been shown in PD, PK/PD study for Insulin. • Phase III design (number of trials, randomized, parallel group, double-blind), duration, route of administration, indication, equivalenc vs non-inferiority, clinical endpoints, surrogate endpoints are clearly defined in product-class specific annexes • In case of multiple indications the most sensitive model/population is recommendet	• Phase III efficacy trials to confirm comparabiliy necessary, unless comparability in efficacy has been shown in PD, PK/PD study. • Phase III in the claimed indication (no guidance in case multiple indications approved for reference product. • Design comparative in nature • Choice of appropriate surrogate endpoint can be considered	• Phase III efficacy trials to confirm comparability necessary • No further guidance on design of stduy	• Phase III comparative trials to confirm comparable efficacy required • Phase III preferably randomized, parallel groups, double-blind • In case of multiple indications a well-esablished and sensitive model should be used. Effective size may be taken from orginator trials • Equivalence (preferred) or non-inferiority design may be acceptable
	• Phase III safety trials to confirm comparability necessary (adequacy of data base in case of combination with Phase III efficacy trial)	• Phase III safety trials to confirm comparability necessary (separate or combined with Phase III efficacy trial)	• Phase III safety trials to confirm comparability necessary (separate of combined with Phase III efficacy trial)	• Phase III safety trials to confirm comparability necessary (may be combined with Phase III efficacy trial)

	Europe	Japan	Canada	WHO guideline
Clinical Studies cont.	• Immunogenicity must be always investigated (part of all clinical trial protocols) • Consider risk in different indications separately • Titer, class of antibody, cross-reactivity and neutralizing activity has to be investigated • Duration and testing interval is defined in product-class specific annexes	• Immunogenicity investigation could be included in clinical safety study • Content, class, affinity, specificity of antibody, neutralizing activity and impact on efficacy and safety has to be investigated	• Immunogenicity investigation and potential impact on safety & efficacy is required. • In case of concern prolongation of study prior to authorization to obtain long-term safety/efficacy • Content, class of antibody, cross-reactivity and neutralizing activity has to be investigated	• Immunogenicity data obtained from clinical efficacy trial in general sufficient • Target population: patient with the highest risk • Titer, class of antibody, cross-reactivity and neutralizing activity has to be investigated
Extrapolation of Indications - Efficacy	• Extrapolation is possible (clinical experience and available literature data, same Mode of Action/receptors involved in the claimed indications) • In product-class specific annexes the required indication for the efficacy trial is specified.	• Extrapolation is possible (same Mode of action)	• Bridging two or more indications by comparative PK(PD data or • Extrapolation is possible (same Mode of action, same pathophysiological mechanism)	• Extrapolation is possible (same Mode of action, same pathophysiological mechanism)

Attachment 3

Overview of Medicinal Product Classification and Approval/License Requirements in Japan