



**MINISTRY OF HEALTH MALAYSIA  
NATIONAL PHARMACEUTICAL CONTROL BUREAU**

**GUIDANCE DOCUMENT AND GUIDELINES FOR REGISTRATION  
OF BIOSIMILARS IN MALAYSIA**

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**GUIDANCE DOCUMENT FOR APPLICANTS :  
INFORMATION AND SUBMISSION REQUIREMENTS FOR  
REGISTRATION OF BIOSIMILARS**

Biotechnology Section  
Centre for Product Registration  
National Pharmaceutical Control Bureau  
Ministry Of Health Malaysia  
**AUGUST 2008**

**NATIONAL PHARMACEUTICAL CONTROL BUREAU (NPCB)  
MINISTRY OF HEALTH MALAYSIA**

**VISION:**

**THE NATIONAL PHARMACEUTICAL CONTROL BUREAU WILL BE A CENTRE OF EXCELLENCE IN PHARMACEUTICAL REGULATORY MATTERS TO ENSURE THE HEALTH AND WELL-BEING OF MANKIND**

**MISSION:**

**THE NATIONAL PHARMACEUTICAL CONTROL BUREAU SHALL ENSURE THE QUALITY, EFFICACY AND SAFETY OF PHARMACEUTICAL PRODUCTS THROUGH THE IMPLEMENTATION OF THE RELEVANT LEGISLATION BY A COMPETENT WORKFORCE WORKING TOGETHER IN STRATEGIC ALLIANCE TOWARDS IMPROVING THE HEALTH OF THE PEOPLE.**

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## FOREWORD

Guidance document is meant to provide assistance to applicants (industry) on how to comply with the governing acts and regulations. It also clearly outlines the registration requirements and/or process to applicants, and elaboration of the policy decisions such as regulatory approach and position on ‘interchangeability’ and substitutability with the reference product.

Guidance document also provides assistance to staff on how National Pharmaceutical Control Bureau’s (NPCB) mandates and objectives should be implemented in a manner that is fair, consistent and effective. It is important to note that NPCB reserves the right to request information or material, or define conditions not specifically described in this document, in order to ensure the safety, efficacy or quality of a therapeutic biologic product. NPCB is committed to ensure that such requests are justifiable and that decisions are clearly documented.

A variety of terms, such as ‘similar biological medicinal products’, ‘follow-on protein products’, ‘subsequent-entry biologics’ or ‘biogenerics’ have been coined by different jurisdictions. For the purpose of this document, a ‘biosimilar’ medicinal product (a short designation for ‘similar biological medicinal product’) is considered as a new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well established, medicinal product.

So far, the European Union (EU) through the European Medicines Agency (EMA) has the most well developed regulatory framework for biosimilars and which is supported by specific guidelines. The information in this guidance is adopted from the EMA guidelines in particular the Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substances, with some adaptations for Malaysian application.

The purpose of this guidance document is:

- To introduce the concept of biosimilars;
- To outline the basic principles to be applied;
- To provide applicants with a ‘user guide’ for the relevant scientific information, in order to substantiate the claim of similarity.

This document should be read in conjunction with the relevant sections of the **Control of Drugs and Cosmetic Regulations 1984 (CDCR 1984)** and the relevant sections of other applicable NPCB guidance documents.

**( Refer to Appendix 1: Relevant NPCB guidance documents )**

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Pharmaceutical Association of Malaysia (PhAMA)

Malaysian Bio-industry Organisation (MBiO)

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## 1.0 INTRODUCTION

Biopharmaceuticals are protein molecules derived from biotechnology methods or other cutting-edge technologies. They were introduced on the market in the early 1980s, setting new milestones in modern pharmaceutical therapy that improve quality of life for many patients with life-threatening, serious, chronic and debilitating diseases. Today, the so-called 'similar' biological medicinal products (also known as biosimilars), their first-generation successors, are poised to go into medical application.

Biologics are large, highly complex molecular entities manufactured using living cells and are inherently variable. The manufacturing process is highly complex and critical to defining the characteristics of the final product. Maintaining batch-to-batch consistency is a challenge. Subtle variations in the production or even transport or storage conditions may potentially result in an altered safety and efficacy profile of the final product in some cases. Hence, the dogma "the process is the product" is often used in reference to biologics.

Based on the current analytical techniques, two biologics produced by different manufacturing processes cannot be shown to be identical, but similar at best. Therefore, the term 'biosimilar' is appropriate and conversely 'biogeneric' is felt by many National Regulatory Authorities (NRAs) to be misleading in this context. Immunogenicity of biotherapeutics is of concern from clinical and safety aspects. Clinical trials and a robust post marketing pharmacovigilance are essential to guarantee the product's safety and efficacy over time.

Biosimilars are an important issue for all parties concerned – from patients to generic and innovative industries, to healthcare authorities. However, delivering these medicines to the patients involves complex technical and regulatory challenges as well as experience with these medicines is limited.

Understandably, there is pressure from patients to make biotherapeutics more widely available and cheaper. The existence of divergent approaches to the regulatory oversight of biosimilars in different countries, revealed a need for defining principles and regulatory expectations for these products on a global level. The World Health Organisation (WHO) shall develop a global regulatory guideline for biosimilar products. Meanwhile, this guidance document and guideline were developed to meet the challenges in biotherapeutics and describe the regulatory oversight for biosimilars in Malaysia, and which will be made to align/harmonise with the global regulatory guideline once available.

## 1.1 Concept of biosimilars

The rationale for creating the new regulatory paradigm for biosimilars is that biotherapeutics/biologics similar to a reference product “*do not usually meet all the conditions to be considered as a generic*”. The term ‘generic medicine’ refers to chemically-derived products which are identical and therapeutically equivalent to the originator product, For such generics, demonstration of bioequivalence with the originator product is usually appropriate to infer therapeutic equivalence.

However, it is unlikely that biotherapeutics can generally follow this standard approach for generics because of their large and complex molecular structures, which are more difficult to adequately characterise in the laboratory.

Based on the current analytical techniques, two biologicals produced by different manufacturing processes cannot be shown to be identical, but similar at best. For these reasons, the standard generic approach is scientifically not applicable to development of biosimilar products and additional non-clinical and clinical data are usually required.

Based on the comparability approach and when supported by state-of-the-art analytical systems, the comparability exercise at the quality level may allow a reduction of the non-clinical and clinical data requirements compared to a full dossier. This in turn, depends on the clinical experience with the substance class and will be a case by case approach.

The aim of the biosimilar approach is to demonstrate close similarity of the ‘biosimilar’ product in terms of quality, safety and efficacy to one chosen reference medicinal product, subsequently referring to the respective dossier.

## 1.2 Guiding Principles

Our primary objective is public health protection and patient safety. Biosimilars should meet the same standards of quality, safety and efficacy as any other registered biotechnological product. Regulation of biosimilars is based on state-of-the-art science. The regulatory paradigm for biosimilars is not intended to be ‘too onerous’, ‘too stringent or too loose’ rather we undertake a cautious and balanced approach and avoiding over-regulation.

And finally, our experience demonstrates that transparent and open dialogue with all relevant stakeholders is key to put in place a robust and adapted regulatory framework in this emerging field whilst creating and promoting a patient-oriented, innovative and favourable regulatory environment. In corollary this will further enhance and promote a dynamic and competitive knowledge-based economy for healthcare biotechnology in Malaysia.



### **1.3 Scope and application**

The concept of a biosimilar applies to biological drug submission in which the manufacturer would, based on demonstrated similarity to a reference medicinal product, rely in part on publicly available information from a previously approved biologic drug in order to present a reduced non-clinical and clinical package as part of submission.

The demonstration of similarity depends upon detailed and comprehensive product characterisation, therefore, information requirements outlined within this document apply to biologic drugs that contain, as the active substances, well characterised proteins derived through modern biotechnological methods such as recombinant DNA, into microbial or cell culture.

Conversely, the biosimilar approach is more difficult to apply to other types of biologics which by their nature are more complex, more difficult to characterise or to those for which little clinical regulatory experience has been gained so far. Therefore, it does not cover complex biologics such as blood-derived products, vaccines, immunologicals and gene and cell therapy products.

Whether a product would be acceptable using the biosimilar paradigm depends on the state-of-the-art of analytical procedures, the manufacturing process employed, as well as clinical and regulatory experiences.

### **1.4 Policy statements**

The following policy statements outline the fundamental concepts and principles constituting the basis of the regulatory framework for biosimilars:

- 1.4.1** The principles within the existing regulatory framework for biologics, biotechnology drugs and generic pharmaceutical drugs shall be the basis of the regulatory framework for biosimilars.
- 1.4.2** In implementing this guidance document, all the relevant Guidelines on biological products containing biotechnology-derived proteins as active substance and the Guidelines on similar biological medicinal products (also known as biosimilars), will be used as the basis for defining the registration requirements and/or process for registration of biosimilars in Malaysia. ( See 1.6 )
- 1.4.3** Biosimilars are not 'generic biologics/biogenerics'. Thus, the classic generic paradigm (i.e demonstration of bioequivalence of the generic drug with the reference product is usually appropriate to infer therapeutic equivalence) and many characteristics associated with approval process used for generic drugs do not apply to biosimilars.

- 1.4.4** Approval of a product through the biosimilar pathway is not an indication that the biosimilar may be automatically substituted with its reference product. The decision for substitutability with the reference product shall be based on science and clinical data.
- 1.4.5** A biosimilar product cannot be used as a reference product by another manufacturer because a reference product has to be approved on the basis of a complete/full quality and clinical data package.
- 1.4.6** Eligibility for a biosimilar pathway hinges on the ability to demonstrate similarity to a reference product. Product employing clearly different approaches to manufacture than the reference product (for example use of transgenic organisms versus cell culture) will not be eligible for the regulatory pathway for biosimilars.
- 1.4.7** The manufacturer must conduct a direct and extensive comparability exercise between its product and the reference product, in order to demonstrate that the two products have a similar profile in terms of quality, safety and efficacy. Only one reference product is allowed throughout this exercise. The rationale for the choice of reference product should be provided by the manufacturer to the NRA.
- 1.4.8** Non-clinical and clinical requirements outlined for biosimilar submission in this guidance document are applicable to biosimilars that have demonstrated to be similar to the reference product, based on results of the comparability exercises from chemistry, manufacturing and control (CMC) perspectives. When similarity of a biosimilar cannot be adequately established, the submission of such a product should be as a stand-alone' biotechnological product with complete non-clinical and clinical data.
- 1.4.9** Non-clinical and clinical issues of specific products are further elaborated in the Committee for Medicinal Products for Human Use (CHMP) product-class specific guidelines which appears as Annexes to the general non-clinical and clinical guidelines for biosimilar.
- 1.4.10** It should be recognised that there maybe subtle differences between biosimilars from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use have been established. Therefore, in order to support pharmacovigilance monitoring, the specific biosimilar given to patient should be clearly identified.
- 1.4.11** It was acknowledged that although International Non-proprietary Names (INNs) served as a useful tool in worldwide pharmacovigilance, for biologicals they could not be relied upon as the only means of product identification, nor as an indicator of the interchangeability of biologicals in

particular biosimilars.

**1.4.12** For a biosimilar manufacturer from countries that is not from Pharmaceutical Inspection Convention/Scheme (PIC/S) Member Countries or from the 8 Reference Countries, a Good Manufacturing Practice (GMP) on-site audit of the manufacturing facilities is required.

**1.5 Definitions ( Refer to APPENDIX IV : Glossary of terms )**

**1.6 Scientific Guidelines applicable to all biosimilar products:**

Committee for Medicinal Product for Human Use (CHMP) Guidelines are available at the following websites EMEA: <http://www.emea.europa.eu> and International Conference of Harmonisation (ICH) Guidelines: <http://www.ich.org>

**1.6.1 Guidelines on Biological products containing biotechnology-derived proteins as active substance**

While developing a biosimilar product and carrying out the comparability exercise to demonstrate that the product is similar to the reference medicinal product, some existing biotechnological product guidelines may be relevant and should therefore be taken into account. For example:

- CPMP/BWP/328/99 Development Pharmaceuticals for Biotechnological and Biological Products – Annex to Note of Guidance on Development Pharmaceuticals (CPMP/QWP/155/96)
- Topic Q5A, Step 4 Note for Guidance on Quality of Biotechnological Products: Viral safety evaluation of Biotechnological Products derived from Cell Lines of Human or Animal Origin (CPMP/ICH/295/95)
- Topic Q5B Note for Guidance on Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products. (CPMP/ICH/139/95)
- Topic Q5C, Step 4 Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (CPMP/ICH/138/95)
- Topic Q5D, Step 4 Note for Guidance on Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (CPMP/ICH/294/95)

- Topic Q5E, Step 4 Note for Guidance on Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (CPMP/ICH/5721/103)
- Topic Q6B, Step 4 Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (CPMP/ICH/365/96)
- Topic S6, Step 4 Note for Preclinical Safety Evaluation of Biotechnology-Derived Products (CPMP/ICH/302/95)

### **1.6.2 Guidelines on similar biological medicinal products ( also known as “ Biosimilar Guidelines “ )**

It should be noted that the CHMP has or may develop additional guidance documents addressing both the quality, non-clinical and clinical aspects for the development of biosimilars. Product-class specific documents on non-clinical and clinical studies to be conducted for the development of defined biosimilar product will be made progressively available.

- Guideline on similar biological medicinal products (EMA/CHMP/437/04)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Quality issues (EMA/CHMP/BWP/49348/2005)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues (EMA/CHMP/42832/2005)
- Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues - Guidance on similar medicinal products containing recombinant human soluble insulin (EMA/CHMP/32775/2005)
- Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues - Guidance on similar medicinal products containing somatropin (EMA/CHMP/94528/2005)
- Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues - Guidance on similar medicinal products containing recombinant erythropoietins (EMA/CHMP/94526/2005)

- Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: Non-clinical and Clinical issues - Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor. (EMA/CHMP/31329/2005)
- Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (EMA/CHMP/14327/2006)
- Guideline on Risk Management Systems for Medicinal Products for human Use (EMA/CHMP/96268/2005)

### **1.7 Harmonisation with other international regulators**

It is National Pharmaceutical Control Bureau's (NPCB) intention to harmonise as much as possible with other competent regulators and international organisations such as World Health Organisation (WHO) and the International Conference of Harmonisation (ICH). It would be expected that guidance on scientific principles that should be involved in evaluating biosimilars would help harmonise requirements worldwide and lead to greater ease and speed of approval and greater assurance of the quality, safety and efficacy of these products worldwide.

## **2.0 GUIDANCE FOR IMPLEMENTATION**

### **2.1 General**

Biosimilars can be approved based in part on an exercise to demonstrate similarity to an already approved reference product. The same reference product should be used throughout the comparability program in order to generate coherent data and conclusions. Comparative quality, non-clinical and clinical studies are needed to substantiate the similarity of structure/composition, quality, safety and efficacy between the biosimilar and the reference product. The pharmaceutical form, strength and route of administration should be the same as that of the reference product. Any differences between the biosimilar and the reference product should be justified by appropriate studies on a case-by-case basis.

### **2.2 QUALITY GUIDELINES**

The quality part of a biosimilar, like all other biologics will comply with established scientific and regulatory standards.

A biosimilar product is derived from a separate and independent master cell bank, using independent manufacturing and control method, and should meet the same quality standards as required for innovator products. A full quality dossier is always required.

In addition the biosimilar manufacturer is required to submit extensive data focussed on the similarity, including comprehensive side-by-side physicochemical and biological characterisation of the biosimilar and the reference product.

The base requirement for a biosimilar is that it is demonstrated to be “highly similar” to the reference product. Due to the heterogenous nature of therapeutic proteins, the limitations of analytical techniques and the unpredictable nature of clinical consequences to structure/biophysical differences, it is not possible to define the exact degree of biophysical similarity that would be considered sufficiently similar to be regarded as biosimilar, and this has to be judged for each product independently.

Applicants should note that the comparability exercise for a biosimilar versus the reference product is an additional element to the requirements of the quality dossier and should be dealt with separately when presenting the data.

Information on the development studies conducted to establish the dosage form, the formulation, manufacturing process, stability study and container closure system including integrity to prevent microbial contamination and usage instructions should be documented.

### **2.2.1 Comparability exercise considerations:**

- The goal of comparability exercise is to ascertain if the biosimilar and the reference products are similar in terms of quality, safety and efficacy.
- Comparability program/exercise to demonstrate similarity should involve all aspects of development, full analytical comparability of quality, and abridged studies for the non-clinical and clinical components
- The same reference product to be used throughout the comparability program.
- Comparability with the chosen reference product should be addressed for both the active substance and drug product.
- It is not expected that the quality attributes in the biosimilar and the reference product will be identical. For example, minor structural differences in the active substance such as variability in post-translational modifications may be acceptable, however, should be justified.
- Quality differences may impact the amount of non-clinical and clinical data needed, and will be a case by case approach.

- If the reference drug substance used for characterisation is isolated from a formulated reference drug product additional studies should be carried out to demonstrate that the isolation process does not affect the important attributes of the drug substance/moiety.

### **2.2.2 Manufacturing process considerations:**

- The biosimilar product is defined by its own specific manufacturing process for both active substance and finished product.
- The process should be developed and optimised taking into account state-of-the-art science and technology on manufacturing processes and consequences on product characteristics.
- A well-defined manufacturing process with its associated process controls assures that an acceptable product is produced on a consistent basis.
- A separate comparability exercise, as described in ICH Q5E, should be conducted whenever change is introduced into the manufacturing process during development.

### **2.2.3 Reference product considerations:**

- Appropriate comparative tests at the level of the isolated active substance from the formulated reference product are generally needed, except in some cases when quality attributes of the active substance can be tested on the finished product.
- The manufacturer should demonstrate that the active substance used in the comparability studies is 'representative of the active substance' of the reference product.
- Comparisons of the active substance in the biosimilar product made against public domain information e.g pharmacopoeial monographs are not sufficient to demonstrate similarity. Reference standards are not appropriate for use as a reference product.
- The same reference product should be used for all three parts of the dossier (i.e Quality, Safety and Efficacy)
- The chosen reference product should have a suitable duration and volume of marketed use such that the demonstration of similarity will bring into relevance a substantial body of acceptable data dealing with safety and efficacy.
- The brand name, pharmaceutical form, formulation and strength of the reference product used in the comparability exercise should be clearly identified.
- The shelf life of the reference product and its effect on the quality profile adequately addressed, where appropriate.

#### 2.2.4 Analytical procedure/techniques considerations:

- Extensive state-of-the-art analytical methods should be applied to maximise the potential for detecting “slight differences” in all relevant quality attributes.
- Methods used in both the characterisation studies and comparability studies should be appropriately qualified and validated [as in ICH Q2(R1)]
- If available, standards and international reference materials [e.g. from European Pharmacopeia (Ph.Eur), WHO etc.] should be used for method qualification and validation.

#### 2.2.5 Characterisations considerations:

- Characterisations of a biotechnological/biological product by appropriate techniques, as described in ICH Q6B, includes the determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity.
- Key points in the conduct of characterisation program/exercise:
  - Physicochemical properties: determination of composition, physical properties and should consider the concept of the desired product (and its variants) as defined in ICH Q6B. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered and properly identified.
  - Biological activity: include an assessment the biological properties towards confirmation of product quality attributes that are useful for characterisation and batch analysis, and in some cases, serve as a link to clinical activity. Limitations of biological assays could prevent detection of differences. A set of relevant functional assays should be considered to evaluate the range of activities.
  - Immunochemical properties: When immunochemical properties are part of characterisation, the manufacturer should confirm that the biosimilar product is comparable to the reference product in terms of specific properties.
  - Purity, impurities and contaminants: Should be assessed both qualitatively and quantitatively using state-of-the-art technologies and firm conclusion on the purity and impurity profiles be made.
- A complete side-by-side characterisations is generally warranted to directly compare the biosimilar and the reference product. However, additional characterisations may be indicated in some cases.
- Accelerated stability studies of the reference and of the biosimilar product can be used to further define and compare the degradation pathways/stability profiles.



- Process-related impurities are expected, but their impact should be confirmed by appropriate studies (including non-clinical and/or clinical studies)
- Measurement of quality attributes in characterisation studies does not necessarily entail the use of validated assays, but the assay should be scientifically sound and provide results that are reliable. Those methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate

#### **2.2.6 Setting specifications:**

- The analytical procedures chosen to define drug substance or drug product specifications alone are not considered adequate to assess product differences since they are chosen to confirm the routine quality of the product rather than to fully characterise it. The manufacturer should confirm that the specifications chosen are appropriate to ensure product quality.
- Specification limits: should not be wider than the range of variability of the reference product.

#### **2.2.7 Stability considerations:**

- Proteins are frequently sensitive to changes, such as those made to buffer composition, processing and holding conditions, and the use of organic solvents.
- Accelerated and stress stability studies are useful tools to establish degradation profiles and can therefore contribute to a direct comparison of biosimilar and the reference product. Appropriate studies should be considered to confirm that storage conditions and controls are selected.
- ICH Q5C and Q 1A(R2) should be consulted to determine the conditions for stability studies that provide relevant data to be compared before and after a change.
- For a biosimilar approach, it would be worth comparing a biosimilar with reference product by accelerated stability studies as these studies at elevated temperature may provide complementary supporting evidence for the comparable degradation profile

## 2.3 NON-CLINICAL AND CLINICAL GUIDELINES

### 2.3.1 General

The information in this section provides only general guidance on non-clinical and clinical data requirements for biosimilars. The non-clinical studies should be conducted prior to the initiation of any clinical studies. These studies should be comparative and aim to detect differences between the biosimilar and the reference product.

The requirements for the drug classes (for example: insulin, growth hormone) may vary. The requirements may also vary depending on various clinical parameters such as therapeutic index, the type and number of indications applied. Efficacy and safety for each indication will either have to be demonstrated or an extrapolation from one indication to another justified.

The final biosimilar product (using the final manufacturing process) should be used for non-clinical and clinical studies. Clinical comparability is done in stages, much like a traditional program.

Proposed indications for biosimilar must be identical or within the scope of indications granted for the reference product. In case the reference product has more than one therapeutic indication, the efficacy and safety of the biosimilar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference product, but this is not automatic.

The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy studies. The section on clinical safety and pharmacovigilance addresses clinical safety studies as well as the risk of management plan with special emphasis on studying immunogenicity of the biosimilar.

### 2.3.2 Non-clinical requirements

- Biosimilars should undergo appropriate non-clinical testing sufficient to justify the conduct of clinical studies in healthy volunteers or patients. These studies should be comparative and aim to detect differences between the biosimilar and the reference product and not just response *per se*.
- Ongoing consideration should be given to the use of emerging technologies (For e.g *In vitro* techniques such as e.g 'real-time' binding assays may prove useful. *In vivo*, the developing genomic/proteomic

microarray sciences may, in the future, present opportunities to detect minor changes in biological response to pharmacologically active substances)

- *In vitro studies:*
  - Receptor-binding studies or cell-based assay (e.g cell-proliferation assay) should be conducted
- *In vivo studies:*
  - Animal pharmacodynamic study where appropriate, relevant to clinical use
  - At least one repeat-dose toxicity study, including toxicokinetic measurements, should be conducted in relevant species.
  - Relevant safety observations (for e.g local tolerance) can be made during the same toxicity study.
- The rationale for request of antibody measurements in the context of the repeat dose toxicity study :
  - Generally, the predictive value of animal models for immunogenicity in humans is considered low. Nevertheless, antibody measurements (e.g antibody titres, neutralising capacity, cross reactivity) as part of repeated dose toxicity studies is required to aid in the interpretation of the toxicokinetic data and to help assess, as part of the comparability exercise, if structural differences exist between the biosimilar and the reference product.
- Other toxicological studies, including safety pharmacology, reproductive toxicology, mutagenicity and carcinogenicity studies are not required for biosimilar unless warranted by the results from repeated toxicological studies.

( *See also Appendix III* )

### 2.3.3 Clinical requirements

#### 2.3.3.1 Pharmacokinetic (PK) studies

- Comparative pharmacokinetic studies should be conducted to demonstrate the similarities in pharmacokinetic (PK) characteristics between biosimilar and the reference product.
- If appropriate from an ethical point of view, healthy volunteers will in most cases represent a sufficiently sensitive and homologous model for such comparative PK studies.
- Choice of designs must be justified and should consider factors such as clearance and terminal half-life, linearity of PK parameters, where applicable the endogenous level and diurnal variations of the protein under study, production of neutralizing antibody, conditions and diseases to be treated.

- The acceptance range/equivalence margin to conclude clinical comparability should be defined prior to the initiation of the study, taking into consideration known PK parameters and their variations, assay methodologies, safety and efficacy of the reference product.
- Other PK studies such as interaction studies or other special populations (e.g children, elderly, patients with renal or hepatic insufficiency) are usually not required.

### **2.3.3.2 Pharmacodynamic (PD) studies**

Parameters should be clinically relevant or a surrogate marker which is clinically validated. The PD study may be combined with a PK study and the PK/PD relationship can be characterised. PD studies should be comparative in nature.

### **2.3.3.3 Confirmatory Pharmacokinetic/Pharmacodynamic (PK/PD) studies**

Comparative PK/PD studies may be sufficient to demonstrate comparable clinical efficacy, provided all the followings are met (however, cases when approval on the basis of PK/PD data might be acceptable are highly limited):

- PK and PD properties of the reference product are well characterised
- Sufficient knowledge of PD parameters is available
- At least one PD marker is accepted as surrogate marker for efficacy
- Dose response is sufficiently characterised (ICH E10)
- Equivalence margin is pre-defined and appropriately justified.

### **2.3.3.4 Clinical efficacy trials**

- Comparative clinical trials (head-to-head adequately powered, randomised, parallel group clinical trials, so-called “equivalence trials”) are required to demonstrate the similarity in efficacy and safety profiles between biosimilar and the reference product. The design of the studies is important. Assay sensitivity must be ensured (ICH E10)
- Equivalence margins should be pre-specified, adequately justified on clinical grounds.
- Equivalent rather than non-inferior efficacy should be shown in order for the biosimilar to adopt the posology of the reference

product and to open the possibility of extrapolation to other indications, which may include different dosages.

#### **2.3.3.5 Clinical safety and Immunogenicity**

- The safety of biosimilar should be demonstrated to be similar to the reference product in terms of nature, seriousness and frequency of adverse events. Thus data from sufficient number of patients and sufficient study duration with sufficient statistical power to detect major safety differences are needed.
- For products intended for administration for longer than 6 months, the size of the safety database should typically conform with the recommendations of ICH E1 on the extent of population exposure to assess clinical safety.
- Data from pre-approval studies are insufficient to identify all differences in safety. Therefore, safety monitoring on an ongoing basis after approval including continued benefit-risk assessment is mandatory.
- A written rationale on the strategy for testing immunogenicity should be provided. State-of-the-art methods should be used, validated and able to characterise antibody content (concentration or titre), neutralising antibody and cross-reactivity.
- Special attention should be paid to the possibility that the immune response seriously affects the endogenous protein and its unique biological function.

#### **2.3.3.6 Pharmacovigilance Plan/Risk Management Plan (RMP)**

- Any post-market Risk Management Plan (RMP) should include detailed information of a systematic testing plan for monitoring immunogenicity of the biosimilar post-market.
- The RMP should include:
  - Risk Identification and characterisation (e.g case definitions, antibody assays);
  - Risk Monitoring (e.g specific framework to associate risk with product);
  - Risk Minimisation and Mitigation strategies (e.g plans to restrict to intravenous use where necessary, actions proposed in response to detected risk etc.);
  - Risk communication (e.g minimising and mitigation messages for patients and physicians)

- Monitoring activities to ensure effectiveness of risk minimisation.

### **3.0 POST MARKET REQUIREMENTS**

- The pharmacovigilance plan must be approved prior to approval of product and the system must be in place to conduct monitoring.
- The pharmacovigilance plan should be designed to monitor and detect both known inherent safety concerns and potentially unknown safety problems that may have resulted from the impurity profiles of a biosimilar.
- The pharmacovigilance, as part of a comprehensive RMP, should include regular testing for consistent manufacturing of the biosimilar.
- The pharmacovigilance plan should be able to distinguish between and tracking different products and manufacturers of products in the same class of medicinal products (e.g epoetins, insulins, interferons). Such capability is essential to help ensure adverse events are properly attributed to the relevant medicinal product (i.e traceability)
- Traceability of the product should involve product identification defined in terms of product name, brand name, pharmaceutical form, formulation, strength, manufacturer's name and batch number(s).
- Periodic Safety Update Reports (PSURs) of biosimilars should be submitted and evaluation of benefit/risk of the biosimilar post-market should be discussed. Such systems should include provisions for passive pharmacovigilance and active evaluations such as registries and post marketing clinical studies.

### **4.0 ORGANISATION OF DATA / DOSSIER**

As regards the amount/kind of data requirements for a biosimilar application, the “one size fits all” approach cannot be applied. This is due to the wide spectrum of molecular complexity among the various products concerned. Thus, the requirements to demonstrate safety and efficacy of a biosimilar are essentially product class-specific.

The data for submission are organised according to the ASEAN Common Technical Dossier (ACTD), with full quality data plus comparability exercise and abridged studies of the non-clinical and clinical components.

The biosimilar approach requires a thorough comparability exercise to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the biosimilar product and the chosen reference product. In other words, the quality data need to be supplemented by a new element – the ‘comparability exercise’.

The demonstration of similarity at the quality level may allow a reduction of the non-clinical and clinical data requirement compared to a full dossier. Demonstration of similarity may also allow extrapolation of efficacy and safety data to other indications of the reference product.

## **5.0 INTERCHANGEABILITY AND SUBSTITUTION**

Biosimilars are not generic products and cannot be identical to their reference products. Further, the formulations may be different and these can have profound effect on their clinical behaviour. In addition, biosimilars do not necessarily have the same indications or clinical use as the reference products. Therefore, given current science, they cannot be considered interchangeable with the reference product or products of the same class. Automatic substitution (i.e the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) and active substance-based prescription cannot apply to biologicals, including biosimilars. Such an approach ensures that treating physicians can make informed decisions about treatments in the interest of patients' safety.

## **6.0 NAME OF PRODUCTS**

In order to facilitate effective pharmacovigilance monitoring and tracing of adverse safety events and to prevent inappropriate substitution, the specific medicinal product (innovator or biosimilar) prescribed by the treating physician and dispensed to the patient should be clearly identified. Therefore, all biosimilars should be distinguishable by name i.e assign a brand name explicitly, using names that are not suggestive towards the originator nor towards other biosimilars.

### **Note:**

In 2006, the WHO Expert Committee on INNs agreed that the INN system should not be altered to reflect regulatory processes associated with the approval of biosimilar. Since INNs are based on information concerning the molecular characteristics and pharmacological class of a product, it was decided that no distinctive INN designation should be used to indicate a biosimilar. Instead, it was proposed that INN policy for naming a biosimilar be the same as that for innovator biologicals. However, there was a need to explain clearly to stakeholders the scientific basis for assigning INNs and their purpose, as well as limitations of this nomenclature for biologicals.

Therefore, for pharmacovigilance purposes, biological product identification should include in addition to the INN, other indicators such as the country of origin, manufacturer's name and batch number(s).

## **7.0 LABELING / PACKAGE INSERT**

The labeling of biosimilars should provide transparent information to healthcare professionals and patients on issues that are relevant to the safe and effective use of the medicinal product.

It is expected that the labeling of biosimilar meet the following criteria:

- A clear indication that the medicine is a biosimilar of a specific reference product.
- The invented name, common or scientific name and the manufacturer's name
- Clinical data for the biosimilar describing the clinical similarity (i.e safety and efficacy) to the reference product and in which indication(s)
- Interchangeability and substitution advice – should clearly and prominently state that the biosimilar is not interchangeable or substitutable with the reference product.

## **8.0 APPENDICES**

**8.1** Appendix I (Relevant NPCB Guidance Documents) :  
<http://www.bpfk.gov.my>

**8.2** Appendix II (Abbreviations and Acronyms)

**8.3** Appendix III (Synopsis of Non-Clinical Study Program for Different Types of Marketing Authorisation Application)

**8.4** Appendix IV (Glossary of terms)



**APPENDIX I:**

**Relevant NPCB Guidance Documents : <http://www.bpfk.gov.my>**

1. Drug Registration Guidance Document March 2008 Revision
2. Guideline for Submission of Analytical Method Validation Documents
3. Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies September 2000
4. Guidance for Application for Registration of Biotechnology/Biological Products December 2002
5. Malaysian Guidelines on Good Clinical Practice 2<sup>nd</sup> Edition 2004
6. Guidelines for Application for Variation of Registered Products June 2003
7. Guidance on GMP Audit of A Foreign Manufacturer January 2008 Draft 5.2
8. Guidelines for Application of Clinical Trial Import Licence and Clinical Trial Exemption in Malaysia 2004
9. Malaysian Guidelines For The Adverse Drug Reactions Reporting and Monitoring 2002
10. ASEAN Guidance on ACTD, September 2002

## **APPENDIX II:**

### **Abbreviations and Acronyms**

ACTD	ASEAN Common Technical Dossier
BWP	Biologics Working Party
CMC	Chemistry, Manufacturing and Controls
CHMP	Committee for Medicinal Products for Human Use
CDCR	Control of Drugs and Cosmetic Regulations
DNA	Deoxyribonucleic Acid
EU	European Union
EMA	European Medicines Agency
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
INN	International Non-proprietary Names
NCE	New Chemical Entity
NRA	National Control Authority
NPCB	National Pharmaceutical Control Bureau
PK/PD	Pharmacokinetic/Pharmacodynamic
Ph Eur	European Pharmacopeia
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PSUR	Periodic Safety Update Reports
QWP	Quality Working Party
RMP	Risk Management Plan
WHO	World Health Organisation

**APPENDIX III:**

**APPENDIX III: Non-clinical study program for different types of Marketing Authorisation Application**

	Chemical Medicinal Products		Biological Medicinal Products	
	New Chemical Entity (NCE)	Generic	New Recombinant Protein	Biosimilar
<b>PHARMACOLOGY</b>				
PD	+	-	+	+
Safety pharmacology	+	-	+	-
Pharmacodynamic drug interactions	+	-	-	-
<b>PHARMACOKINETICS</b>	+	-	+	-***
<b>TOXICOLOGY</b>				
Acute toxicity	+	-	+	-
Repeat dose toxicity	+	-	+*	+*
Genotoxicity	+	-	(+)	-
Carcinogenicity	(+)	-	(+)	-
Local tolerance	(+)	-	+**	+**
Antigenicity/ immunogenicity	+	-	+	-***
Reproductive and developmental toxicity	+	-	+	-

\* Including toxicokinetics and antibody measurements

\*\* If feasible, part of repeat dose toxicity

\*\*\* Repeat dose toxicity

( ) Only applicable in specific cases

## **APPENDIX IV:**

### **GLOSSARY OF TERMS**

#### **Antibody**

A spectrum of proteins of the immunoglobulin family that is produced, in the human (or animal) body, in response to an antigen (e.g., a virus or bacterium, or a foreign protein unknown to the body's immune system). Antibodies are able to combine with and neutralize the antigen, as well as to stimulate the immune system for defense reactions.

Retrieved from "<http://www.biology-online.org/dictionary/Antibody>" :This page was last modified at 21:16, October 3, 2005.

#### **Antigen**

A substance that reacts with the products of a specific immune response.

#### **API (Active Pharmaceutical Ingredient, or Drug Substance)**

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product by formulation with excipients and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

(ICH Q7A, [http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272\\_96843](http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272_96843))

#### **Biogeneric**

Term sometimes used for therapeutic protein drugs similar to an originator's product launched after patent expiry of the originator's product. However, since the standard generic approach for marketing authorization application (i.e., demonstration that it is the same active ingredient and of bioequivalence with a reference medicinal product), which is normally applied to chemically derived medicinal products, is scientifically not appropriate for biological/biotechnology-derived products due to their complexity, the term "biogeneric" does not describe these products in an appropriate way. Therefore, the regulatory authorities have chosen to describe these products as "similar biological medicinal products" (or "biosimilars") in the European Union, and "follow-on protein products" (or "follow-on biologics") in the U.S., respectively.

#### **Biologic (Biological medicinal product)**

Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. They often are at the forefront of biomedical research and may be used to treat a variety of medical conditions for which no other treatments are available.

(Taken from: <http://www.fda.gov/Cber/faq.htm#3>).

#### **Biosimilar (or similar biological medicinal product)**

A new biological medicinal product claimed to be "similar" to an already approved reference medicinal product, which is marketed by an independent applicant, subject to all applicable data protection periods and/or intellectual property rights in the originator product.. In Europe, the term "biosimilar" is used as a short designation for "similar biological medicinal

products". The requirements for the Marketing Authorization Applications for biosimilars are based on the demonstration of the similar nature of the two biological medicinal products (biosimilars versus reference product) and require comparative quality, non-clinical and clinical studies to demonstrate safety and efficacy.

For details, see <http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf>.

### **Biosimilar (or similar biological medicinal product)**

A new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well established, medicinal product.

(Malaysian Biosimilar Document)

### **Biotechnology**

A set of tools that employ living organism (or part of organism) to make or modify products, to improve plants and animals, or to develop microorganisms for specific uses.

or A collection of technologies that use living cells and/or biological molecules to solve problems or make useful products (<http://www.ncbiotech.org/biotech101/glossary.cfm>)

Accordingly, modern technology includes the use of the new genetic tools of recombinant DNA to make a new genetically modified organism.

### **Biotherapeutics**

Therapeutic biological products, some of which are produced by recombinant DNA technology

### **CMC (Chemistry, Manufacturing, and Control)**

The section of a submission dealing with the substance properties, manufacturing and quality control, intended for evaluating the provided information in the context of the current standards in chemical science and technology, and the current regulations.

### **Comparability**

A conclusion that a given product has highly similar quality attributes before and after manufacturing process changes, and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, non-clinical or clinical data might contribute to the conclusion. (ICH Q5E, <http://www.ich.org/LOB/media/MEDIA1196.pdf>)

### **Comparability**

Regarding "comparability" in this guidance document it is used as a scientific term. This is why "similarity" is not the central term for biosimilars. It is a general scientific approach, although the "comparability approach" of ICH Q5E for a single product is acknowledged.

In the case of a biosimilar product, additional non-clinical and clinical data are usually necessary for the demonstration of comparable efficacy and safety to the reference medicinal product.

### **Comparability Exercise**

The activities including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.

(ICH Q5E, <http://www.ich.org/LOB/media/MEDIA1196.pdf>)

### **Drug substance**

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological

activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. Also termed “active pharmaceutical ingredient” (API). (<http://www.fda.gov/CDER/guidance/4286fnl.htm>).

### **Drug product**

The dosage form of a medicinal product in the final immediate packaging intended for marketing.

(ICH Q1A, <http://www.ich.org/LOB/media/MEDIA419.pdf>).

### **Equivalent**

Equal or virtually identical in the parameter of interest. Small non-relevant differences may exist. Equivalent efficacy of two medicinal products means they have similar (no better or no worse) efficacy and any observed differences are of no clinical relevance.

### **Follow-on Biologic**

Term used to describe similar biological medicinal products (biosimilars) in the U.S.

### **Follow-on Protein Product**

Term used to describe similar biological medicinal products (biosimilars) in the U.S. The term follow-on protein products generally refers to protein and peptide products that are intended to be sufficiently similar to a product already approved or licensed to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product.

(Taken from: <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>).

### **Formulation**

Formulation is the process of devising a recipe or formula for a product, i.e. deciding what quantities of what ingredients/excipients should be added in what sequence, and what processing steps should be taken to provide the final product. This recipe is then termed a formula or a formulation.

(Adapted from: <http://en.wikipedia.org/wiki/Formulation>)

### **Generic medicine**

A generic medicine contains the same active ingredient as and is bioequivalent to an innovator prescription medicine and is marketed by an independent applicant, subject to all applicable data protection periods and/or intellectual property rights in the originator product.. Generic medicines can be approved by abbreviated regulatory procedures, such as under section 505(j) of the FD&C Act in the U.S., established through the 1984 Hatch-Waxman Amendments, or based on the concept of “essential similarity” as described in the European Community legislation. However, for complex drug substances such as proteins where “sameness” of the active ingredients cannot be demonstrated the generics approval pathways are considered inappropriate.

### **Glycoform**

A glycoform is defined as an isoform of a glycosylated protein with identical polypeptide sequence, but with different sugar (saccharide) structures attached to the sites of glycosylation by either post-translational or co-translational modification. Such differences in glycosylation may affect properties of the glycoprotein such as biological activity, half-life, receptor binding, etc.

### **Glycosylation**

Glycosylation is the process or result of enzyme-catalyzed addition of sugar residues

(saccharides) to proteins and lipids. The process is one of the principal co-translational and post-translational modification steps in the synthesis of membrane and secreted proteins.

### **ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)**

ICH is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

For more information, see <http://www.ich.org/>.

### **Immunogen**

Any substance that is recognized as “foreign” by the immune system in a (particular) higher organism and induces an immune response which may include the formation of antibodies and developing immunity, hypersensitivity to the antigen, and tolerance.

### **Immunogenicity**

The ability of a substance to trigger an immune response in a particular organism.

### **Impurity**

Any component present in the intermediate or API that is not the desired entity.

(Taken from: [http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272\\_96843](http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272_96843))

### **Impurity**

In drug substance : Any component of the new drug substance that is not the chemical entity defined as the new drug substance

(ICH Q3A, <http://www.ich.org/LOB/media/MEDIA422.pdf>)

In drug product : Any component of the new drug product that is not the drug substance or an excipient in the drug product.

(ICH Q3B, <http://www.ich.org/LOB/media/MEDIA421.pdf>)

### **In-process control (or: Process control)**

Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

(Taken from: ICH Q7A, [http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272\\_96843](http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272_96843))

### **Interchangeability**

A product is interchangeable with another if both products are approved for the same indication, and can be used for the said indication. For interchangeable products, one or the other can be used (prescribed) but these products can not be substituted with one another during a treatment period. Hence, interchangeability does not imply substitutability.

### **Isoform**

A protein isoform is a version of a protein with some small differences, e.g. a splice variant or the product of some posttranslational modification (such as glycosylation).

### **Originator product**

An originator product is defined as the product for which a marketing authorization is granted to a given marketing authorization holder (MAH) for a given active substance based upon a complete dossier.

(Taken from: [http://medagencies.org/mrfg/docs/rec/rec annexII.pdf](http://medagencies.org/mrfg/docs/rec/rec%20annexII.pdf))

### **Pegylation**

Pegylation is the covalent (chemical) attachment of polyethylene glycol (abbreviated PEG), a chemically inert and non-toxic polymer, to another substance or material, e.g. to a protein. In drug development, pegylation is an established method to improve on the pharmacokinetic profile of therapeutic compounds. Pegylation has been very successfully applied to the development of second-generation biotherapeutics, such as pegylated interferon-alpha.

### **Pharmacovigilance**

According to the WHO definition, pharmacovigilance is “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.” The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient populations and the number of patients exposed. In particular, during the early post-marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use.

(For details, see <http://www.emea.eu.int/pdfs/human/ich/571603en.pdf>)

### **Pre-clinical (non-clinical)**

During preclinical drug development (which precedes the clinical trials in patients), a sponsor evaluates the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing. Generally, genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. (Taken from:

<http://www.fda.gov/cder/handbook/preclin.htm>)

### **Reference product**

A medicinal product already approved/registered in Malaysia on the basis of a complete dossier (quality, safety and efficacy) chosen as a reference product by the biosimilar manufacturer. The chosen reference medicinal product should be used throughout the development program for quality, safety and efficacy studies during the development of a biosimilar product. Alternatively, a medicinal product registered in the reference countries (Australia, Canada, EU (via centralised procedure), United Kingdom, France, Japan, Sweden, Switzerland, USA) is considered acceptable.

### **Similarity**

If a company chooses to develop a new biological medicinal product claimed to be “similar” to a reference medicinal product, comparative studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product.

(eg. <http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf>)

### **Specification**

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.



“Conformance to specification” means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval. (ICH Q6B, <http://www.ich.org/LOB/media/MEDIA432.pdf>)

### **Structure (primary, secondary, tertiary, quaternary)**

Terms used to describe the two- and three-dimensional arrangement of the polypeptide chain in a protein. “Primary structure” is a synonym for the sequence of amino acid residues; the “secondary structure” is formally defined by hydrogen bonds between backbone amide groups (forming structure elements such as the  $\alpha$ -helix and the  $\beta$ -pleated sheet), whereas “tertiary structure” describes the protein’s overall shape, also known as its “fold”. The arrangement of multiple folded protein subunits which are assembled in a multi-subunit complex is called “quaternary structure”.

### **Substitution, generic**

Generic substitution is the dispensing of a different brand or an unbranded drug product for the drug product prescribed; i.e., the exact same chemical entity in the same dosage form but distributed by a different company.

(Taken from: World Medical Association Statement on Generic Drug Substitution, 1989/2005, see <http://www.wma.net/e/policy/d9.htm>)

### **Substitutability**

Two products are substitutable with each other if they can both be used in lieu of the other during the same treatment period. Substitutable products are interchangeable with each other. Cross-over studies are required to demonstrate substitutability.

### **Validation**

The process of demonstrating that the system (or process) under consideration meets in all respects the specification of that system or process. Also, the process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements. In the manufacturing of medicinal products, production processes, cleaning procedures, analytical methods, in-process control test procedures, and computerized systems all have to be validated according to the ICH guidelines for Good Manufacturing Practice.

(see <http://www.ich.org/LOB/media/MEDIA433.pdf>)

### **Well-characterized biologic**

A well-characterized biologic is “a chemical entity whose identity, purity, impurities, potency and quantity can be determined and controlled”. Most of these products are recombinant DNA-derived proteins or monoclonal antibodies. For DNA-derived proteins, determining identity requires establishing the primary and secondary structures, including amino acid sequence, disulfide linkages (if possible), and post-translational modifications such as glycosylation (the attachment of carbohydrate side chains to the protein). Monoclonal antibodies can be identified with “rigorous physicochemical and immunochemical assays”. Purity and impurities must be quantifiable, with impurities being identified if possible; the biological activity and the quantity must be measurable.

(see <http://pubs.acs.org/hotartcl/ac/96/nov/fda.html>)