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# Meeting Report

# WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products

## WHO Headquarters, Geneva,

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World Health Organization

* Disclaimer: This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.

## Abstract

This report reflects the discussion and conclusions of an informal consultation held on 19-20 April 2007 at the World Health Organization concerning the regulatory evaluation of therapeutic biological medicinal products. The objectives of this meeting were to discuss the current status of so-called "similar" biological medicinal products (biosimilars) and to review regulatory pathways and challenges in evaluating the quality, safety and efficacy of these products. Biosimilars are products that are subject to licensing with a reduced data package due to a proven 'similarity'.

The meeting was attended by experts in biotherapeutics from regulatory agencies, industry and academia representing sixteen countries worldwide. Dr. Elwyn Griffiths (Canada) acted as Chairman and Dr. James Robertson (UK) was the Rapporteur. The meeting strongly focused on the usage of biosimilars and the current regulatory situation in many different countries. The application of International Nonproprietary Names (INN) to biosimilars, their potential immunogenicity, and WHO international standards and reference materials were also discussed, alongside presentations from the innovator and generic manufacturing industries.

The consultation recognized the importance of the terminology as well as a definition of biosimilars for future considerations of these products. However, achieving a global consensus on the terminology for these new challenging products was not attempted at the Consultation, and it was decided that a future WHO working group should act on this issue as a next step. For purposes of this meeting report only, the term 'biosimilars' is temporarily used to refer to this category of products. It became clear that biotherapeutics authorized on the basis of a reduced data package are available and being used in some countries, with more appearing on the market. The existence of divergent approaches to the regulatory oversight of biosimilars in different countries revealed a need for defining regulatory expectations for these products at the global level. While many countries are following the guideline developed within the EU for quality aspects, discrepancies remain regarding the non-clinical and clinical studies of these products. The Consultation recommended that the WHO should develop a guideline in this area in order to provide a framework for the development of regulatory pathways for these products worldwide. For

this purpose, agreement on the scope, definition and terminology of these products was deemed necessary. The interchangeability and substitution of products were also flagged as areas in need of harmonization. A WHO working group should be established to develop a guideline that would promote global consensus on the regulation of biosimilars, assist in their registration and enhance the availability of safe and effective biosimilar products worldwide.

## 1. Introduction

Control of chronic diseases is a major challenge for public health systems in developed and developing countries. Biotherapeutic products have been successful in treating many life-threatening chronic diseases. However, the cost of innovative biotherapeutics has often been prohibitive, thereby limiting their use, particularly in developing countries. The expiration of the patents on many biotherapeutic products such as insulin, human growth hormone and erythropoietin is opening the door for licensing these products as biosimilars. This might contribute to increased access to these medicines at an affordable price. However, many Member States are uncertain how to regulate these products and requested assistance from WHO.

### *1.1 Opening remarks* Dr. David Wood

The meeting was opened by Dr. Wood, Coordinator of Quality, Safety and Standards Unit (QSS) of the Immunization, Vaccines and Biologicals Department (IVB), WHO. He outlined the WHO's constitutional responsibilities in the area of biological standardization. This essentially means developing, establishing and promoting norms and standards for biological products including biotherapeutics. He noted that WHO had supported science-based biotherapeutic products for many years by developing relevant guidelines on biological products derived from recombinant DNA technology[1,2] and establishing WHO reference materials for many cytokines/growth factors and endocrinological substances[3]. Also, he reported the advice from WHO oversight bodies, or consultation groups. For example, the International Conference of Drug Regulatory

Authorities (ICDRA) in 2006[4], noted that "Biosimilars are a reality in several countries and will be a major challenge for years to come. Global regulatory consensus and guidance is lacking"; meanwhile, the 56th Expert Committee on Biological Standardization[5] recommended that WHO should develop a consensus on the global needs, priorities and potential role for global standardization in the area of biotherapeutics. The WHO should facilitate the strengthening of technical capacity in National Regulatory Authorities (NRAs) for biological therapeutics and also collate information on substandard or counterfeit biological medicines for chronic diseases. Overall, Dr. Wood emphasized the benefits to be obtained from the development of a global consensus on future regulation of biotherapeutics.

### *1.2 INN current situation* Dr. Raffaella Balocco Mattavelli

Dr. Balocco Mattavelli (Quality Assurance and Safety; Medicine unit of Medicines Policy and Standards Department, WHO) introduced the WHO INN Program and explained the general policies of assigning INNs for biological and biotechnological substances. The INN program was initiated in 1950 and has operated since 1953. Its purpose is to assign nonproprietary names to pharmaceutical substances so that each would be recognized globally by a unique name. The INNs also form an essential part of the regulatory process in many countries where a nonproprietary name is required for licensing. Dr. Balocco Mattavelli explained that assigning INNs to biologically and biotechnologically derived medicinal products is more difficult to manage than chemical drugs. The biotechnology field is still expanding, not only in developed countries but also in developing regions of the world, with many new and innovative medicinal products reaching the clinical trial stage of development, including recently—as patents come to an end—the so-called biosimilar products. Emerging biosimilar products introduced challenges in defining nomenclature as well as in setting up regulatory practice. The issue of nomenclature for biosimilars was considered at the WHO consultation on September 4-5, 2006. As per the recommendation of that meeting[6], Dr. Balocco Mattavelli reported that these products do not require special consideration in terms of nomenclature .

However, the distinction between regulatory and nomenclature roles and responsibilities was emphasized.

### *1.3 Objectives of the meeting* Dr. Jeewon Joung

Dr. Joung (QSS IVB WHO) presented the outcomes of the survey conducted prior to this Consultation. The survey noted that many regulatory agencies as well as industry desired WHO guidance for biosimilar products, with the format of a WHO concept paper or general recommendations. Experts suggested a variety of terms for this type of product such as biosimilar products, subsequent entry biologicals, follow-on biologics, follow-on protein products and biogenerics. In the survey, it was found that defining criteria for proof of similarity was the major issue requiring guidance. For quality and non-clinical data, most noted that the relevant European Medicines Agency (EMEA) guidelines would be appropriate. For clinical studies, responses for proving clinical equivalence were varied. There were many comments about the selection criteria for the reference products (comparators) and the need for developing reference materials and associated collaborative studies.

## 2. Scientific basis of regulatory evaluation of biological therapeutics

### *2.1 Overall Issues* Professor Huub Schellekens

Professor Schellekens (Utrecht University, The Netherlands) reviewed general issues regarding biosimilars. Biologicals are produced under specific conditions but are still very sensitive to production parameters. Minor changes can have major impacts on biological activity. Biopharmaceutical manufacturing is complex and has many variables. Typically, more than 2000 tests are required in the process of manufacturing a biopharmaceutical while fewer than 100 product quality tests are required for small molecule drugs. The biological and clinical properties of biologics cannot at present be predicted fully by physico-chemical means. A key issue in the discussion of biosimilars is their potential immunogenicity. Most biopharmaceuticals induce antibodies. Foreign

therapeutic proteins such as streptokinase induce antibodies by a classical, vaccine-type, immune reaction while most therapeutic proteins which are human homologues like the interferon, interleukine-2 and others induce antibodies by breaking B-cell tolerance. Various factors are known to influence immunogenicity but impurities and aggregates are considered to be the main cause in breaking tolerance. Epoetin-related pure red cell aplasia (PRCA) was a key event concerning the safety of therapeutic recombinant proteins. In 2002, 13 such cases, all with antibodies associated with epoetin treatment were reported by Dr. N. Casadevall[7]. The product concerned, Eprex® had been safely used for many years before being associated with PRCA. Factors potentially contributing to the immunogenicity of Eprex® were formation of micelles associated with epoetin[8], silicon droplets in the prefilled syringes, leachates from rubber stoppers and/or mishandling. Lessons learned from the Eprex® incident are that biotherapeutics can induce severe side-effects even after years of safe use, but such side-effects cannot necessarily be predicted. Post marketing surveillance is generally deficient and companies cannot be a reliable source of this information. Dr. Schellekens concluded his talk by asserting that biosimilars will come, but that there are still a number of unanswered questions such as a scientific definition, naming, labelling, and the safety monitoring in terms of sensitivity, background data, and standardization. However, the issues raised for biosimilars have implications for biopharmaceuticals as a whole, and independent international evaluation of possible immune responses to recombinant proteins will be important.

### *2.2 Issues in clinical studies* Dr. Martina Weise

Dr Weise (Federal Institute for Drugs and Medical Devices, Germany) described the principles of the clinical comparability exercise of the EMEA guidelines for biosimilars and the issues in clinical studies, using the experience of two approved biosimilar somatropin-containing medicinal products and from scientific advice for biosimilar epoetins. Extrapolation of indications remains an on-going debate. If comparable efficacy and safety have been demonstrated for one indication, extrapolation to other indications of the reference product may be possible if a sensitive model has been used, if the

mechanisms of action and/or receptors are the same, and if immunogenicity has been sufficiently assessed with the model used and route of administration. Lessons learned from the first biosimilar somatropins authorized via the EMEA were that guidelines can be implemented with realistic requirements, all aspects of the comparability exercised are important (quality, safety, efficacy), the use of different host systems for the manufacture of the biosimilar and the reference product is in principle possible, the reference product must be approved in the EU, there should be no switch of the reference product during development, and impurities such as host cell derived protein may enhance an immune response. The risk management plan for biosimilar product is usually inherited from the reference product if it concerns class-effects or indication-related issues and, in addition, if it contains issues specific to the biosimilar product and identified during the review process, such as antibody testing in a larger patient cohort or for a longer period of time during the post marketing phase.

## 3. Existing regulatory directions and perspectives

A wide range of biosimilars was reported as being available in the countries represented at this meeting. Countries such as China, India, and South Korea reported a high number of licensed biosimilars within their existing regulatory framework. Examples of such products marketed in these countries include interleukins, interferons, erythropoietins, growth factors, hormones, enzymes and monoclonal antibodies. In contrast, there are fewer such products on the European market; nevertheless the EU has an advanced regulatory framework for biosimilar products. Regulatory oversight is under discussion in the USA, Canada, and Japan. The presentations revealed differences between countries in terms of the classification of products as biosimilars, and highlighted the need for a harmonized approach.

### **3.1 China** Dr. Wang Junzhi

Chinese regulations are in place to cope with biotherapeutics including biosimilars, and requirements and specifications already exist in the Chinese pharmacopoeia. The Chinese

NRA requires complete conformity in the characterization of biosimilar products with reference products. In clinical studies, it was emphasized that comparison based on pharmacokinetics (PK) and pharmacodynamics (PD) should be highly accurate and quantifiable; for example, an important basis for the evaluation of generic drugs within the Chinese system is the use of the same dose and delivery system as the reference products, and such considerations should be used for biosimilars. The Chinese NRA endorsed the development of WHO guidance for biosimilar products, and the speaker proposed that a series of related documents could be drafted such as technical requirements for individual products as well as general guidance.

### **3.2 India** Dr. Shri Parthajyoti Gogoi

In India, the terminology ‘biosimilars’ is not in use; they are called 'biogeneric products'. However, they are defined as new drugs and as such, the regulatory procedures are based on current approaches for new molecules/new drugs/biotech products. The first biogeneric product was approved in 1997 and for 10 years, significant benefit to patients was achieved with no major issues or adverse events in clinical practice. The Indian NRA is now developing specific quality related guidance and monographs for Granulocyte-Colony Stimulating Factor (G-CSF), erythropoietin and interferon alpha 2b. The Indian approval system is midway between that for pharmaceutical generics and new drug approval, and ensures quality, safety and efficacy as well as process consistency.

### **3.3 Iran** Dr. Majid Cheraghali

Dr. Cheraghali (IBTO, Iran) strongly supported the development of biogeneric products, speaking from the perspective of a developing country. He emphasized that biogeneric is not a new concept and some of the very complex biological products such as blood components, plasma derived medicines and vaccines have been used interchangeably for decades. Therefore, regulatory experience of these products may be used for the regulation of recombinant biogenerics. He noted that generic medicines mostly benefited developing countries and this might be repeated with biogenerics. Due to great progress

in knowledge of biotech medicines and considering that this type of medicine is prescribed in specialized health centers, biogenerics could be managed well and pharmacovigilance could be easily conducted. Safety issues of biogenerics and innovator's products should be the first priority for national medicine regulatory agencies. However, this should not be exaggerated or over-regulated, or the global availability of biogenerics may be adversely impacted. Dr. Cheraghali also described the status within Iran, which has requirements for the registration of biogenerics. Iran approaches these on a case-by-case basis and uses the brand generic names when registering.

### **3.4 EU/EMEA** Dr. Peter Richardson

The EU has legislation (2001/83, as amended) defining biosimilars and their regulatory process, and guidelines are also in place. The guidelines are composed of an overarching guideline on biosimilar products[9] and general guidelines on quality[10], non-clinical and clinical issues[11]. Product-specific guidelines are also available, detailing the non-clinical and clinical requirements in a number of areas (insulin, Granulocyte-Colony Stimulating Factor (G-CSF), somatropin, and erythropoietin)[12-15]. The EMEA currently applies its biosimilar policy to biotechnology-derived recombinant proteins; however, its application to other biologicals is not ruled out, although the ability to well characterize the active substance and product becomes critical. The EMEA is developing more product-specific guidelines for materials such as interferon alpha and low molecular weight heparin, and plans to update guidelines as new information becomes available.

Post-meeting note: since this consultation, three biosimilar epoetin alfa containing products have been approved in the EU.

### **3.5 USA** Dr. Keith Webber

In the USA, legal pathways exist for review and approval of some smaller, well characterized proteins such as human growth hormone and insulin, which are regulated under the Federal Food, Drug, & Cosmetic Act; however, for other biotherapeutics such

as interleukins and interferons, which are regulated under the Public Health Service Act (PHSA), there is currently no abbreviated authorization pathway. Proposed modifications to the PHSA are currently being debated in the US Congress. The Food and Drug Administration (FDA) has published a summary of previous assessments of follow-on protein products[16]. Guidance for industry is forth-coming and will address scientific considerations for safety and effectiveness, chemistry, manufacturing and control (CMC) issues, and immunogenicity.

### **3.6 Canada** Dr. Kwasi Nyarko

Canada also has no specific legislation in place and is currently developing a new regulatory framework for 'subsequent entry biologicals'. Dr. Nyarko (Health Canada, Canada) introduced this emerging policy direction. Regulation of subsequent entry biologicals will be based on existing frameworks for biologics, pharmaceuticals, and generic pharmaceuticals. Where appropriate, the principles and practices for generic pharmaceuticals will be applied to subsequent entry biologicals. However, the term, 'generic biologic' does not accurately define a biologic that will be approved through this new framework, so marketing authorization issued for a subsequent entry biological will not confer substitutability with the reference product. It is expected that the reference product (comparator) should usually be approved and marketed in Canada, but due to the small market size, the introduction of some flexibility in choice of reference product is under discussion.

### **3.7 Japan** Dr. Teruhide Yamaguchi

In Japan, the regulation of biosimilars currently follows the principle applied to changes in manufacture and comparability evaluation such as the International Conference on Harmonization (ICH) guideline Q5E, where quality attributes are highly similar and there is sufficient knowledge to indicate that any quality differences will not impact safety or efficacy. This category of product will not be called 'generic', but ‘follow-on biologicals’. Regulatory requirements for generic drugs exist in Japan, but, as in Canada, a new

regulatory framework and guideline for follow-on biologicals is currently under development.

### 3.8 Korea Dr. Yeowon Sohn

The Republic of Korea has a regulatory pathway for the approval of biosimilar products, but has no exact definition and criteria for them. A full data package of quality and non-clinical studies for these products is required, while simplified clinical study data which would be considered confirmatory are acceptable. Nevertheless, the Korean NRA does not grant an extrapolation of the clinical indication of biosimilars. Recently, Korea adopted the INN when authorizing medicinal products and the non-proprietary names of biosimilars will follow the INN of the innovator product. However, there are inconsistencies in the current naming schemes. Korea believes the INN scheme should be clarified and the descriptions for biologicals standardized.

## 4. An example illustrating challenges that require regulatory support : Erythropoietin (EPO)

### 4.1 Innovator's point of view Dr. Andrew Fox

Dr. Fox (Amgen, UK) reported on the comparison of the biophysical characteristics of their own innovator product Epogen® to those of erythropoietins from a variety of manufacturers worldwide, and concluded that as a consequence of the use of different cell lines and manufacturing processes, variability in biophysical characteristics do exist. Product differences detected by physico-chemical tests cannot be correlated directly to different clinical characteristics; therefore, the need for clinical efficacy and safety data with biosimilar products should be stressed. He emphasized the importance of demonstrating clinical equivalence to a reference product in terms of both safety and efficacy, and the necessity of 'pre-approval immunogenicity testing'. Different products present different risks of immunogenicity even though they may be similar versions of a given product, such as interferon beta or interferon alpha. Pre-approval testing should

exclude a gross incidence of antibody formation before approval; their presence may be indicative of a quality and clinical problem.

### 4.2 Generic Industry's point of view Dr. Martin Schiestl

Dr. Schiestl (Sandoz, Austria) explained that biosimilar development is based on a complete stand-alone development of the production process taking all relevant guidelines into account. He claimed that current analytical technologies enable the complete physicochemical and biological characterization of erythropoietin required for biosimilar development. Any difference with regard to reference product parameters has to be justified and this can be confirmed by preclinical and clinical data. He asserted that claims of epoetin-related side effects such as hypertension and thrombosis are known exaggerated pharmacodynamic effects. Possible angiogenic and tumor promoting effects should be discussed. Enhanced development of pure red cell aplasia was related to a formulation change of Eprex® – according to announcements of the innovator – and probably due to high levels of leachates from the primary packaging material. Regardless of whether or not leachates caused the problem, this is an example of a quality issue, which has to be considered for both innovative and biosimilar product development.

## 5. Reference standards for biotherapeutics

### 5.1 Issues regarding the reference materials Dr. Adrian Bristow

Dr. Bristow (NIBSC, UK) highlighted the issues surrounding reference materials, using erythropoietin as an exemplar because erythropoietin is a major biotech product, and with the expiry of its patent, it is already the subject of biosimilar activity. Both a WHO International Standard and a European Pharmacopoeia reference substance exist for erythropoietin, as well as European pharmacopoeia specifications, in which the potency, identity and even purity are heavily dependent on comparative tests requiring the use of a reference material. The WHO International Standard is the primary reference material, defining the international unit for a bioassay. However, it contains a limited (less than 1

μg) quantity of material per ampoule and is not suitable as a physico-chemical analytical standard. The European Pharmacopoeia reference substance is a secondary standard and is of sufficient quantity for biological and physico-chemical method standardization; however, it is applicable to the drug substance and not the drug product, and this as well as other features limit the usefulness of the European Pharmacopoeia reference substance. Therefore, significant limitations appear to restrict the utility of both types of reference material in promoting the development of biosimilars. Dr. Bristow noted that to extend the provision of the current international reference material, to develop reference material-independent analytical methods and to develop analytical methods aimed at the level of formulated product, would be the way forward to solve these issues. However, transfer of unitage from WHO standards to innovator products and to biosimilar preparations requires careful analysis.

### 5.2 Low molecular heparins - Lesson Learned Dr. Elaine Gray

Low molecular weight heparin is a heterogeneous polysaccharide of 3000-5000 daltons molecular weight range and prepared from unfractionated heparin. It is still debatable as to whether the different commercial preparations of low molecular weight heparin differ with respect to safety and efficacy for the same clinical indication. Even with this diversity, low molecular weight heparin is considered to be a biosimilar and EMEA guidance for these products are in the process of being drafted, including *in vitro* characterization based on monograph specification, pharmacodynamics, immunogenicity, bleeding risk and bioequivalence. But Dr. Gray (NIBSC, UK) claimed that assessing low molecular weight heparin biosimilars is very difficult because their molecular weight and distribution are varied, and their *in vitro* characterization such as anti-Xa activity and the anti-Xa:anti-IIa ratio are usually different between innovator products and biosimilar products. She pointed out that *in vitro* characterization based on pharmacopoeial monograph specification may not be enough, and biosimilar products should have tighter limits for comparison. Standards are available for anticoagulant activity and for molecular weight calibration, but additional reference materials such as a reference panel of low molecular weight heparins for nuclear magnetic resonance will be useful.

## 6. Industry perspectives on the regulation of biosimilars

### 6.1 Innovator's point of view Dr. Jacques Mascaro

Dr. Mascaro (Hoffman La Roche, Switzerland) proposed parameters for what may be considered as important in the regulatory evaluation of biosimilars. He claimed that a pure comparability approach is not applicable to products made by independently developed processes because a biosimilar cannot be strictly identical to the reference product. Public standard material or commercial products are not suitable to establish evidence for quality comparison, and quality assessment alone cannot guide non-clinical and clinical similarity assessment. It is important for a regulatory framework to ensure that safe and efficacious biosimilar products with consistent quality are placed on the market. Dr. Mascaro pointed out some of the key factors necessary to maintain these principles, such as requiring sufficient clinical data, determining the benefit/risk profile of the biosimilar in comparison to the reference product, establishing stronger risk management plans, and identifying all biosimilars on the market for pharmacovigilance purposes. There is no harmonized worldwide regulatory system for biosimilar products. The EU is currently the most advanced region in terms of having a developed regulatory pathway for these products, but in many other regions, national regulatory plans are limited or in some cases, absent. He suggested that when developing a global guideline on biosimilars, the use of the existing experience, particularly the increasing experience in the EU, could be considered as a model to avoid the duplication of efforts. At the same time, a regulatory framework needs to maintain incentives for innovation.

### 6.2 Generic's point of view Dr. Martin Schiestl

Dr. Shiestl (Sandoz, Austria) presented the generic industry's position on the regulation of biosimilars. The development of a biosimilar product is targeted to match the reference medicinal product through the application of state-of-the-art science and technology in head-to-head studies. The criteria for the comparison of the biosimilar candidate and the

reference product are based on an understanding of the batch-to-batch variability of the reference medicinal product, on classification of the product variants into product-related substances or impurities, and on an understanding of the relevance of subtle differences on safety and efficacy. The manufacturing process for the biosimilar is systematically designed to meet the required comparability criteria (the so-called 'quality by design' concept) and it will comply with established scientific and regulatory standards. Dr. Schiestl suggested that WHO guidance would be welcome, and would facilitate the development of global standards for the regulation of biosimilars. In developing this guideline, general principles and requirements concerning interchangeability and substitution based on comparability should be defined.

## 7. Proposed topics to be included in the draft guidance

### 7.1 Terminology and regulatory pathway

It was clear from the discussions that the terminology currently used was not consistent between the various countries and jurisdictions. In the EU, the term 'similar biological medicinal products', commonly referred to as 'biosimilars, is defined in the legislation. Within the EU, a biosimilar is a biological medicinal product which is authorized on the basis of abridged non-clinical and clinical data and is compared directly against a reference product. The terminology and the EMEA regulatory guidelines for biosimilars have been adopted in Australia also. In the USA, they are termed 'follow-on protein products'[†], and 'follow-on biologicals' in Japan. In Canada they are referred to as 'subsequent entry biologics'. In India they are usually referred to as bio-generics, as they are in Iran.

Overall, there was consensus that the simple term 'generic' did not apply, as biosimilars could not be regulated in the same way as generic pharmaceuticals, due to the complex nature of biologics and their manufacture. There was general agreement that biosimilar products can be approved by an abbreviated regulatory process based on a claim of similarity to a reference product (an existing licensed product). It was acknowledged that

[†] post meeting note : 'biosimilars' has recently been proposed in the US[17].

existing national legislation governing generic pharmaceuticals is generally inadequate for a biosimilar since additional data, in particular on the toxicological and clinical profile, need to be provided.

There are numerous biosimilars on the market in various countries, which include primarily interleukins, interferons, erythropoietins, growth factors, hormones and various enzymes. Although the current debate concerns regulatory pathways for biosimilar recombinant therapeutic proteins, it is not clear whether this should be extended to other protein biologicals and non-proteinacious biological medicines such as low molecular weight heparins.

## 7.2 Proof of Similarity

*General:* A biosimilar product can be approved by an abbreviated regulatory process based on a claim that it is similar to an existing licensed product. This is achieved by a demonstration of similarity to the licensed reference product. There was consensus that a comparability programme should involve all aspects of drug development, with full analytical comparability of quality, and abridged studies for the non-clinical and clinical components of a licence application.

*Quality:* There was an agreement that a full quality dossier is required, including complete information on product development and the manufacturing process. In the EU, quality data comparing the biosimilar to the reference product are also required.

*Non-clinical and clinical:* There were clear differences in the approach to non-clinical and clinical studies for biosimilars. Although there was a strong view that comparative studies remain central to an abbreviated regulatory process, in some countries non-clinical studies might be reduced to non-comparative studies for toxicity (single and/or repeated-dose), where the goal is solely to establish the non-clinical safety of the biosimilars. In contrast, within the EU for example, studies should principally be comparative between the biosimilar and the reference product.

For clinical assessment, there was agreement that reduced studies compared to a stand-alone licence application would be acceptable; however there was no clear consensus on the details of a reduced clinical assessment package. Generally, confirmatory phase III studies for safety and efficacy involving pharmacokinetic and pharmacodynamic tests would be required, along with safe dose ranging. However, views varied as to the extent to which these studies need to be comparative or not. It was also unclear whether the studies should demonstrate non-inferiority or equivalence. In the EU, a demonstration of therapeutic equivalence is required in order to adopt the posology (dose recommendations) of the reference product. There was agreement though that comprehensive post marketing pharmacovigilance is important.

It was also acknowledged that in some cases the effort that would be required to perform the comparability study might be greater than to license the biotherapeutic as a stand-alone medicinal product; it would be the responsibility of the sponsor of biosimilars to choose the desired licensure pathway.

### 7.3 The comparator

A common feature in this process is the comparator (or reference) medicinal product. Generally, countries expect this to be a locally registered product, but it has to be considered that a company might wish to register the biotherapeutic in a country where the comparator is not (and is unlikely ever to be) licensed. In deriving new regulations, Canada, for one, is taking this matter into consideration.

The full analytical quality dataset that the innovator manufacturer has created is proprietary information and cannot be assessed by a biosimilar manufacturer. Consequently, the full analytical comparability has to be generated by the biosimilar applicant, although it might be difficult to show comparability at the drug substance level, and usually it is the drug product that is used.

### 7.4 Indication

There was differing opinion regarding the indication(s) that might or should be granted upon licensure of a biosimilar, from its restriction to the indication which was assessed within the clinical trial, to a much broader range of indication as might have been granted for the comparator product. In the EU, legislation permits extrapolation of indications on certain conditions. In other countries extrapolation is not accepted and any indication required for the biosimilar has to be proven with clinical data from non-inferiority studies or non-comparative confirmatory studies.

Interchangeability and substitution were also debated, with no clear outcome. These points need to be addressed in a WHO guideline.

### 7.5 Immunogenicity

It is known that biotherapeutics have a potential to be immunogenic, and this can impact on patient safety and product effectiveness. Further, characterization and preclinical studies of such products cannot predict their immunogenic potential in the clinic. Consequently, it was emphasized by some participants that immunogenicity testing should be included in the pre-approval requirements as well as in post marketing surveillance. Within the EU, one year of pre-licensing immunogenicity data in the case of chronic administration is usually required.

## 8. Conclusion

It was agreed that WHO should develop a global regulatory guideline for biosimilar products. Issues of critical importance that should be addressed in this guideline include the principles for the evaluation of these products, as well as regulatory pathways for their licensing and regulatory oversight. Furthermore, the need for international standards and reference preparations for product evaluation should be considered. As a first step towards the development of guideline, a WHO working group should be established to take this issue forward. The conclusions of this Consultation will be presented to the

WHO Expert Committee on Biological Standardization at its meeting in October 2007 for consideration, advice and action.

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16. Woodcock J, Griffin J, Behrman R, Cherney B, Crescenzi T, Fraser B, et al. The FDA's assessment of follow-on protein products: a historical perspective. Nat Rev Drug Discov 2007;6:437-42.
17. A letter sent by Michael Leavitt, the secretary of Health and Human Services, on 26 June 2007 to US senate laying our the Department's current view on biosimilars.

Jeewon Joung[a], James S Robertson[b], Elwyn Griffiths[c], Ivana Knezevic[a]**

on behalf of the WHO Informal Consultation Group[‡]

[a] World Health Organization, Department of Immunization, Vaccines and Biologicals, Quality, Safety and Standards, 20 Avenue Appia, CH-1211 Geneva, Switzerland

[b] National Institute for Biological Standards and Control, Potters Bar, Hertfordshire, EN6 3QG,UK

[c] Biologics and Genetic Therapies Directorate, Health Canada, HPB Building #7 (Locator 0702E), Tunney's Pasture, Ottawa, ON K1A 0L2, Canada

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[‡] The WHO Informal Consultation Group: Dr. Adrian Bristow, Dr. Elaine Gray, Dr. Robin Thorpe, and Dr. James S Robertson, National Institute for Biological Standardization and Control, Potters Bar, London, UK; Dr. Majid Cheraghali, Iran Blood Transfusion Organization, Tehran, Iran; Dr. Laura Gomes Castanheira and Dr. Granville Garcia de Oliveira, Agencia Nacional da Vigilancia Sanitaria, Brasília, Brazil; Dr. Elwyn Griffiths and Dr. Kwasi Nyarko, Health Canada, Ottawa, Canada; Dr. Ulrich Kalinke, Paul-Ehrlich-Institut, Langen, Germany; Dr. Toru Kawanishi and Dr. Teruhide Yamaguchi, National Institute for Health and Science, Tokyo, Japan; Dr. Jean Christian Krayenbühl and Ms Monika Schmid-Appert, Swissmedic, Bern, Switzerland; Ms Maria Poulis, Therapeutic Goods Administration, Wooden, Australia; Dr. Huub Schellekens, Utrecht University, Utrecht, Netherlands; Dr. Yeowon Sohn, Korea Food and Drug Administration, Seoul, Republic of Korea; Dr. James Southern, Ministry of Health, CapeTown, South Africa; Dr. Keith Webber, Food and Drug Administration, Silverspring, Maryland, USA; Dr. Martina Weise, Federal Institute for Drugs and Medical Devices, Bonn, Germany; Dr. Shri Parthajyoti Gogoi, Ministry of Health & Family Welfare, Guwahati, India; Dr. Wang Junzhi, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China; Dr. Peter Richardson, European Medicines Agency, London, UK; Dr. Sunil Gairola, Serum Institute of India Ltd, Pune, India, Representative of the Developing Country Vaccine Manufacturing Network (DVCMN); Dr. Jacques Mascaro, Hoffman La Roche, Basel, Switzerland, Representative of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA); Dr. Andrew Fox, Amgen, Cambridge, UK, Representative of IFPMA; Dr. Ryoko Krause, IFPMA, Geneva, Switzerland; Dr. Martin Schiestl, Sandoz, Kundl/Tirol, Austria, Representative of the European Generic medicines Association (EGA); Ms Suzette Kox, EGA, Brussels, Belgium; Dr. Aliza Eshkol, International Association for Biologicals (IABS), Geneva, Switzerland; Dr. Raffaella Balocco-Mattavelli, Dr. Sophie Lasseur, Dr. Ji-Cui Dong, Quality Assurance and Safety: Medicines unit, Medicines Policy and Standards Department, World Health Organization, Geneva, Switzerland; Dr. David Wood, Dr. Ivana Knezevic, Dr. Jeewon Joung, Quality, Safety and Standards unit, Immunization, Vaccines and Biologicals Department, World Health Organization, Geneva, Switzerland.

** Corresponding author. Tel : +41 22 791 3136
Fax : +41 22 791 4971
E-mail : knezevici@who.int