

第3回 PMDA 国際バイオリジクスシンポジウム  
**PMDA 3<sup>rd</sup> International Symposium on  
Biologics**

バイオ後続品

**Follow-on biologics (Biosimilar)**

平成21年2月17日 ヤクルトホール 東京

**17th February, 2009  
Yakult Hall, Tokyo, Japan**

独立行政法人 医薬品医療機器総合機構  
**Pharmaceuticals and Medical Devices Agency (PMDA)**

# AGENDA

Overall Chair: Dr. Tadano, PMDA

## **Opening Remarks & Keynote Speech**

Chair: Dr. Toyoshima, PMDA

- 10:00-10:10 Opening Remarks (近藤 達也、独立行政法人医薬品医療機器総合機構 理事長: Dr. Tatsuya Kondo, Chief Executive, PMDA)
- 10:10-10:30 Current status of Japanese Regulation and Development on Biologics. (成田 昌稔、独立行政法人医薬品医療機器総合機構 上席審議役 生物系審査第一部 部長: Mr. Masatoshi Narita, Associate Executive Director, Center for Product Evaluation and Director, Office of Biologics I, PMDA)

## **Session I**

Chair: Dr. Richardson, EMEA & Dr. Arato, PMDA

- 10:30-11:05 Quality, Safety and Efficacy of Follow-on Biologics. (山口 照英、国立医薬品食品衛生研究所 生物薬品部 部長: Dr. Teruhide Yamaguchi, Division Head, Division of Biological Chemistry and Biologicals, NIHS)
- 11:05-11:30 Innovator's Perspective of Follow-on Biologics. (野村 英昭、協和発酵キリン株式会社 製品戦略部マネージャー/製薬協: Mr. Hideaki Nomura, Manager, Strategic Product Planning Department, Kyowa Hakko Kirin Co., Ltd., JPMA)

## **Session II**

Chair: Dr. Yamaguchi, NIHS & Dr. Nyarko, HC

- 11:30-12:05 Regulation of Biopharmaceuticals in the United States of America. (Dr. Keith Webber, Deputy Director, Office of Pharmaceutical Science CDER, FDA)
- 12:05-12:30 PhRMA Perspective on Follow-on Biologics. (Dr. Marie A. Vodicka, Assistant Vice President, Biologics & Biotechnology, PhRMA)
- 12:30-13:40 Lunch

## **Session III**

Chair: Dr. Webber, FDA & Dr. Shikano, PMDA

- 13:40-14:15 Biosimilar Medicines in EU. (Dr. Peter Richardson, Scientific Administrator, Quality of Medicines Sector Human Unit Pre-Authorisation, EMEA)
- 14:15-14:40 Scientific Aspects for the Establishment of Biosimilar Guidelines, the Perspective of EFPIA and EBE. (Dr. Stephan Fischer, SVP Biologics Research and Strategy Pharma Research Penzberg, Roche Diagnostics GmbH, EBE-EFPIA)
- 14:40-15:05 EGA's perspective on Biosimilar Products. (Dr. Martin Schiestl, Head, Analytics and Pharmaceutical Development Sandoz GmbH, EGA)

15:05-15:20 Break

**Session IV**

Chair: Mr. Narita, PMDA & Mr. Sato, PMDA

15:20-15:55 Evaluation of similar biotherapeutic products: WHO Guidelines. (Dr. Ivana Knezevic, Scientist, Quality, Safety and Standards Team, Immunizations, Vaccines and Biologicals, Department Family and Community Health Cluster WHO)

15:55-16:30 Canadian Approach to the Regulation of Subsequent Entry Biologics. (Dr. Kwasi A. Nyarko, Manager - Special Projects Unit, Policy and Promotion Division, Center for Policy and Regulatory Affairs, Biologics and Genetic Therapies Directorate Health Canada)

**Conclusion & Closing Remarks**

Chair: Mr. Narita, PMDA

16:30-16:50 Summary Report (豊島 聡、独立行政法人医薬品医療機器総合機構 理事・審査センター長: Dr. Satoshi Toyoshima, Executive Director and Director, Center for Product Evaluation, PMDA)

## **Speakers**

**(Abstract, Curriculum Vitae & Slides)**

## **Opening Remarks**

近藤 達也

独立行政法人医薬品医療機器総合機構 理事長

Dr. Tatsuya Kondo, Chief Executive, PMDA

## **Curriculum Vitae**

He has a lot of clinical experiences as a neurosurgeon since he graduated from Medical Department of the University of Tokyo in 1968. He worked for the department of neurosurgery in the 1<sup>st</sup> national hospital (1972 ~ 1974) and the department of Neurosurgery, Faculty of Medicine, The University of Tokyo (1974 ~ 1978).

He studied the biology of brain tumor as a visiting researcher with Max-Planck scholarship at Max-Planck Institute, West Germany from March to December of 1977.

He served as a neurosurgeon at International Medical Center of Japan from 1978 to 2003 and he contributed to hospital management and clinical discipline as the Director of the hospital, International Medical Center of Japan from April, 2003 to March, 2008.

## **Keynote Speech**

### **Current status of Japanese Regulation and Development on Biologics.**

成田 昌稔

独立行政法人医薬品医療機器総合機構 上席審議役 生物系審査第一部長

Mr. Masatoshi Narita, Associate Executive Director, Center for Product Evaluation and Director, Office of Biologics I, PMDA

#### **Abstract**

While Biologics are expected of their useful effects in the medical field, because they are made out of the substances derived from biological sources, it is important to evaluate the infectious agents such as viruses, and control them appropriately.

Thus, some biologics need to be paid careful attention, and in Japan there are standards for biological source materials, standards for manufacture, and so on.. Moreover, there is a system to evaluate the safety of gene-therapy products and cell/tissue-derived products before starting clinical trials.

With the developments in biotechnology, one-third of the NDA approved in Japan has become Biologics. Noteworthy approved biologics in recent years are autologous cultured keratinocytes, several types monoclonal antibodies, human serum albumin-recombinant, and so on.

The ongoing research and development of Biologics, there are antibody-products, blood component-products, gene-therapy products, vaccines by tissue culture, cancer vaccines, RNA-products, regenerative medicine, animal factory (GE-animals), and plant factory (GE-plants).

In addition, to facilitate the development of innovative medicines and medical devices intensively, the Special Districts for Development of Advanced Medical Care (Super Special Districts) have been established in the year 2008.

To promote the development and to improve quality, safety and efficacy of biologics, it is important to establish the adequate guidelines. It is also required to improve the collaboration between academia, industry and regulatory agencies.

The MHLW and the PMDA have established the guidelines for autologous human cells/tissue-based products, and allogeneic human cells/tissue based products in 2008. Currently, the PMDA is working on creating the guidelines for the vaccines, adjuvants, regenerative medicines for cardiac muscle or cornea, stem-cells, ES-cells and iPS-cells. The guideline for the follow-on biologics (biosimilar and so on) is in its final stage of establishment.

The theme of today's 3<sup>rd</sup> PMDA Biologics Symposium is "The follow-on Biologics (Biosimilar)", which is internationally controversial subject. We highly expect that the symposium will be a great opportunity to have lively discussions among all parties over the scope of Biologics or how to ensure their quality and safety.

#### **Curriculum Vitae**

Mr. Masatoshi Narita is currently the Associate Executive Director, Center for Product Evaluation of Pharmaceuticals and Medical Devices Agency (PMDA). He is responsible for the evaluation of the Biologics.

He received master of degree from University of Tokyo. He is a pharmacist and his specialized field was regulatory sciences. He has been in governmental service since 1982 and worked on evaluation of pharmaceuticals, food safety, chemical safety, and research coordination in MHLW. He has served as the Planning Director for Research, Health Sciences Division(2003), and the Director, office of Chemical Safety, Pharmaceutical and Food Safety Bureau(2004). He served as a Director-Department of Planning and Coordination at the National Institute of Biomedical Innovation (NIBIO) (2005~2008)

## Session I

### Quality, Safety and Efficacy of Follow-on Biologics.

山口 照英

国立医薬品食品衛生研究所 生物薬品部 部長

Dr. Teruhide Yamaguchi, Division Head, Division of Biological Chemistry and Biologics, National Institute of Health Sciences

#### Abstract

A Follow-on biologics is a drug to be developed by a different company as a biotechnological product that is assessed the comparability of biotechnology-derived products already approved in regionally (hereinafter “original biologics as a reference”). Follow-on biologics can be generally developed on the basis of data obtained from a comparison with the original biologics as a reference demonstrating comparability in respect of quality, safety and efficacy; or relevant data.

Since the biotechnology-derived products generally have unique characteristics such as their structural complexity in being comprised from several functional domain sites, specific bioactivity, instability and immunogenicity, unlike small chemically synthesized drugs, it is often difficult to approve the identity of the active ingredient of follow-on biologics with that of the pre-approved reference product (original biologics), and then, generally it appears that the same approach as with the generic products of small chemically synthesized drugs cannot be applied. Therefore another approach to evaluate the follow-on biologics different from the regulation of generic drugs is required.

Recently, Ministry of Health, Labor and Welfare (MHLW) has published a draft guideline on follow-on biologics for the collection of public comment. In this presentation, I would like to introduce the concept and the background of the draft guideline.

#### Curriculum Vitae

He is the director of the division of Biological Chemistry and Biologics at National Institute of Health Sciences, Japan.

His research work was started at Tokyo Metropolitan Institute of Medical Sciences in 1976. In 1987 he became a Senior Staff Scientist at National Institute of Health Sciences (NIHS). In 2002, he joined the Division of Cellular and Gene Therapies Products, as a Director. In 2006, he joined current position, and is engaged in investigating for evaluation of the safety, quality and efficacy of biotechnology-derived products and relevant fundamental researches. He is member of the Pharmaceutical and Food Affairs Council in Japan and is contributing to review quality aspects of registration applications of new drugs. He is also contributing to ICH activity as the member of Gene Therapy Discussion Group.



## Session I

### Innovator's Perspective of Follow-on Biologics.

野村 英昭

協和発酵キリン株式会社 製品戦略部マネージャー／製薬協

Mr. Hideaki Nomura, Manager, Strategic Product Planning Department, Kyowa Hakko Kirin Co., Ltd., JPMA

#### Abstract

In these a few decades many biological products have been developed and supplied as new therapeutics for difficult-to-treat diseases by conventional treatments, such as cancer, cardiovascular disease, anemia, and rheumatism, etc. The biological products have now become an integral part of the treatments for many serious diseases, which have been established by tremendous efforts of investigators including scientists, researchers and clinicians, and by many clinical trials with a number of patient enrollments. It is also a great challenge for innovators to apply frontier science to practical medical use by their own efforts.

Time went by and the patents of several of those biological products expired and, taking this opportunity, some companies started to develop follow-on biologics. Simultaneously authority in each country and /or territory has been considering the regulatory approval process and EMEA issued the guideline for follow-on biologics. And finally recombinant human growth hormone, erythropoietin, and granulocyte colony stimulating factor have been approved in EU. Here, in Japan, MHLW issued a draft of the guideline and has collected public comments.

From an innovator's standpoint we understand that follow-on biologics, unless they infringe innovators' intellectual properties, are allowed to be developed, approved, and launched if they are safe and effective as much as original innovative products. From our experiences as an innovator, we would like to indicate important issues when follow-on biologics are developed and marketed. At first patient's safety should be respected before everything. In general, safety and efficacy are demonstrated by clinical studies with numbers of patients. However, it is not always enough to prove the safety completely even when the safety is assessed in some clinical studies. Innovator has observed the safety carefully for long time after launch. Such post-marketing commitment is a very important issue to concrete the product safety. Another important point is that a follow-on biologic is similar and not identical of original innovative product. Since any minor difference in a product profile may potentially cause a serious difference in clinical settings, follow-on biologic companies should understand this issue and carefully develop it with sufficient scientific approaches.

On the other hand innovators may need to review their own innovative product. The follow-on biologics will be developed with current technology and science, but those with which original innovative products were developed become past. Innovators may have to consider whether the latest technology and science can be adopted to improve the product if needed.

**Keywords:** biological products, follow-on biologics, growth hormone, erythropoietin,

granulocyte-colony stimulating factor

**Curriculum Vitae**

Kyowa Hakko Kirin, Co., Ltd Strategic Product Planning Department  
Manager (October 2008 – present)

Kirin Pharma, Co., Ltd Strategic Product Planning Department  
G-CSF Product Manager (2007 – 2008)

Kirin Brewery Co., Ltd Planning Department, Pharmaceutical Division  
G-CSF Product Manager (2001 – 2007)

Kirin Brewery Co., Ltd Pharmaceutical Development Laboratory (1988 – 2001)  
Tokyo Science University  
Master of Science, Pharmaceutics, 1988

## Session II

### Regulation of Biopharmaceuticals in the United States of America.

Dr. Keith Webber, Deputy Director, Office of Pharmaceutical Science CDER, FDA

#### Abstract

Federal regulation of drugs in the United States of America is authorized primarily by two distinct laws: the Federal Food, Drug, and Cosmetic Act of 1938 (FFD&C Act) and the Public Health Service Act of 1944 (PHS Act). The PHS Act specifically regulates biological products derived from living organisms, for example blood, blood products, vaccines, and anti-serum. On the other hand, protein products extracted from human or animal organs (for example, insulin, calcitonin, and growth hormone) are regulated under the FFD&C Act. Recombinant versions of a product are regulated under the same statute as its naturally-derived counterpart. As such, monoclonal antibodies, interferons, cellular growth & differentiation factors are regulated under the PHS Act.

Although the FFD&C Act has provisions for approval of drug marketing applications that rely to some extent on prior findings clinical safety and efficacy, the PHS Act has no such provision. Therefore, approval of follow-on biologics is currently not legal in the USA. Legislation that will amend the PHS Act in order to allow follow-on biological products is anticipated.

In many ways, biological products are more complex than synthetically-produced drugs. From a physical-chemical perspective, biological products have a much greater molecular weight and are often heterogeneous mixtures of components due to post-translational modifications. Also, it is characteristic of proteins to fold into specific secondary and tertiary structures that are necessary for them to be bioactive. The ability of a protein to fold properly is generally dependent on factors within the cell where it is expressed. As such, the complexity of a protein product is impacted not only by its structure but also by how it is produced. Furthermore, the folded structures are susceptible to thermodynamic damage that may occur during production or storage. Improperly folded proteins can aggregate and be more immunogenic than they are in their native conformation.

In addition to structural complexity, biological products may have a functional complexity that is rare for synthetically-produced drugs. Whereas synthetic drugs act as either agonists or antagonists at receptors for endogenous ligands, biological products often have a functional activity of their own. For example, the enzymes have catalytic activity and many antibodies have an effector function that is necessary for their full activity. Similarly, while the bioavailability of a synthetic drug is correlated to its blood level, this is not necessarily so for a biological product whose biodistribution is not determined by its hydrophobicity/hydrophilicity index. These factors add another layer of potential complexity to the in vivo activity of biological products.

Although we are awaiting new legislation that will allow approval of follow-on biologics in the USA, we anticipate that these products will require more extensive data to support their safety and efficacy than is needed for generic drugs.

### **Curriculum Vitae**

Keith Webber is Deputy Director of the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research at the FDA. The Office of Pharmaceutical Science oversees the regulation of manufacturing of drugs produced synthetically or via biotechnology.

He holds a Bachelor of Science degree in Chemistry from the University of Denver, Colorado and a Doctorate in Biological Chemistry from the University of Michigan.

He has been in government service since 1988 and at the FDA since 1995. Prior to his current position, he has served as Director of the Division of Monoclonal Antibodies and Acting Director of the Office of Biotechnology Products.

He is a member of numerous policy-making committees at the FDA, including the Council on Pharmaceutical Quality, the Senior Science Council, the Follow-on Biologics Steering Committee, the Manufacturing Sciences Working Group, and the Standards Working Group.

## Session II

### PhRMA Perspective on Follow-on Biologics.

Dr. Marie A. Vodicka, Assistant Vice President, Biologics & Biotechnology, PhRMA

#### Abstract

The Pharmaceutical Research and Manufacturers of America think that abbreviated regulatory pathways for the approval of follow-on biologics should be science-based, put patients first and promote incentives for innovation. Such regulatory approval pathways should include the following elements:

- 1. Clear regulatory approval pathway for new product category distinct from small-molecule generics: Follow-on Biologics**
  - The pathway should be developed using an open, transparent process with category-specific guidance, including a stepwise approach for products to be covered.
  - The authority should only be able to use reference products that have extensive clinical data and market experience, approved with full data package and review.
  - The pathway should include a system for distinct naming and labeling (clear prescribing, dispensing and surveillance).
- 2. Adequate quality standards**
  - Products need to have demonstrated similar molecular structural properties as the innovative product .
  - Robust comparative physico-chemical and biological characterization to be specified.
  - Follow-on biologics should meet the same high quality standards as for innovative products.
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- 3. Adequate pre-clinical and clinical testing requirements**
  - Case-by-case approach within the scope of pre-defined non-clinical and clinical requirements, demonstrating safety and efficacy.
  - Clinical data should be required for each indication unless otherwise scientifically justified.
  - Appropriate risk management and active pharmacovigilance.
- 4. Appropriate use**
  - Science currently does not support automatic interchangeability/substitution.

The PMDA and other global regulatory authorities have the advantage of learning from the European experience with biosimilars under the regulatory approval pathway implemented by the European Medicines Agency (EMA).

#### Curriculum Vitae

Marie oversees the biologics and biotechnology portfolio at the Pharmaceutical

Research and Manufacturers of America, where she is an Assistant Vice President in the Scientific and Regulatory Affairs department. Previously, Marie served at the State Department, in the Bureau of East Asian and Pacific Affairs, where she was an Economic Policy and APEC Affairs Officer. Marie has a B.A., magna cum laude, in Biology from Amherst College and a Ph.D. in Molecular and Cell Biology from the University of California, Berkeley. Prior to joining the State Department, she completed a post-doctoral fellowship at the Fred Hutchinson Cancer Research Center in Seattle, where she carried out a research program on HIV interactions with the host cell. Before moving into the policy arena, Marie published in peer-reviewed international journals of science and was the recipient of many grant and fellowship awards: *National Institute of Allergy and Infectious Diseases, post-doctoral fellowship and R01; Special Fellow of the Leukemia and Lymphoma Society; James Pendleton AIDS Fellow; Center For AIDS Research New Investigator Award.*

## Session III

### Biosimilar Medicines in EU.

Dr. Peter Richardson, Scientific Administrator, Quality of Medicines Sector Human Unit Pre-Authorisation, EMEA

#### Abstract

The legal and regulatory structures within the European Union were adapted recently to enable the authorisation of biological medicinal products based on reduced or abridged data packages. In the EU these are termed Similar Biological Medicinal Products or biosimilar products. The biosimilar product is directly compared versus a reference (i.e. Originator's) product.

This presentation will give an overview of the evolution of the legal and regulatory process leading to the successful introduction of biosimilar products in the EU, focusing on regulatory guidelines and their ongoing development.

The EU pharmaceutical legislation refers to a guideline which outlines general principles for Similar Biological Medicinal Products. This guideline (CHMP/437/04) has been termed an "overarching guideline", which provides the philosophy and defines the expectations of which product types would be appropriate for the biosimilar approach. The biosimilar approach is legally applicable to all biological products, however, the ability to characterise the biological substance to a high degree is fundamental to the biosimilar strategy and as a result, products derived from rDNA biotechnology are considered to be appropriate cases to consider. Also factors such as clinical and regulatory experience with the product being studied are taken into account.

Following from the general guideline there is a portfolio of additional guidelines: more general guidance for quality and (non) clinical issues and further class specific guidelines for the development of similar biological medicinal products containing r-DNA insulin, granulocyte colony stimulating factors, somatropin and epoetins. The non-clinical and clinical data requirements are reduced as much as possible, taking into consideration the complexity of the product and experiences gained with use of the originator's product.

A number of products have been authorised in the EU to date and a large body of scientific experience has been gained through these applications and also requests from sponsors for scientific advice through the EMEA system. Scientific advice can be requested on any subject, however, comparability considerations are the main substance of these requests and also which clinical end points will be best suited to the demonstration of comparability.

In the EU regulatory system, the European Commission is responsible for developing the pharmaceutical legislation and also Marketing Authorisations via the Centralised Procedure. This is supported by the scientific committees of the EMEA, notably the Committee for Medicinal Products for Human Use (CHMP), which in turn has sub-committees or Working Parties which specialise in particular areas. Working parties which provide the main contribution on scientific matters for biosimilar products are the Biologics Working Party (BWP) which addresses quality issues for biological medicinal products and the Biosimilar Medicines Working Party (BMWP), which is a

multi-disciplinary group, however, focused towards non-clinical and clinical aspects.

The EMEA has conducted an extensive consultation on the introduction of biosimilars which has enabled the introduction of these products with the support of major stakeholders. Interest in this field continues to grow and EMEA is actively engaged in sharing the philosophy and experience gained to date.

### **Curriculum Vitae**

Dr Richardson is a pharmacist, with a Ph.D. in pharmaceuticals from The Queens University, Belfast. He worked for a number of years in the pharmaceutical industry in the UK and Italy in the area of formulation research and development, with companies such as Bristol-Myers Squibb, SmithKline Beecham, Pfizer and Serono, concentrated mainly on the development of drug delivery systems. He has worked for the UK MHRA as a pharmaceutical assessor, with some time assessing chemical and abridged applications and wide ranging experience of biotechnology / biological applications. He was UK delegate for the Biologics Working Party of the CHMP prior to joining the EMEA, Quality Sector, where his role as scientific administrator requires scientific and regulatory input into many aspects of biotechnology and biological medicinal products, CHMP, Biologics, Vaccines and Similar Biologicals Working Parties activities. He is secretary to the CHMP Vaccines Working Party.



## **Session III**

### **Scientific Aspects for the Establishment of Biosimilar Guidelines, the Perspective of EFPIA and EBE.**

Dr. Stephan Fischer, SVP Biologics Research and Strategy Pharma Research Penzberg, Roche Diagnostics GmbH, EBE-EFPIA

#### **Abstract**

The presentation will address the underlying scientific aspects to those challenges. The first and obviously relevant factor is the complexity and intrinsic heterogeneity of native and recombinant proteins. The order of magnitude of this heterogeneity has been underestimated for a long time and detailed experiences with product development and products have been shared publicly only recently in the context of the discussion on biosimilars. Despite the significant progress of analytical technologies for chemical analysis of proteins the complexity remains huge and the prediction of effects on the efficacy and safety of these products based on chemical analysis seems to be far from being possible. In contrast, recent findings on specific mechanisms of monoclonal antibodies and other proteins indicate that even changes which would have been considered very small will have significant impact on the biological activity. A second aspect is the very close link between the manufacturing process and the product obtained from such a process. Due to the fact that the source is a living organism one has to anticipate a significant variability of the product dependent on the in vitro cultivation conditions of recombinant cell lines. In addition, the purification process with its specific protocol and in-process controls will determine which fractions of the complex mixture derived from the cultivation will be isolated as the final drug substance. All these elements, the cell line, the cultivation and the purification process, as well as in-process controls contribute to the product composition. Since all these factors are unique for a given process are not available for a manufacturer of a biosimilar product it is essentially impossible to obtain an exact copy of a licensed product from an independently developed, new process. As a result from this analysis one has to acknowledge that a product from a different process may be different. The predictive value of chemical analysis as well as preclinical models on clinical efficacy and safety is also not certain. This uncertainty triggers the need to conduct clinical studies to assess efficacy and safety for a biosimilar product.

The presentation will summarize the conclusions which can be obtained from such a scientific analysis. These conclusions will lead to proposals which important points may have to be considered for the establishment of guidelines for the development of similar biological medicinal products.

The development of recombinant biologics as follow-on products of originator products presents new challenges. Those are linked to the specific characteristics of such medicines and to the processes and technologies which are used for manufacturing. In Europe such products have been named “similar biological medicinal products”, or biosimilars.

#### **Curriculum Vitae**

Stephan Fischer obtained his PhD in Microbiology from the Technical University of Munich. He has spent more than 25 years in the area of recombinant proteins in various roles. He was a Post Doc at the European Molecular Biology Laboratory where he focused on protein structure research. He then joined Boehringer Mannheim as a Senior Scientist where he developed technologies and products for Diagnostics and Pharma. Stephan was a member of the team that brought recombinant erythropoietin to the market. As the research project leader and later as international project manager he also contributed to take reteplase from discovery to launch in Europe and the US. During this task he became a Director of Pharma Project Management. After the acquisition of Boehringer Mannheim by Roche he became a Program Director Oncology and was a member of the global management team for Oncology research. Today, Dr. Fischer is a Senior VP for Biologics R&D within Roche Pharma Research in Penzberg, Germany.

## Session III

### EGA's perspective on Biosimilar Products.

Dr. Martin Schiestl, Head, Analytics and Pharmaceutical Development Sandoz GmbH, EGA

#### Abstract

The first biosimilar medicines developed according to the new EMEA biosimilar guidelines have been approved in the European Union. Examples are the Somatropin products approved in 2006, followed by Epoetin in 2007 and most recently Filgrastim in 2008.

The presentation gives an overview of the pivotal concepts of the biosimilar product development including the development of manufacturing processes according to the target directed approach and the subsequent comparability exercise with the comparator biologic (in EU terminology: reference product). These concepts reflect state-of-the-art science and are based on the increasing clinical experience and the ongoing significant improvements in analytical and process technology. After the first approval of the complex biosimilar glycoprotein Epoetin, the current edge of the biosimilar development is marked by the monoclonal antibodies. The current innovator pipelines and approvals in the biotech are dominated by these products as they provide great opportunities to fulfill unmet medical needs. Due to their complexity and multiple biological characteristics, it is a challenging task to develop biosimilar monoclonal antibodies. However, the tools, which are required for the development and the assessment are already available and will be discussed.

The current situation in Europe demonstrates that biosimilar products are competitive in the market place and help to reduce the costs of the health care systems. However, just as innovator medicines are increasingly developed on a global basis, with analytical, preclinical and clinical data developed anywhere in the world acceptable for regulatory submission in any jurisdiction, the data supporting the dossiers of biosimilar products should also be globally acceptable. This would enable broader access to biosimilar products and also enable greater competition and cost savings. This requires that a biosimilar be able to be developed globally to an essentially single comparator biologic of one of these jurisdictions. Points to consider are the evaluation of the global status of the comparator biologic, based on public information and physicochemical and biological characterization, and the principles of ICH 5E (Ethnic Factors on the Acceptability of Foreign Clinical Data). Under these aspects, it should not be required to duplicate preclinical and clinical studies for each country/region. The regulatory systems should allow such a global development of biosimilar products based on scientific rationale. This would allow meeting the objectives of access and economy that biosimilar products offer to be made available to the health care systems and patients that need them on a global basis.

**Keywords:** Biosimilar products, monoclonal antibodies, global development

#### Curriculum Vitae

Dr. Martin Schiestl obtained his degree in chemistry with focus on analytical sciences

from the university of Innsbruck/Austria. He characterized therapeutic proteins for his master and Ph.D thesis at Biochemie GmbH and obtained his Ph.D. in 1996. He joined Biochemie/Sandoz in 1996 and has been working since then with increasing responsibilities in the quality development of biopharmaceuticals. Since 2005 he is heading the analytical and pharmaceutical development group at Sandoz Austria. He is member of the Expert Group No. 6 for Biological Substances at the European Pharmacopoeia since 2003, and member of the Expert Committee for Proteins and Polysaccharides at the United States Pharmacopeia since 2005.

## Session IV

### Evaluation of similar biotherapeutic products: WHO Guidelines.

Dr. Ivana Knezevic, Scientist, Quality, Safety and Standards Team, Immunizations, Vaccines and Biologicals, Department Family and Community Health Cluster WHO

#### Abstract

Access to biological therapeutic products is of critical importance for successful treatment of many life-threatening chronic diseases. Due to the fact that the cost of innovative biological therapeutics is often prohibitive, development of "similar" biological products was recognized as a solution for making biological therapeutics broadly available at an affordable price. However, the concept of "biosimilar" product posed a number of challenges for public health authorities, regulators in particular.

Licensing and use of similar biological product was recognized as one of the areas where immediate WHO assistance to its member states is needed. Consultation with regulators, manufacturers of biotherapeutics and other experts began in April 2007 and revealed that marked differences in regulatory pathways for these products exist. It was agreed that WHO should develop a global regulatory guideline for abbreviated licensing pathways with a set of principles for evaluation of similar biological products. In response to this request, first draft of WHO guidelines was prepared by the WHO drafting group in March 2008 and was circulated among experts worldwide for comments. In May 2008, the WHO and Korea FDA co-organized Consultation in Seoul to review key issues in the evaluation of similar biologicals products and to advise WHO on how to improve the document. A number of suggestions were incorporated into the guidelines and updated document was presented to the Expert Committee on Biological Standardization (ECBS) in October 2008. Key principles in the evaluation of similar biotherapeutics were also presented to the International Conference of Drug Regulatory Authorities (ICDRA), in September 2008.

The ECBS affirmed that reduced data packages may be suitable to provide sufficient assurance for the quality, safety and efficacy of certain biotherapeutic products. The Committee recommended revision of the document with particular attention to the following: 1) clarification of the scope; 2) differences in the data packages provided for abbreviated pathways from those required for innovative product and 3) design and specific requirements for clinical data to support licensing of similar biological products. The ECBS requested that a revised version of the document be prepared and submitted for public comment, and re-submitted to the ECBS in 2009. In line with this, WHO drafting group is meeting in February 2009 to take these recommendations forward and to improve guidelines accordingly.

#### Curriculum Vitae

##### Education

- 1990 Medical Doctor - Medical School, University of Novi Sad, Yugoslavia.
- 1992 License as a physician - Ministry of Health of Republic of Serbia, Yugoslavia.
- 1997 Specialist in Medical Microbiology and Parasitology - Medical School, University of Belgrade, Yugoslavia.

- 1998 M.Sc. in Medicine (Microbiology) - Medical School, University of Belgrade, Yugoslavia.
- 2007 Ph.D. in Medicine (Virology) - Medical School, University of Belgrade, Republic of Serbia.

#### Experience

Dr Knezevic has fifteen years of professional experience in biological standardization and regulation of biologicals. During the first seven years, the expertise in the production, quality control and overall evaluation of vaccines and biological therapeutics was built. As part of the regulation of these products at the national level, she was involved in a broad range of laboratory testing as well as in the review of non-clinical and clinical data. In 2000, Dr Knezevic joined WHO Biological Standardization Programme and since then her activities have been devoted to the standardization and evaluation of biologicals at the global level. This includes development and establishment of WHO International Standards as well as the assistance to the regulators, manufacturers and other users of these standards. Since 2006, she is leading standardization of vaccines and some biological therapeutics, working as a Scientist in the Quality, Safety and Standards Team of the Immunization, Vaccines and Biologicals department of WHO. Dr Knezevic led development of WHO guidelines on various aspects of vaccine evaluation (ie, stability, non-clinical and clinical), recommendations for production, control and evaluation of selected vaccines, published in WHO Technical Report Series. She is also the author of several publications that made broad audience aware of WHO initiative in the development, establishment and implementation of standards for vaccines and some other biological products.

## Session IV

### **Canadian Approach to the Regulation of Subsequent Entry Biologics.**

Dr. Kwasi A. Nyarko, Manager - Special Projects Unit, Policy and Promotion Division, Center for Policy and Regulatory Affairs, Biologics and Genetic Therapies Directorate Health Canada

#### **Abstract**

The Canadian approach to the regulation of Subsequent entry biologics (SEBs) (also known termed biosimilars) is based on science and the regulatory principles existing within the Food and Drugs Act and Regulations. The principles within regulatory frameworks for biologic, pharmaceutical, and generic pharmaceutical drugs have been the basis for developing oversight for SEBs. The basis for a product being authorized as a SEB hinges on the ability to demonstrate similarity to a suitable reference biologic product. Full quality (chemistry and manufacturing) data in addition data from comparability between SEB and the reference biologic product is required for authorization of a SEB. The reference biologic product should be a biologic product authorized for use and marketed in Canada. The use of a reference biologic product that is not approved in Canada may be considered on request to the Minister. Results from the comparability exercise determine the extent of reduction in the non-clinical and clinical data required to support a SEB. Comparative clinical trials are required to demonstrate the similarity in efficacy and safety profiles between the SEB and the reference biologic product. Clinical studies are to be provided for each indication being sought and indications granted to a SEB are based on data provided by the sponsor. Full and complete non-clinical and clinical data is required to support the application for authorization of the product when similarity to the reference product cannot be established. A risk management plan is part of the post market surveillance requirements for SEBs. Canada is using its existing New Drug Submission pathway for new biologic drugs for the authorization of SEBs. All the laws, patent and intellectual property principles outlined within the Food and Drug Regulations (Data Protection), and Patented Medicines Notice of Compliance Regulations are applicable to SEBs. The authorization of a SEB is not a declaration of therapeutic or pharmaceutical equivalence with the reference biologic product. Canada's intention is to harmonize as much as possible with other competent regulators and international organizations. The Canadian approach to regulation of SEBs will ensure that SEBs that meets the standards of safety, efficacy, and quality to meet the needs of Canadians. The regulatory framework is also flexible to enable the Regulator and sponsors adapt to the needs of the different classes of products and the changing legislative environment.

**Keywords:** Canada, Subsequent entry biologics, reference biologic product, similarity, data requirements, regulation of SEBs.

#### **Curriculum Vitae**

Kwasi Nyarko is the Manager, Special Projects Unit, Policy and Promotion Division, Centre for Policy and Regulatory Affairs, Biologics and Genetic Therapies Directorate

(BGTD), Health Canada. At Health Canada he has also worked with the Marketed Health Products Directorate with a unit responsible for post-market surveillance for biological products, including blood. Dr. Nyarko obtained his doctorate in Biomedical Sciences from the University of Guelph, Ontario, Canada.

Dr. Nyarko is actively involved in the development of regulatory frameworks for a wide range of biological products regulated by BGTD. Recently, Dr. Nyarko has been actively involved the development of regulatory frameworks for vaccines, pharmacogenomics, subsequent entry biologics (biosimilars), and plant molecular farming products. The Special Projects Unit at BGTD contributes to enhancing the efficiency of the regulatory process of biologics and genetic therapies. Dr. Nyarko has been involved in developing national and international safety standards, guidance documents, and regulatory capacity building initiatives.



## **Conclusion & Closing Remarks**

### **Summary Report**

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### **Curriculum Vitae**

Dr. Satoshi Toyoshima is currently Executive Director, Director of Center for Product Evaluation at the Pharmaceuticals and Medical Devices Agency (PMDA). He is responsible for the review and evaluation of NDA, Biologics, OTC/Generic Drugs, Medical Devices and Conformity Audit.

He received his Ph.D. from University of Tokyo in 1975. His Specialized Field was Biochemistry, Immunology, and Regulatory Science.

His career includes a post doctoral fellow at the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), USA (1977-1979), an Associate Professor at University of Tokyo, Faculty of Pharmaceutical Sciences (Xenobiotics Immunochemistry) (1980-1992), Deputy Director-General of Pharmaceutical Basic Institute of Japan Tobacco Co. Ltd. (1992-1995), and a Professor at Hoshi University (Biochemistry) (1995-2000), before joining Pharmaceuticals and Medical Devices Evaluation Center (PMDEC), the predecessor of PMDA, as the Center Director in 2000.