Asia-Pacific
Economic Cooperation

APEC Harmonization Center Biosimilar Workshop

The 2nd Workshop of the APEC Harmonization Center

2009

APEC Life Sciences Innovation Forum

AHC
APEC Harmonization Center

APEC HARMONIZATION CENTER BIOSIMILAR WORKSHOP

The 2nd Workshop of the APEC Harmonization Center

2009

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APEC Life Sciences Innovation Forum
APEC Harmonization Center

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I. Executive Summary

1. Summary of Proceedings

The APEC Harmonization Center Biosimilar workshop is the second project of the Advancing the Regional Economic Integration through Regulatory Harmonization of APEC Harmonization Center. 434 participants from government authorities, industry and academia of 13 economies participated in the workshop. Especially, 12 government officials of the regulatory authorities of the APEC travel-eligible economies, including Malaysia, Thailand, Peru, Indonesia, Vietnam, and Philippines, were invited to participate in the workshop. As the self-funded project of the government of Korea, the workshop was supported by the APEC Life Sciences Innovation Forum (LSIF), hosted by the Korea Food and Drug Administration (KFDA) and organized by the Korea Health Industry Development Institute (KHIDI).

The main objectives of the workshop were: 1) to educate and engage participants in an interactive discussion on the specific harmonization issue of multi-regional clinical trials, demonstrating the complexity of the issue and the importance of a coordinated and collaborative approach; and 2) to place the specialized training in the regulatory issues of multi-regional clinical trials within the broader context of the harmonization of standards and regulatory procedures in life science products in order to show how such harmonization responds to APEC's goal of effective facilitation and liberalization of trade and investment among the APEC economies.

The workshop was divided into three sessions.

Session One. *The Opportunities and Challenges of Biological Medicines.* The session dealt with the presentations on: 1) Biotechnology Medicines: Opportunities & Challenges, 2) Biological & Biosimilar.

Session Two. *Regulatory Issues for Biosimilars.* Three presentations were made on: 1) Biosimilar FOB/FOPP SEB…., 2) From recombinant proteins to LMWHs (Low Molecular Weight Heparins) the EU regulatory expectations, 3) Biosimilars – Industry Perspective.

Session Three. *Regulatory Landscape on Biosimilars*. Speakers shared their views on: 1) Health Canada Perspective on Biosimilars, 2) ICH Overview & Impacts of Efficacy Guideline in Global Drug Development.

2. Summary of the Workshop Evaluation

The participants to the APEC Harmonization Center Biosimilar Workshop were asked to fill out a simple evaluation form composed of 13 questions.

The participants completed the evaluation showed greatest satisfaction on the knowledgeable speakers - 92.9% of the respondents said they are very satisfied (50%) or satisfied (42.9%) with the speakers' presentations, and 92.8% said they are very satisfied (35.7%) or satisfied (57.1%) with the accuracy and clarity of the presentations. The presentations were given by the experts who can best analyze and address the current situation.

All the respondents said that the workshop met their expectations (very satisfied - 25%, satisfied - 75%). The participants who submitted the evaluation also showed their satisfaction on: the presentation material provided by the organizer (42.9% very satisfied, 57.1% satisfied); the scope of information presented (46.2% very satisfied, 53.8% satisfied) and; the usefulness of the information (46.2% very satisfied, 53.8% satisfied).

II. APEC Harmonization Center Biosimilar Workshop

1. Participants

- **VIPs, Speakers, and Moderators**

	**Opening Remarks** ***Seung Hee Kim (Korea)*** Director, APEC Harmonization Center President, National Institute of Food and Drug Safety Evaluation
	**Welcoming Address** ***Sang Yong Lee (Korea)*** Deputy Commissioner, Korea Food and Drug Administration
	**Welcoming Address** ***Bup Wan Kim (Korea)*** President, Korea Health Industry Development Institute
	**Session I** ***Chiyoung Ahn (Korea)*** Director, Advanced Therapy Products Division, Biopharmaceuticals and Herbal Medicine Bureau, Korea Food and Drug Administration
	**Session I** ***Jacques Turgeon (Canada)*** Director of Research, Centre Hospitalier de L'Université de Montreal
	**Session I** ***Kum Cheun Wong (Singapore)*** Director, Global Regulatory Affairs, Strategic Policy and Intelligence, Asia Pacific Johnson & Johnson Pharmaceuticals Group

	**Session I, III** ***Michael Müenzberg (Germany)*** Global Head of Medical Affairs, Marketing/Medical BP, Sandoz International GmbH
	**Session II** ***Eric Bigaud (France)*** Head of Regulatory & Technical support, Asia Pacific & Russia, Sanofi-Aventis
	**Session II** ***Estelle Michael (Belgium)*** Senior Manager, Regulatory Policy, GlaxoSmithKline Biologicals
	**Session II, III** ***Anthony Ridgway (Canada)*** Senior Regulatory Scientist, Biologics and Genetic Therapies Directorate, Health Canada
	**Session III** ***Arpah Abas (Malaysia)*** Head of Biotech Section, National Pharmaceutical Control Bureau, Ministry of Health, Malaysia
	**Session III** ***Prapassorn Thanaphollert (Thailand)*** Senior Pharmacist, Biological Products Group, Drug Control Division, Thai FDA
	**Session III** ***Soo-kyoung Suh (Korea)*** Senior Scientific Officer, Advanced Therapy Products Division, Biopharmaceuticals and Herbal Medicine Bureau, Korea Food and Drug Administration

- **Delegates**

Herawati (Indonesia) Head, Section of New Drug Evaluation, NADFC-Indonesia
Muhti Okayani (Indonesia) Head, Section of Therapeutic Product Standardization, NADFC-Indonesia
Bin Shahrir Mohamed Shahrizan (Malaysia) Assistant Director, Centre for Product Registration, Ministry of Health, Malaysia
Lis Sie Tan (Malaysia) Senior Principal Assistant Director, Centre for Post Registration, Ministry of Health, Malaysia
Aura Amelia Castro Balarezo (Peru) Pharmaceutical Chemist, Ministry of Health (DIGEMID)
Hans Demetrio Vasquez Soplopuco (Peru) Senior Specialist, Ministry of Health (DIGEMID)
Arlyn Magno (Philippines) Food-Drug Regulation Officer I, Philippines Bureau of Food and Drugs
Christine Senõron (Philippines) Food and Drug Regulation Officer II/Laboratory Analyst, Philippine Food and Drug Administration Satellite Laboratory for Mindanao
Vinit Usavakidviree (Thailand) Director of Drug Control Division, Thai FDA
Pinpong Intarapanich (Thailand) Senior Pharmacist, Thai FDA
Le Van Giao (Vietnam) Chief of Officer, Vietnam Medical Device Association
Trinh Duc Nam (Vietnam) Expert, Ministry of Health Vietnam

2. Proceedings of the Workshop

2.1 Workshop Program

Day One

Wednesday, September 16, 2009	
9:00 – 10:00	***Registration***
10:00 – 12:30	**Opening Ceremony and Plenary Session (BIO KOREA)** • **Dr. Tim Hunt (Sir Richard Timothy Hunt),** Principal Scientist**,** Cancer Research UK Clare Hall Laboratories • **G. Steven Burrill,** CEO**,** Burrill & Company • **Dr. Jeong-Sun Seo,** Professor, College of Medicine, Seoul National University, Chairman, Macrogen Inc.
12:30 – 14:00	***Lunch***
14:00 – 18:20	**BIO KOREA Conference** • **Track 1: Bioindustry in UK & Korea** - Microfluidics System - High Throughput Analysis for Diagnosis and Drug Discovery • **Track 2: Issues to Address in Life Science BD & Funding** - Update on Changing Trends in Venture Investments - Critical Issues for Successful IR of Life Science Venture Companies • **Track 3: Technology Transfer and Licensing** - Building and Enforcing IP Value in Korea - The Journey from Discovery to the Market in the Life Sciences • **Track 4: Traditional Medicine** - Recent Trends of R&D for Traditional Medicine in East-Asia - Recent Policy Trends of Traditional Medicine in East-Asia • **Track 5: Korea-Scotland Joint Symposium** • **Track 6: Recent Advances of Stem Cell Differentiation** - Cell Differentiation from Human ES Cells - Derivation of Tissue Specific Stem Cell
18:30 -	***Welcoming Reception***

Day Two

Thursday, September 17, 2009	
8:30 – 9:00	***Welcome and Introduction***
9:00 – 10:30	**Session I: The Opportunities and Challenges of Biological Medicines** ***Description:*** • Background on special features of biological medicines • Role of biologics, including biosimilars, in medicine • Challenges with biologics and biosimilars
10:30 – 11:00	***Morning Refreshments***
11:00 – 12:30	**Session II : Regulatory Issues for Biosimilars** ***Description:*** • Key considerations for regulatory evaluation of a biosimilar product: -Biosimilar Paradigm—what allows for abbreviated pre-clinical and clinical data - Quality Issues - Safety and Efficacy issues • Case Study: European model and experience
12:30 – 14:00	***Lunch***
14:00 – 16:00	**Session III: Regulatory Landscape on Biosimilars** ***Description:*** • Current status of laws and regulations in the APEC Region: Australia, Canada, Chinese Taipei, Japan, Korea, Malaysia, Singapore and the U.S. • Current status of WHO draft guidelines
16:00 – 16:30	***Afternoon Refreshments***
16:30 – 17:30	**Plenary- Feedback from the Sessions** **Summary/ Next Steps/ Meeting Adjourned**
17:30 – 18:00	***Group Photo Session***
18:00 –	***Networking, Wine & Cheese Reception***

Day Three

Friday, September 18, 2009
Half Day Seoul City Tour & GMP Tour

Program at Glance

<table>
<tr><th></th><th>DAY 1 (Sept. 16)</th><th>DAY 2 (Sept. 17)</th><th>DAY3 (Sept. 18)</th></tr>
<tr><td>08:30 – 09:00</td><td rowspan="2">Registration</td><td>Welcome and Introduction</td><td rowspan="9">BIO KOREA

Exhibition/ Conference/ Business Forum

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AHC

GMP Were Visit/ Half Day Seoul Tour</td></tr>
<tr><td>09:00 – 10:30</td><td rowspan="3">BIO KOREA

Opening Ceremony and Plenary Session</td><td>Session I:
The Opportunities and Challenges of Biological Medicines</td></tr>
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<tr><td>14:00 – 16:00</td><td>BIO KOREA Conference Tracks 1-6</td><td>Session III:
Regulatory Landscape on Biosimilars</td></tr>
<tr><td>16:00 – 16:30</td><td>Afternoon Refreshments</td><td>Afternoon Refreshments</td></tr>
<tr><td>16:30 – 17:30</td><td rowspan="2">BIO KOREA Conference Tracks 1-6</td><td>Plenary - Feedback from Sessions
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<tr><td>18:00 –</td><td>Welcoming Reception</td><td>Networking, Wine & Cheese Reception</td></tr>
</table>

2.2 Presentations from the Workshop

- **Session I: The Opportunities and Challenges of Biological Medicines**

Biotechnology Medicines: Opportunities & Challenges

Speaker:

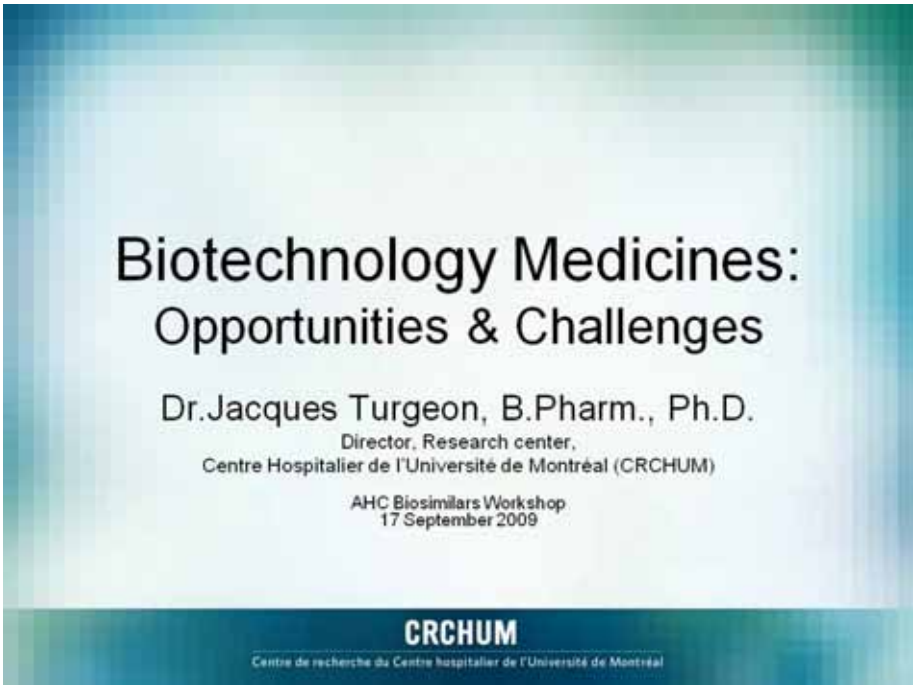
Jacques Turgeon (Canada)

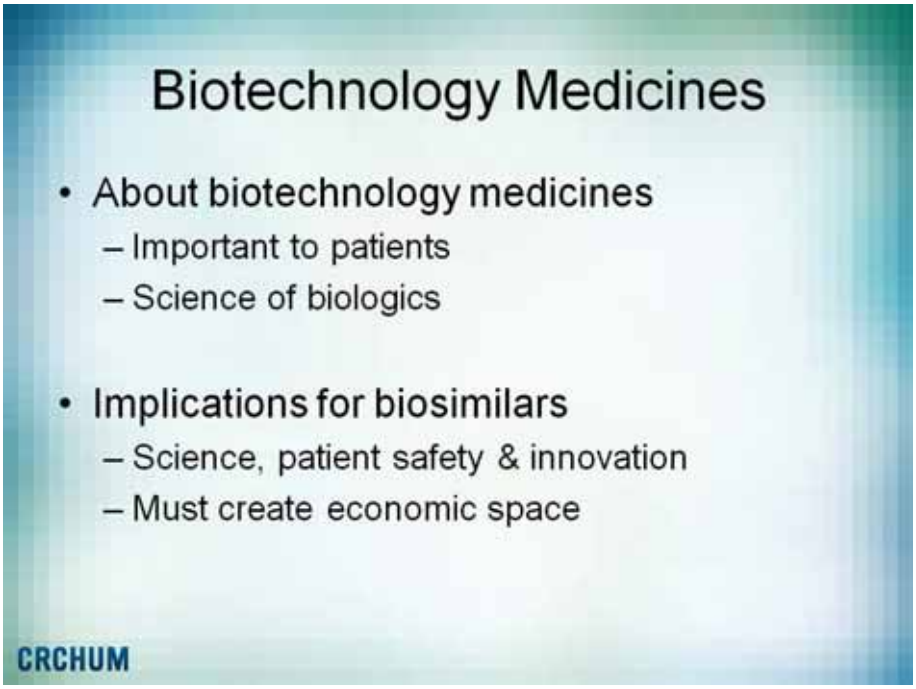
Director of Research

Centre Hospitalier de L'Université de Montreal

Abstracts

Biotechnology medicines hold some of the greatest promise for medical breakthroughs. There are more than 160 currently available biotechnology medicines to treat and cure serious diseases ranging from multiple sclerosis to leukemia and hepatitis and more than 350 new biotech medicines in development. These medicines are complex and made from living things, requiring a high degree of sophistication in production and distribution to help ensure safety and efficacy. With recent advances in technologies, there is a growing interest in making "biosimilar" versions of these breakthrough biotech medicines. Care must be taken that biosimilars are produced to a high level of quality and undergo appropriate biochemical, pre-clinical and clinical testing to ensure they are safe and effective. The future success of new biotech medicines and biosimilars depends on using the best science and putting patients first.


Biotechnology Medicines:
Opportunities & Challenges
Dr.Jacques Turgeon, B.Pharm., Ph.D.
Director, Research center,
Centre Hospitalier de l'Université de Montréal (CRCHUM)
AHC Biosimilars Workshop
17 September 2009
CRCHUM
Centre de recherche du Centre hospitalier de l'Université de Montréal


Biotechnology Medicines
• About biotechnology medicines
– Important to patients
– Science of biologics
• Implications for biosimilars
– Science, patient safety & innovation
– Must create economic space
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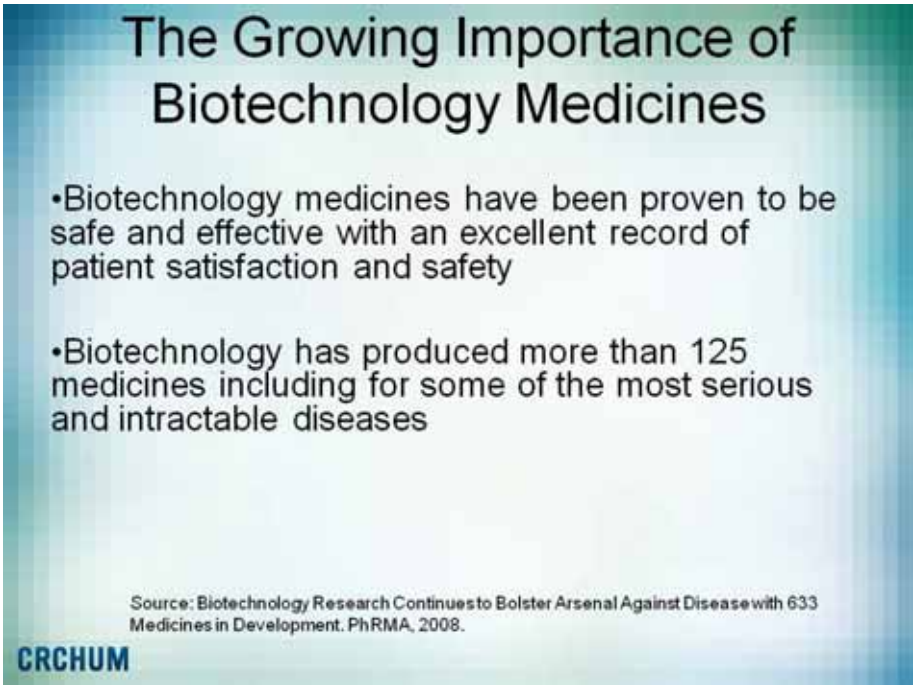
The Growing Importance of Biotechnology Medicines
•Biotechnology medicines have been proven to be safe and effective with an excellent record of patient satisfaction and safety
•Biotechnology has produced more than 125 medicines including for some of the most serious and intractable diseases
Source: Biotechnology Research Continues to Bolster Arsenal Against Disease with 633 Medicines in Development. PhRMA, 2008.
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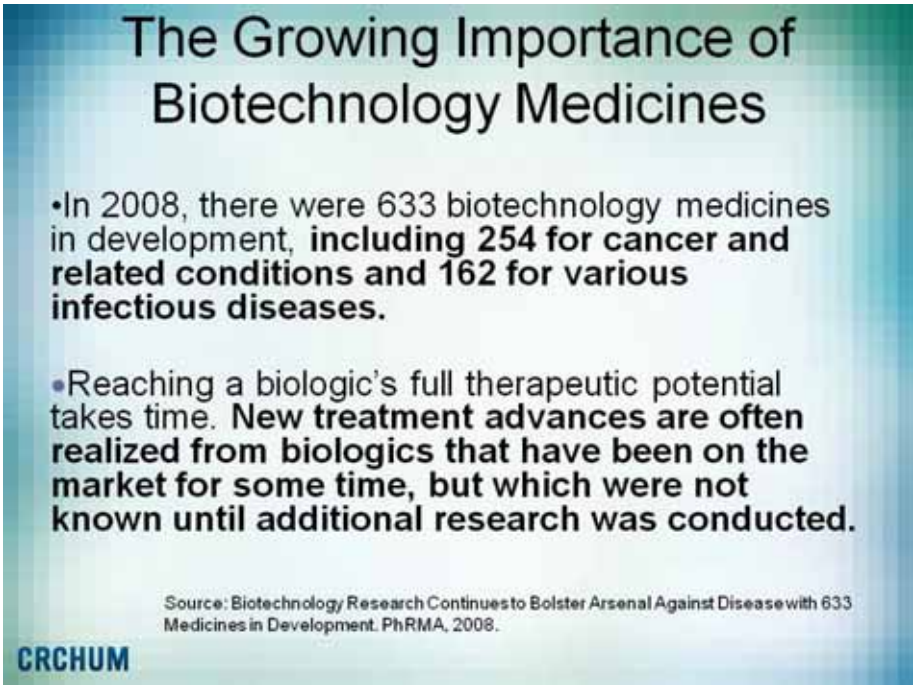
The Growing Importance of Biotechnology Medicines
•In 2008, there were 633 biotechnology medicines in development, **including 254 for cancer and related conditions and 162 for various infectious diseases.**
•Reaching a biologic's full therapeutic potential takes time. **New treatment advances are often realized from biologics that have been on the market for some time, but which were not known until additional research was conducted.**
Source: Biotechnology Research Continues to Bolster Arsenal Against Disease with 633 Medicines in Development. PhRMA, 2008.
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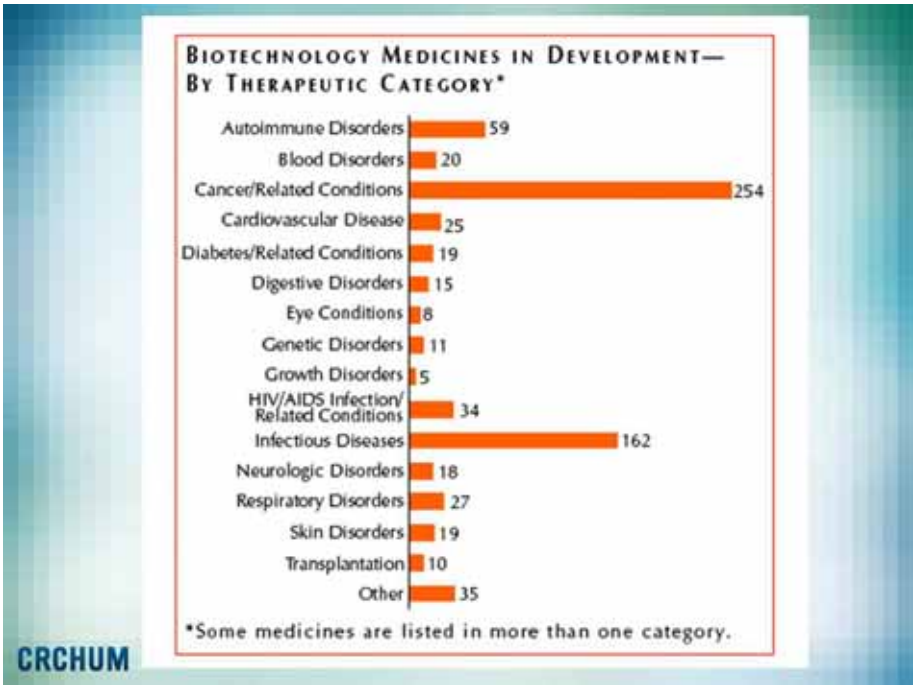

Importance of Biologics for Patients
Example--Herceptin

- **Herceptin** (trastuzumab)
  - One of the earliest and most common examples of personalized medicine.
  - About 30% of women have a form of breast cancer that over-expresses a protein called HER2, which is not responsive to standard therapy.
  - Approved for patients with HER2 positive tumors in 1998
  - Further research showed in 2005, that it reduced recurrence by 52% in combination with chemotherapy.
  - *New England Journal of Medicine* commentary: findings suggested "a dramatic and perhaps permanent perturbation of the natural history of the disease, maybe even a cure."

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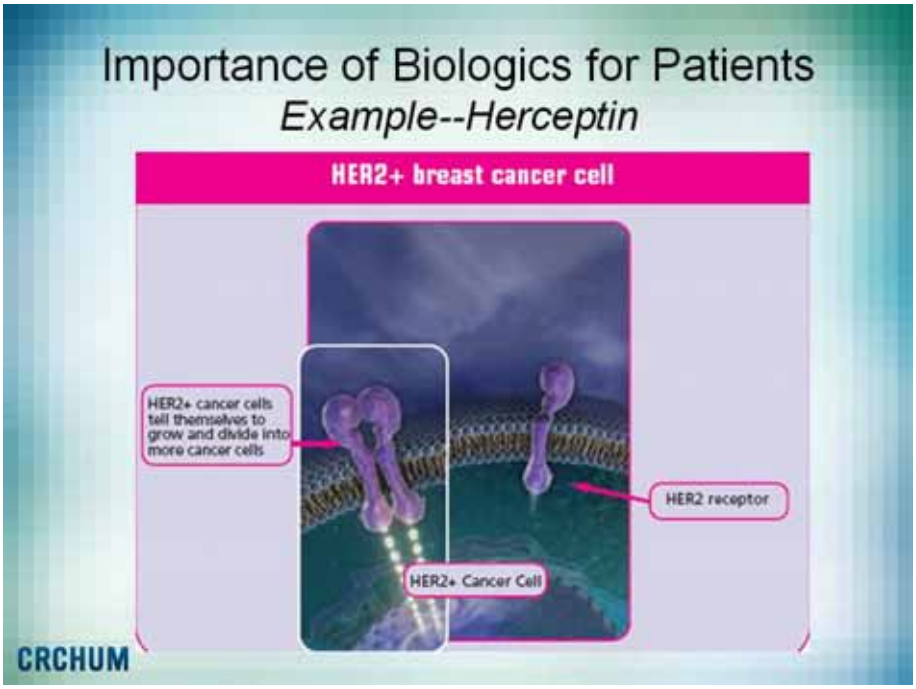
Importance of Biologics for Patients
Example--Herceptin
HER2+ breast cancer cell
HER2+ cancer cells tell themselves to grow and divide into more cancer cells
HER2 receptor
HER2+ Cancer Cell
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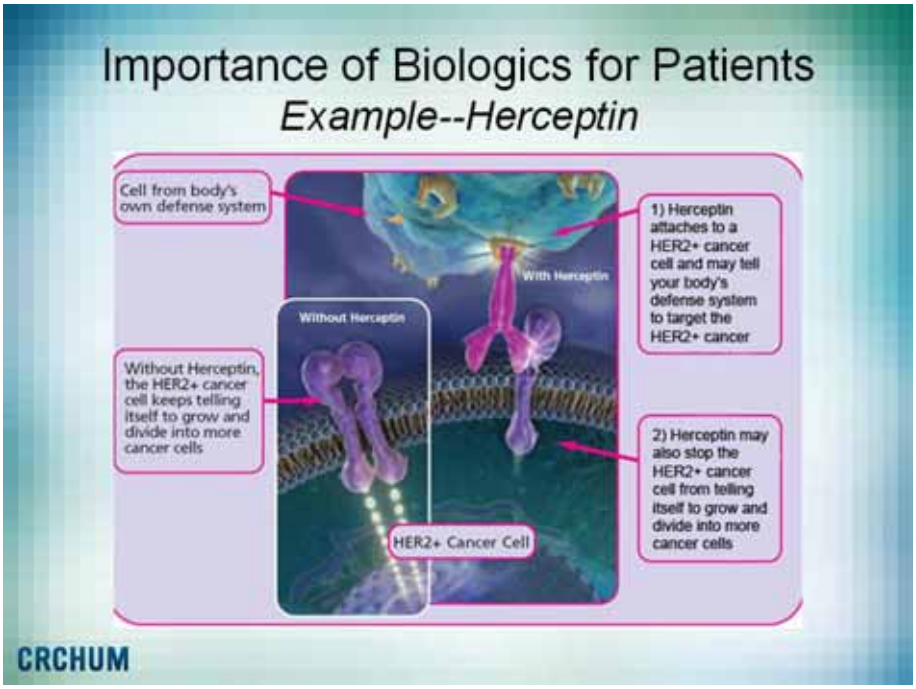
Importance of Biologics for Patients
Example--Herceptin
Cell from body's own defense system
With Herceptin
Without Herceptin
1) Herceptin attaches to a HER2+ cancer cell and may tell your body's defense system to target the HER2+ cancer
Without Herceptin, the HER2+ cancer cell keeps telling itself to grow and divide into more cancer cells
2) Herceptin may also stop the HER2+ cancer cell from telling itself to grow and divide into more cancer cells
HER2+ Cancer Cell
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Importance of Biologics for Patients
Example--Avastin

- **Avastin** (bevacizumab)
  - New approach to attacking tumors by cutting off blood supply (angiogenesis inhibitor)
  - 30 years of research
  - Approved in 2004 to treat metastatic colorectal cancer
  - Since then Avastin has been "a mini-pipeline all by itself" proving effective treatment against several other forms of cancer.
    - For non-small cell lung cancer patients, Avastin combined with chemotherapies can slow cancer growth by up to 25%.

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Importance of Biologics for Patients
Example--Rituxan

- **Rituxan** (rituximab)
  - First therapeutic antibody approved to treat cancer in the U.S.
  - Approved in 1997 to treat a type of non-Hodgkin's lymphoma.
  - Since been approved as a first-of-its-kind treatment for rheumatoid arthritis (RA).
    - Because it works differently than all other RA treatments, Rituxan is viewed as an "important new treatment approach for patients who do not respond adequately to [other treatments]."

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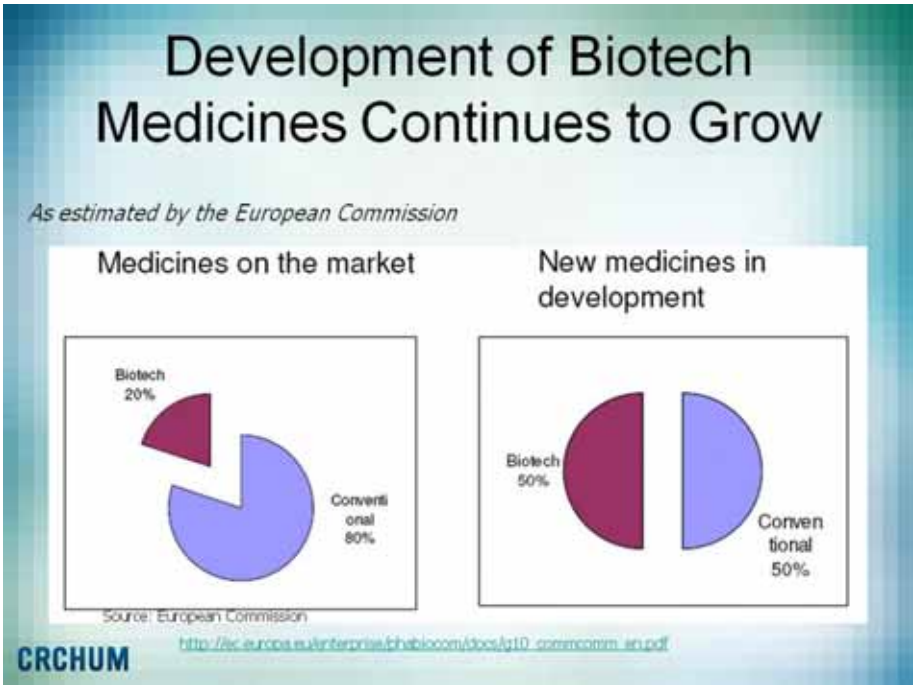
Development of Biotech Medicines Continues to Grow
As estimated by the European Commission
Medicines on the market
New medicines in development
Biotech 20%
Conventional 80%
Biotech 50%
Conventional 50%
Source: European Commission
http://ec.europa.eu/enterprise/pharmaceuticals/docs/g10_commcomm_en.pdf
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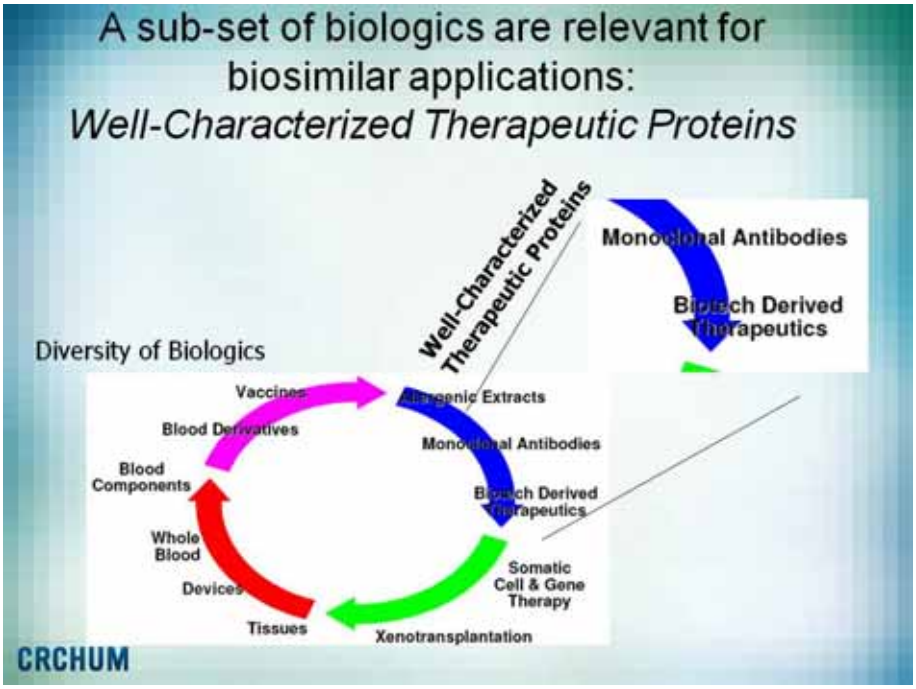
A sub-set of biologics are relevant for biosimilar applications:
Well-Characterized Therapeutic Proteins
Well-Characterized Therapeutic Proteins
Monoclonal Antibodies
Biotech Derived Therapeutics
Diversity of Biologics
Vaccines
Blood Derivatives
Blood Components
Whole Blood
Devices
Tissues
Allergenic Extracts
Monoclonal Antibodies
Biotech Derived Therapeutics
Somatic Cell & Gene Therapy
Xenotransplantation
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Focus on Biotechnology Medicines

- Derived from living material
- Usually based on protein and/or nucleic acid
- Genetic engineering (not organic chemistry)
- Used for the treatment of diseases in humans

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Focus on Biotechnology Medicines

- Recombinant DNA
- Monoclonal antibodies
- Antisense therapy
- Gene therapy
- Rational drug design

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Biotechnology Medicines are Different from Small Molecule Drugs

- Composition, Size, Structure
  - Larger, more complex, more heterogeneous
- Manufacturing
  - Genetic engineering vs. organic chemistry
  - Synthesis by living cells/organisms
- Clinical Safety
  - Species specificity limits standard pre-clinical models for safety testing
  - Usually injected
  - Immunogenicity

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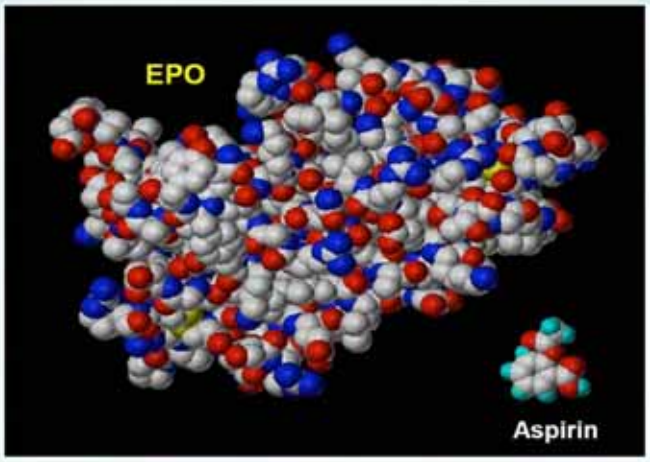
Aspirin versus a hormone



Source: Dr. Adrian Thomas, Johnson & Johnson

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Characteristics of Biotech Medicines Production Process

- Biotech medicines are made from live cells
- Takes months, not weeks, to produce a run or batch
- To obtain consistent results, precise controlling necessary

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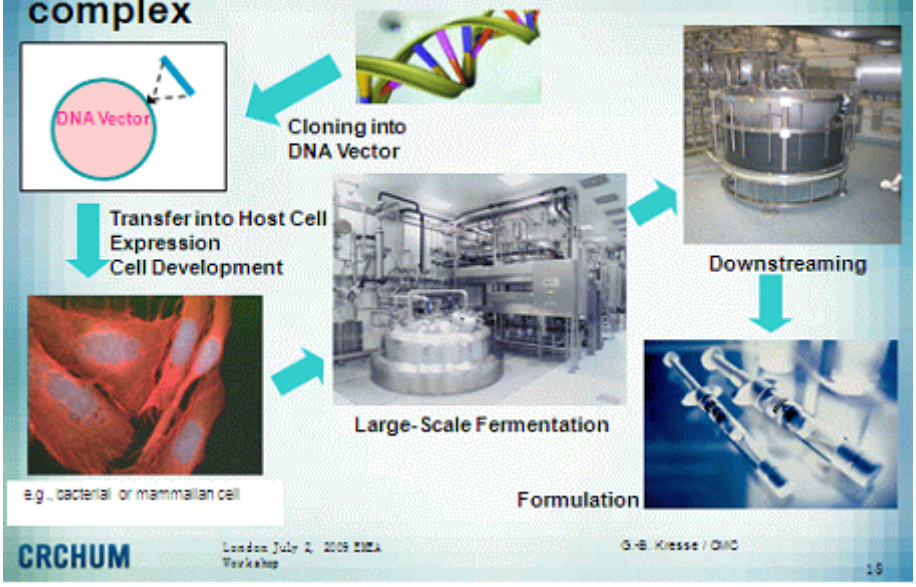
Manufacturing of recombinant proteins is complex



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Immunogenicity—clinical concern for biotech medicines, not for small molecule medicines

- Small molecule drugs rarely elicit immune responses
- Proteins (biotech medicines) are capable of triggering immune responses with varying consequences
- Immunogenicity of biologic drugs is unpredictable, unforeseeable
- Small changes in a biologic molecule can completely shift its immunogenicity profile

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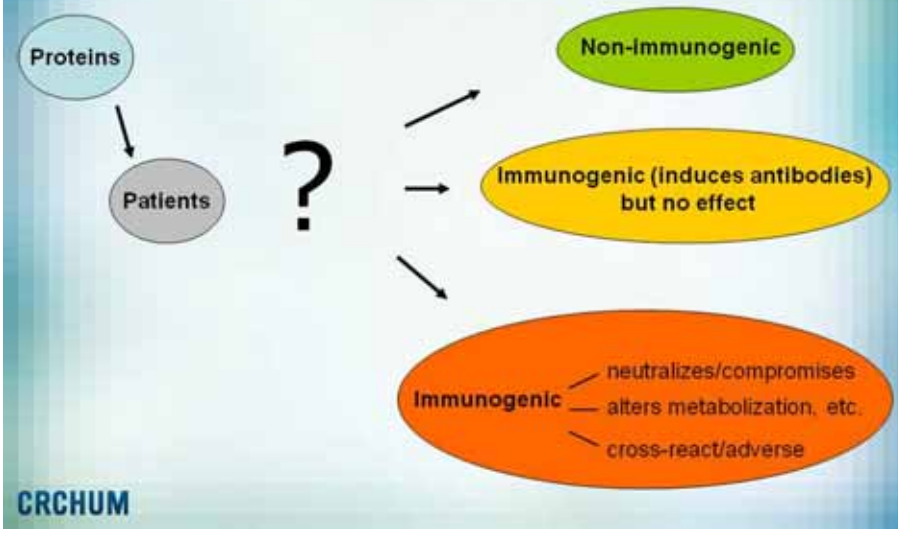
Unwanted Immunogenicity Unpredictable



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Biotechnology Medicines

- Important for treatment and cure of serious disease
- Complex, difficult to make and ensure consistency for safety and efficacy in patients
- Potential for breakthrough in disease treatment

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Implications for Biosimilars

- Biosimilars
- Subsequent Entry Biologics (SEB)
- Follow-on Biologics (FOB)
- Similar Biotherapeutic Products (SBP)

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Equivalent, same, different, similar

- The generic drug considered to be **equivalent** to a brand-name drug will elicit the **same clinical effects** at a **lower cost** for the **patient** and the **society.**
- The few exceptions to the first assumption can be predicted *a priori*

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Equivalent, same, different, similar

- Drug products are considered to be **therapeutic equivalents** only if they are **pharmaceutical equivalents** and if they can be expected to have the **same clinical effect and safety profile** when administered to patients under the conditions specified in the labeling.

* Orange Book

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Equivalent, same, different, similar

- **Drug products are considered pharmaceutical equivalents if they:**
  - Contain the same active ingredient(s)
    - Salt, enantiomer, purity, …
  - Are of the same dosage form
  - Have the same route of administration
  - Are identical in strength

* Orange Book

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Biosimilars
Scientific basis for approval

- Similar ≠ Same
  - Everything else follows from this:
    - Require Clinical trials
    - Different names
    - No scientific basis for automatic substitution

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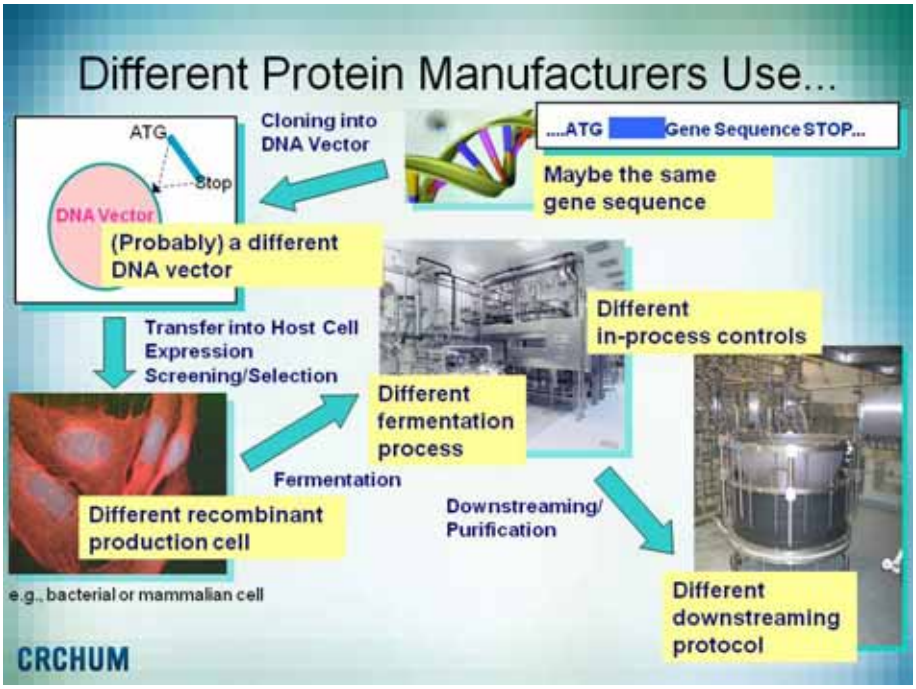

Same, different, similar

- Generic drug approval pathway premised on ability to make and show that generic drug is the equivalent to the innovator drug (exposure)
  - Not better, not worse
- Biotech medicines from different and unrelated manufacturers may be similar, not the same
- At this time, biosimilars are not (cannot be) evaluated by processes as stringent as those developed for generics
  - The regulatory pathway should reflect this in the approval requirements.

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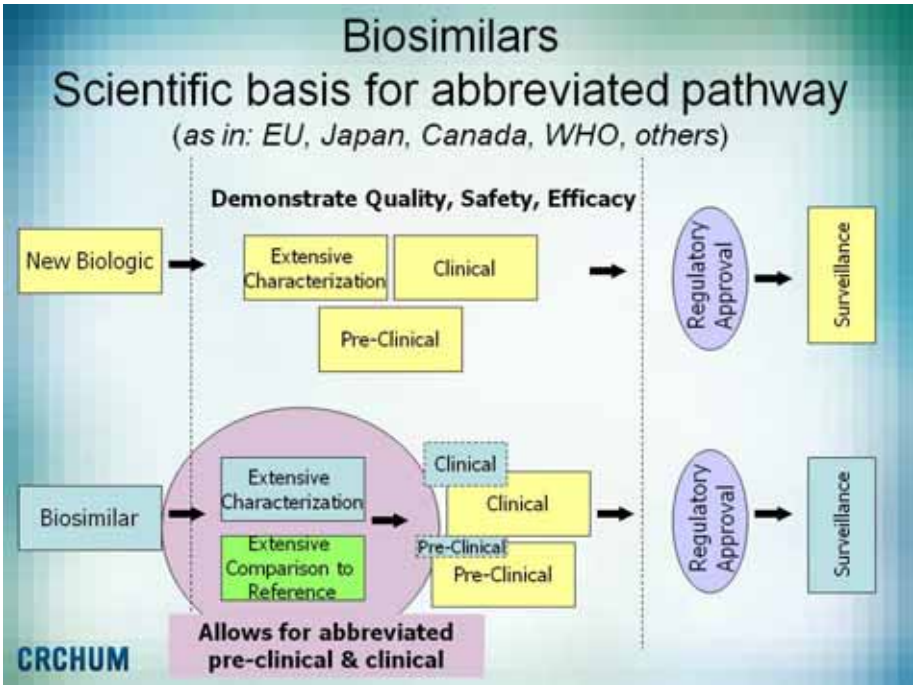
Biosimilars
Scientific basis for abbreviated pathway
(as in: EU, Japan, Canada, WHO, others)
Demonstrate Quality, Safety, Efficacy
New Biologic
Extensive Characterization
Clinical
Pre-Clinical
Regulatory Approval
Surveillance
Biosimilar
Extensive Characterization
Extensive Comparison to Reference
Clinical
Clinical
Pre-Clinical
Pre-Clinical
Regulatory Approval
Surveillance
Allows for abbreviated pre-clinical & clinical
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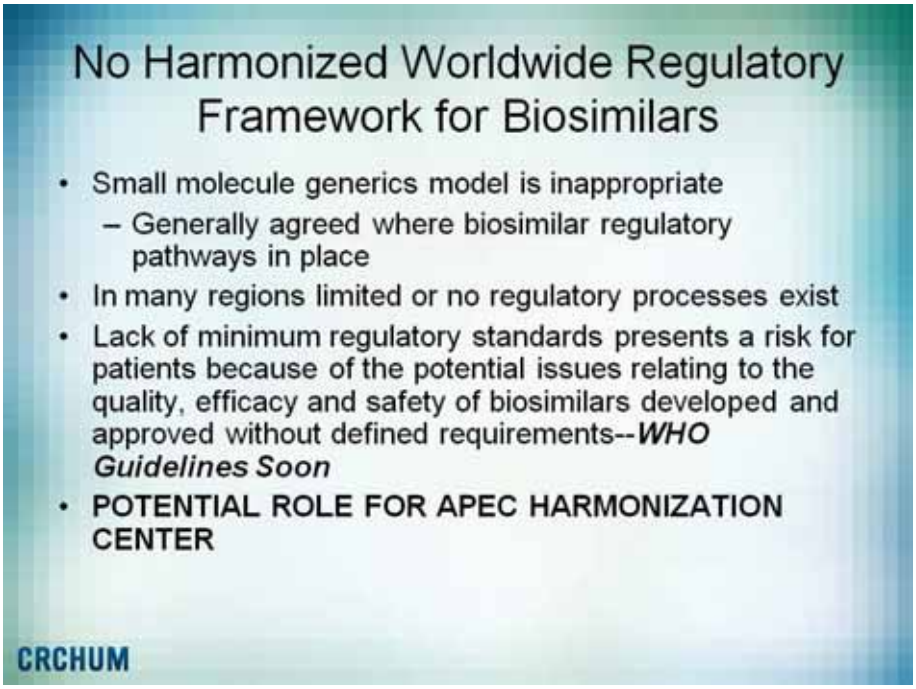
No Harmonized Worldwide Regulatory Framework for Biosimilars
• Small molecule generics model is inappropriate
– Generally agreed where biosimilar regulatory pathways in place
• In many regions limited or no regulatory processes exist
• Lack of minimum regulatory standards presents a risk for patients because of the potential issues relating to the quality, efficacy and safety of biosimilars developed and approved without defined requirements--*WHO Guidelines Soon*
• POTENTIAL ROLE FOR APEC HARMONIZATION CENTER
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Fingerprints of the products

- Biotechnology companies
  - Most active elements in the product
  - Other active elements
  - Modulatory elements
  - Other elements
- Biosimilar companies
  - Most provide an equivalent biological profile for all identified products
  - Regulatory control on each element to be compared
  - Intra-batch, and inter-batch variability compare to BioTech
- Methods
  - metabolomics (in vitro, in vivo)
  - Proteomics
  - LC-MS-NMR

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In brief…to use the generic pathway

- Biosimilars must be "the same"
- Biosimilars must be cheaper
- Biosimilars must be designed for the same indication as a previous innovative biologic
- Biosimilars must be prescribed to save money

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In Conclusion
• Biotechnology medicines are complex
• Patient safety and sound science are fundamental
• Strong intellectual property protections are essential to promoting innovation that meets patients' needs through new biotech medicines.
• Biosimilars may provide less expensive alternatives
– They should create economic space for new biologics or drugs
• But only with the appropriate regulatory control to ensure safety and efficacy for patients
– Topics covered in Sessions II & III
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Thank you!
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New Medicine Development is Lengthy, Costly, and Risky

- New medicine development is a lengthy process: The average development time has increased to between 10 and 15 years.[1]
- The R&D process is very risky: For every 5,000 to 10,000 compounds tested, just 5 will make it to clinical trials and, of those, only 1 will eventually receive FDA approval.
- R&D expenditures for each new biologic averaged $1.24 billion in 2006.[1]
- Only 2 in 10 approved medicines bring in enough revenue to recoup the average cost of development.
- Individual company returns reflect the high risk and long lead times inherent in drug discovery and development.

> *It is virtually impossible to find other historical examples [outside of the biotech sector], at least at the industry level, for which such a large fraction of new entrants can be expected to endure such prolonged periods of losses and for which the vast majority may never become viable economic entities.*[2]
>
> — *Gary Pisano, Harvard Business School*

Sources: [1] DiMasi, JA and Grabowski, HG. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 28:469-79 (Jun. 2007); PhRMA. "Drug Discovery and Development: Understanding the R&D Process." (2007). [2] Pisano, GP. "Science Business – the Promise, the Reality, and the Future of Biotech."

CRCHUM

Protections to encourage R&D for New Biotech Medicines

- R&D efforts need protection
  - Patents (e.g. composition of matter, methods of using products and methods of manufacturing)
  - Trade secrets
  - Data and market exclusivity

CRCHUM

- **Session I: The Opportunities and Challenges of Biological Medicines**

Biological & Biosimilar

Speaker:
Kum Cheun Wong (Singapore)
Director,
Global Regulatory Affairs, Strategic Policy and Intelligence
Johnson & Johnson Pharmaceuticals Group

Abstracts

Biologics has enabled us to find cures for some of the most serious known diseases.

Today, patients have access to more than 150 biopharmaceuticals. However, biologics is a complicated science as they are produced using a living systems or organism. They are different from small molecules medicines and a better understanding is needed. The complexity in structure, manufacturing process and risk of immunogenecity the generic drug review process cannot be applied to biosimilar products. There is a need for health authority in the region to regulate the biosimilars in a scientific way to ensure safety, efficacy and quality.

EMEA is the 1st regulatory authority in the world to publish biosimilar guidance. Other regulatory authority in Asia has began to develop guidelines biosmilars in their respective countries. Other considerations such as naming of biosimilar, immunogenecity and substitution are issues to considered in developing any guidance.

Biological & Biosimilar

APEC Harmonization Center Biosmilar Workshop

Wong Kum Cheun, Director
Global Regulatory Affairs Strategic Policy & Support
Johnson & Johnson Pharmaceuticals group

Johnson & Johnson

Overview

- Value of biologics
- Why biopharmaceuticals are different
- Regulation of biosimilar
- Points to consider

Cornerstones in biotechnology history which have influenced the production of biologics

1953: Discovery of DNA structure

1973: Discovery of DNA restriction enzymes

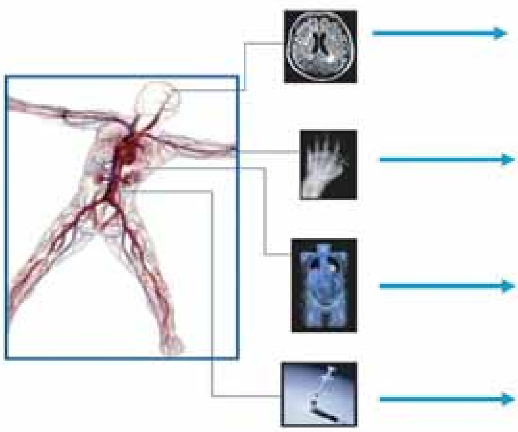
1977: Genentech, first biotech-enterprise founded

1982: First biopharmaceutical approved by FDA: recombinant human insulin

1986: First recombinant vaccine (HepB) is approved for human use, first recombinant anti-cancer drug (Interferon) is produced

2003: Human genome sequenced

Biologics Help Treat Severe Diseases



Multiple Sclerosis: the use of recombinant interferon-beta has dramatically improved MS patients' quality of life by reducing crisis by 30% [1]

Rheumatoid arthritis: New therapies counteract the deterioration of joints after 48 hours of having initiated the treatment [2]

Cancer: New monoclonal antibodies attack only cancerous cells and are less toxic than chemotherapy [3]

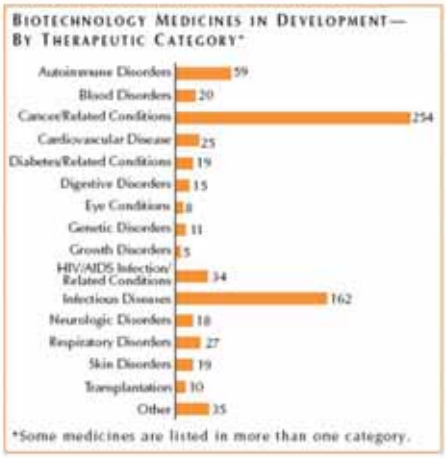
Diabetes: insulin analogs allow for a better control of blood sugar levels and reduce complications stemming from the disease [4]

1- National Institute of Neurological Disorders and Stroke. NINDS Multiple Sclerosis Information Page [illegible]
2- [illegible]
3- [illegible]
4- Israel Hartman. Insulin Analogs: Impact on Treatment Success, Satisfaction, Quality of Life, and Adherence. Clinical Medicine and Research. Vol 6 (2) 54-67. 2008

Examples of important biologic products

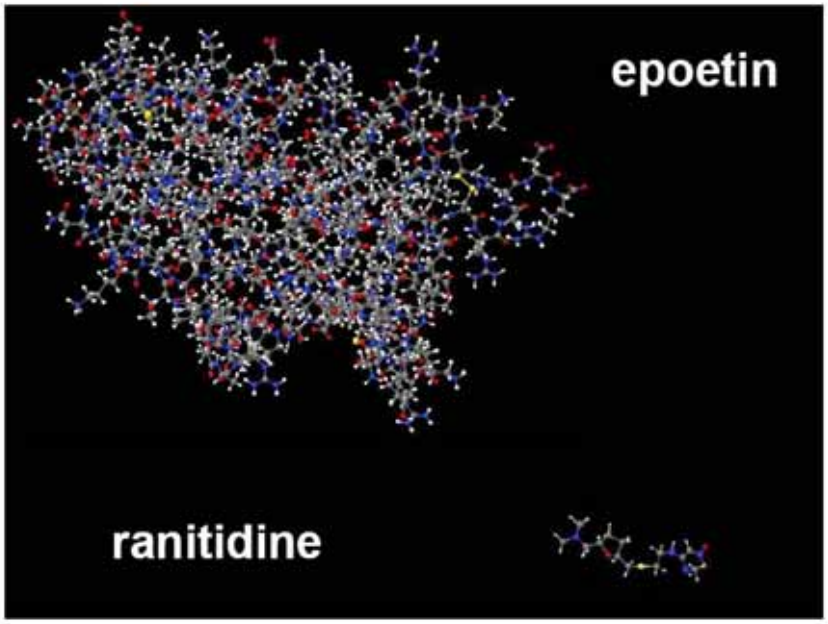
Trade name (US)	*Used to treat*	*Developed by*
Epogen® Procrit®	Anemia	Amgen
Rebotron® Intron-A® Roferon®	Hepatitis B,C,D Leukemia, Lymphoma	Schering-Plough Roche
Humulin® Lantus® Levemir®	Diabetes	Eli Lilly, Sanofi Aventis NovoNordisk
Betaseron® Rebif®	Multiple sclerosis	Bayer Serono
Saizen®	Growth control	Serono
Enbrel®	Arthritis, Psoriasis,	Amgen, Wyeth

Biotech Medicines in Development



Source: http://www.phrma.org/files/Biotech%202008.pdf

Why biopharmaceuticals are different



Biological Products are Different

Product	Molecular Weight
CHEMICAL	
Aspirin	180
Ranitidine (Zantac®)	351
Atorvastatin (Lipitor®)	1209
BIOLOGICAL	
Insulin	~5800*
Epoetin	~30000*
Factor VIII	~266000*

*depends on brand

Source: Biotechnology Industry Organization: "Follow-On Biologics: An Introduction"

Why biopharmaceuticals are different

- High molecular weight
- Complex three-dimensional structure
- Complex manufacturing process
- Produced by living organisms, therefore often heterogeneous
- Difficult to characterize completely by physico-chemical analytical methods or bioassays
- Dependence of biological activity on reproducibility of the production process, in-house standards, and maintaining cold chain integrity
- Prone to eliciting an immune response

Biosimilars are *not* generic biopharmaceuticals

Crommelin DJA, et al. Int J Pharm 2003;266:3-16.

Manufacturing

- The manufacturing process for a biopharmaceutical is far more complex than that for a low molecular weight drug
- Chemically-based drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions

  – This is Organic Chemistry
- Biopharmaceuticals are made by harvesting the substances produced and secreted by constructed cells

  – This is Genetic Engineering

These differences clearly apply to biosimilars as well as to original biopharmaceuticals

Biologics' Complex Manufacturing Process

Clinical Safety

- Species specificity limits standard pre-clinical models for safety testing
- Usually injected
- Immunogenicity

Immunogenicity

- Human reaction to the introduction of a foreign protein*
- Small molecule drugs rarely elicit immune responses
- Macromolecules (proteins) like biologic drugs are capable of triggering immune responses with varying consequences, e.g.,
  - Antibodies may neutralize the molecule making it therapeutically ineffective
  - There may be no clinical effect
  - Rare but serious autoimmune responses can be life-threatening
- Immunogenicity of biologic drugs is unpredictable, unforeseeable
- Small changes in a macromolecule can completely shift its immunogenicity profile

*H. Schellekens. Factors influencing the immunogenicity of therapeutic proteins. Nephrol Dial Transplant (2005). 20 (Suppl 6): vi3-vi9

What is biosimilar?

"A biological medicinal product referring to an existing one and submitted to regulatory authorities for marketing authorization by an independent application after the time of the protection of the data has expired for the original product."

Source: Dan Crommelin, et. Al. Pharmaceutical evaluation of biosimilars: important differences from generic low-molecular-weight pharmaceuticals. EJHP. Vol 11 (1):11-17. 2005.

What is biosimilar?

- EU it is known as "similar biological medicinal product"
  Directive 2001/83/EC, as amended – Article 10.4: Definition
  - " Where a biological medicinal product which is similar to a reference biological product does not meet the definition of a generic medicinal product, owing to, in particular, differences in raw material or differences in manufacturing processes of the biological and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines"

Regulation of Biosimilar

No Harmonized Worldwide Regulatory Framework for Biosimilars

- Small molecule generics model is inappropriate
- In many regions limited or no regulatory processes exist
- Lack of minimum regulatory standards presents a risk for patients because of the potential issues relating to the quality, efficacy and safety of biosimilars developed and approved without defined requirements
- The EU is currently the most advanced region in terms of having a developed regulatory pathway for biosimilar medicines

Overview of biosimilar regulations

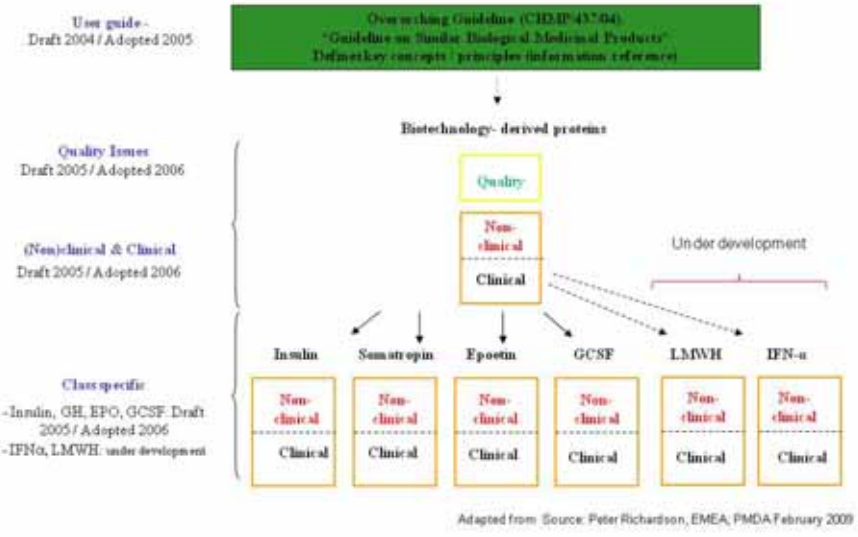
- EU
  - ❖ First region to address pathway
  - ❖ Legislation and regulations final
  - ❖ Based on science
- US
  - ❖ No legislation or regulations
  - ❖ Highly charged politically
  - ❖ FOB legislation timing… 2009?
  - WHO – Draft guideline
- AP
  - ❖ Countries in AP with specific guideline e.g Australia, Malaysia, Taiwan, Japan, S. Korea & Singapore.

EU Legal framework for biosimilars

- Directive 2004/27/EC - Article 10:
  - 2.(b) "generic medicinal product": same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.
  - 4. Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.
  - The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in the Annex and the related detailed guidelines…

Concept of 'biosimilarity' ≠ from concept of 'essential similarity'

EMEA Biosimilar Guidelines



Overarching guideline on biosimilars: key aspects

- Outlines concepts and basic principles of the legislation
  - Biosimilars are not generic medicines
  - Consideration of analytical methods, ability to characterise the product, manufacturing process, clinical and regulatory experience
- Choice of reference product
  - Authorised in the EU
  - Similar in molecular and biological terms
  - Same reference product to be used in quality, safety and efficacy studies
  - Same pharmaceutical form, strength and route of administration
- Subtle differences between biosimilar and the reference product can be expected
  - Specific product given to patient should be clearly identified to support pharmacovigilance monitoring post-marketing

Comparability Exercise for Quality

Manufacturing Process	Qualities Criteria To Compared
• Demonstration of the consistency and robustness of the manufacturing process • Demonstration of the suitability of the formulation with regards to stability, comparability, and integrity of the active substance	• Physicochemical properties • Biological activities • Purity and impurities

Comparability Exercise for Non-Clinical and Clinical Data

Non-Clinical Data (safety)	Clinical Studies (efficacy)
• In vitro studies • In vivo studies	• Pharmacokinetics studies (PK) • Pharmacodynamic studies (PD) • Confirmatory (PK/PD) studies • Efficacy trials

Comparability Exercise for Non-Clinical and Clinical Data

Clinical Safety and Pharmacovigilance Requirements

- Comparison of the type, severity and frequency of the common adverse reaction
- Pharmacogivilance and risk management plan

Immunogenicity

- Clinical trials to investigate immunogenicity
- Optimal antibody-testing strategy

Biosimilar approval in Europe

Product Name	INN	Sponsor	Status	Date
Omnitrope	Somatropin	Sandoz	Authorized	Apr 2006
Valtropin	Somatropin	Biopartners	Authorized	Apr 2006
Binocrit	Epoetin alfa	Sandoz	Authorized	Aug 2007
Epoetin alfa Hexal	Epoetin alfa	Hexal	Authorized	Aug 2007
Abseamed	Epoetin alfa	Medice	Authorized	Aug 2007
Silapo	Epoetin zeta	Stada	Authorized	Dec 2007
Retacrit	Epoetin zeta	Hospira	Authorized	Dec 2007
Filgrastim Ratiopharm	Filgrastim	Ratiopharm	Authorized	Sept 2008
Ratiograstim	Filgrastim	Ratiopharm	Authorized	Sep 2008
Biograstim	Filgrastim	CT Arzneimittel	Authorized	Sep 2008
Tevagrastim	Filgrastim	Teva	Authorized	Sep 2008
Filgrastim Hexal4	Filgrastim	Hexal	Authorized	Feb 2009
Zarzio	Filgrastim	Sandoz	Authorized	Feb 2009
Filgrastim Hexal	Filgrastim	Hexal	Authorized	Feb 2009

Source: EMEA. EPARs for authorised medicinal products for human use, as of June 2009 at: http://www.emea.europa.eu/htms/human/epar/a.htm

Products which failed to show biosimilarity or application withdrawn in Europe

Product Name	INN	Sponsor	Status	Date
Alpheon	Interferon alfa-2a	Biopartners	Reject	Jun 2006
Insulin Human Rapid Marvel	Human insulin	Marvel Life Sciences	Withdrawn	Jan 2008
Insulin Human Long Marvel	Human insulin	Marvel Life Sciences	Withdrawn	Jan 2008
Insulin Human 30/70 Mix Marvel	Human insulin	Marvel Life Sciences	Withdrawn	Jan 2008

Source: EMEA. EPARs for authorised medicinal products for human use, as of June 2009 at: http://www.emea.europa.eu/htms/human/epar/a.htm

Biosimilar status in the US

Legislation

- No legislations or regulations approved by Congress
- Bills have been introduced to Congress
  Waxman; Inslee; Shumer/Clinton; Gregg/Burr/Coborn; Kennedy/Enzi/Clinton; Eshoo
- Issues with the Bills
- FOB legislation timing…2009?

WHO draft guideline

- WHO issues draft "Guideline on evaluation of similar biotherapeutic products (SBPs)" for public comments (http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/BS2110Dft_guidelines_Final_HK_IK_29July_09.pdf)
- The draft guideline recognizes the complexity of biotherapeutic products and the challenges linked to the development, manufacturing and approval for use on the market. Biotherapeutics consists of relatively large, and complex proteins that are difficult to characterize
- The draft guideline recognizes the approach established for generic medicines is NOT suitable for development, evaluation and licensing of SBPs

AP Country With Biosimilar Guideline

Country	Date of Issue	Notes
Australia	May 2005	1. Adoption of EMEA guidelines
Malaysia	August 2008	1. No product specific guideline
Taiwan	November 2008	1. Four product specific guidelines for *'somatropin', 'recombinant human soluble insulin', 'granulocyte-colony stimulating factor' and 'recombinant erythropoietins'*

AP Country With Biosimilar Guideline

Country	Effective Date	Notes
Japan	March 2009	1. Different nonproprietary names given to biosimilar product 2. No product specific guideline
South Korea	July 2009	1. No product specific guideline
Singapore	August 2009	1. No product specific guideline 2. Biosimilar product must first be approved for sale in any one of HSA's reference agency

Points to consider

Points to consider

- Naming of biosimilar
  - Need to assess the adequacy of the current INN system to describe biopharmaceuticals including biosimilars due to the complex nature of these products
- Traceability
  - Important to identify specific product causing ADR
  - Unique names are needed for pharmacovigilance because they provide a mechanism to track and attribute adverse events to the appropriate product.
- Immunogenecity
  - Biologicals have inherent to provoke immune reactions and it is currently not possible to accurately predict immunogenicity in humans as immune reactions can differ from product to product
  - Risk Management Plan is essential

Points to consider

- Interchangeability
  - Regulatory agencies such as EMEA do not assess the interchangeability or substitutability of a biosimilar when granting a positive opinion for a marketing authorization application
  - Currently no clinical studies have been designed or undertaken to asses clinical outcome or repeated switches of a biological medicine
  - A need for scientific evidence and approval of prescribing physician prior to interchangeability
- Substitution
  - A practice where substitution takes places place without the prior consent of the prescribers cannot be applied to biological products
  - A number of countries in EU have either established legislative measures to prohibit the automatic substitution of biotech medicines or given regulatory advice on the use of generic medicines

Conclusions

- Biopharmaceutical will continue to play important role in treating wide ranging diseases
- Biopharmaceutical are different from small molecule chemical
- Generic drug review process cannot be applied to biological products
- Patient safety and sound science are fundamental; biopharmaceutical raise unique concerns because of the close relationship between a product's manufacturing process and its clinical attributes
- A prudent approach that protects patient safety and incentives for innovation in pursuing science based regulation

Thank You

- Session II: Regulatory Issues for Biosimilars

Biosimilar FOB/FOPP/SEB...

Speaker:

Michael Müenzberg (Germany)

Global Head of Medical Affairs, Marketing/Medical BP,

Sandoz International GmbH

Contents

- Biosimilars - general considerations and EMEA pathway
  - Biosimilar-What does it mean?
  - Comparison of requirements for MAAs
  - Biosimilars - legal framework
  - List of Biosimilar Guidelines

- Biosimilars - SANDOZ approach
  - Biosimilars Approved in Europe as of to Date
  - Quality by Design: Definition of the Target for Development
  - How Close is Close Enough?... Demonstrating Comparability
  - Post-marketing surveillance (PMS)

- Biosimilars - Looking Forward
  - Biosimilars - cui bono?
  - The Safety and Efficacy of EU Biosimilars
  - Forward looking statement

Biosimilar

FOB/FOPP

SEB

.....

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Agenda

- Biosimilars – general considerations and EMEA pathway
- Biosimilars – SANDOZ approach
- Biosimilars – Looking Forward

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Agenda

- **Biosimilars – general considerations and EMEA pathway**
- Biosimilars – SANDOZ approach
- Biosimilars – Looking Forward

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Biosimilar - What does it mean?

'Biosimilar' is not a scientific definition of a product

'Biosimilar' is a *regulatory* term, introduced by the EMEA

The term 'biosimilar' is used to denote a biopharmaceutical approved under the biosimilar regulatory pathway

Thus products not approved by the biosimilar pathway are no biosimilars

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Biosimilar - What does it mean?

Nomenclature is not internationally harmonised

- EMEA: 'Similar Biological Medicinal Product' (Biosimilar)
- FDA: 'Follow-on Protein Product' (FOPP), 'Follow-on Biologic' (FOB)
- Health Canada: 'Subsequent Entry Biologic' (SEB)
- Japan: 'Follow-on Biologic'

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What is a Biosimilar/FOB/FOPP/SEB

- A biosimilar is a successor of a biopharmaceutical for which patent protection no longer applies
- Biosimilars are manufactured by recombinant DNA technology (insertion of gene into the host cell to produce the protein)
- Biosimilars are comparable with the selected reference product in terms of quality, safety and efficacy
- A biosimilar is usually approved for the same indications as the reference product given that they share the same mode of actions

A Biosimilar is <u>NOT</u> a Generic Biopharmaceutical

BIOGENERICS do not exist

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Comparison of requirements for MAAs

	Generic	Biosimilar	New Product (full dossier)
Quality	"Standalone" Program Comparison with reference product	"Standalone" Program Very comprehensive comparison with reference product	"Standalone" Program
Preclinical	No data required	Abbreviated programme – depending on complexity of molecule e.g. subchronic Tox (4 w); Local tolerance, PK/PD	Full preclinical programme
Clinical	BE Study Ph I – No Ph II – No Ph III - No	Ph I - PK/PD Study Ph II - No Ph III - Study in one representative indication Risk Management Plan	Ph I Ph II Ph III in all indications Risk Management Plan

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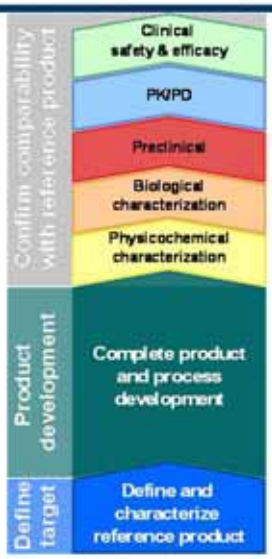
The comparability exercise – the core element in the biosimilar product development



The comparability/similarity with the reference product must be demonstrated on all levels of product development:

- Level 5 Comparability in clinical phase III
- Level 4 Comparability in clinical phase I
- Level 3 Preclinical comparability

→ Confirming similarity

- Level 2 Comparability in biological activity
- Level 1 Physico-chemical comparability

→Establishing similarity

A biosimilar product is designed to meet the criteria of the reference product with regards to quality, safety and efficacy.

This rigorous comparability exercise qualifies Biosimilar for therapeutic interchange

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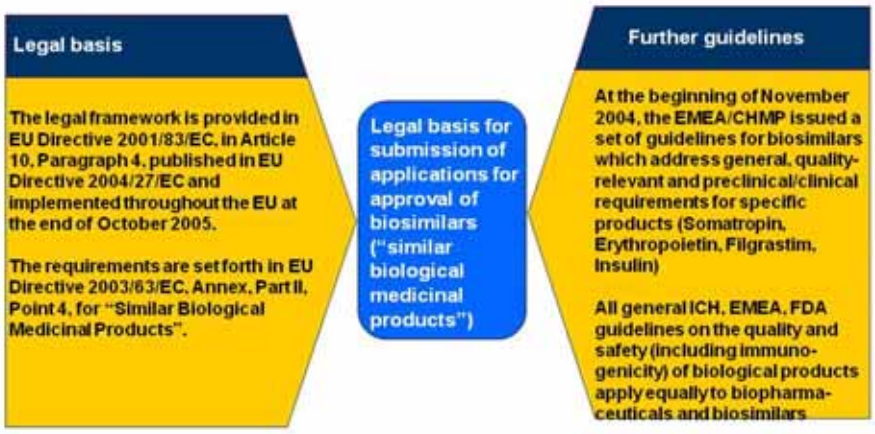
Biosimilars – legal framework



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Regulatory EMEA/CHMP guidance concerning biosimilars - three levels

Overarching Guideline

- *The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues* lays down the quality requirements for a biological medicinal product claiming to be similar to another one already marketed
- *The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* describes the animal and clinical studies required for a biological medicinal product claiming to be similar to another one already marketed. For most biosimilars comparative clinical trials are considered to be necessary to demonstrate clinical comparability
- *Immunogenicity assessment of biotechnology-derived therapeutic proteins* concerns biologics in general but has major implications for the marketing authorization of biosimilars

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Four product class-specific guidelines

- recombinant human erythropoietin (EPO)
- somatropin
- human insulin
- human granulocyte colony-stimulating factor (G-CSF)

Two additional product-class specific guidelines concerning

- low molecular heparins
- interferon alpha

are expected to be released in 2009

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List of Biosimilar Guidelines

Overarching Guideline

CHMP/437/04 Guideline on Similar Biological Medicinal Products.

http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf

General guidelines on quality and non-clinical/clinical issues

EMEA/CHMP/49348/05 Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues.

http://www.emea.eu.int/pdfs/human/biosimilar/4934805en.pdf

EMEA/CHMP/42832/05 Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues.

http://www.emea.eu.int/pdfs/human/biosimilar/4283205en.pdf

EMEA/CHMP/BMWP/101695/2006 Draft Guidance on Comparability of Biotechnology-Derived Medicinal Products after a change in the Manufacturing Process - Non-Clinical and Clinical Issues.

EMEA/CHMP/BMWP/14327/2006 Draft Guidance on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins

Product specific Annexes for non-clinical and clinical issues

EMEA/CHMP/32775/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Recombinant Human Insulin.

EMEA/CHMP/31329/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Biosimilar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor.

EMEA/CHMP/94526/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Somatropin.

EMEA/CHMP/94526/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Recombinant Erythropoietins.

Risk Management Plan (EU-RMP)
EMEA/CHMP/96268/2005 **Guideline on risk management systems for medicinal products for human use**

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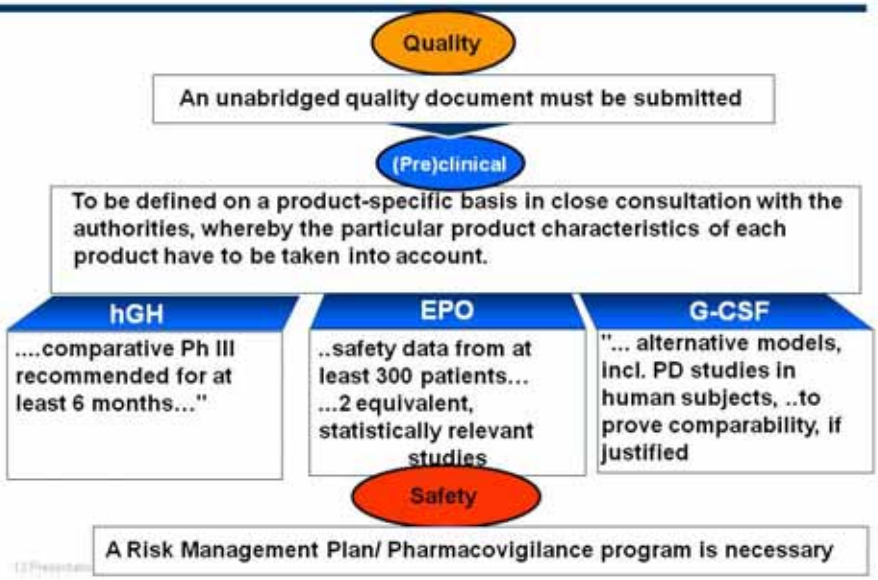
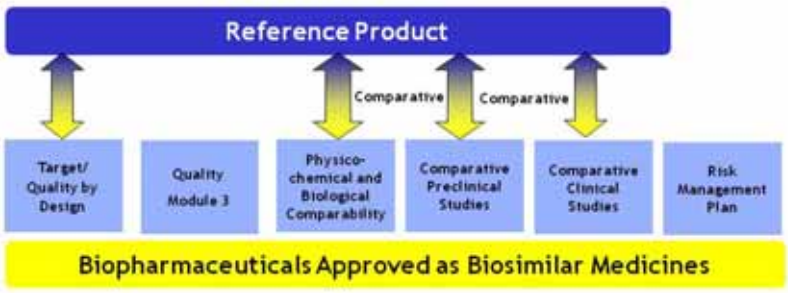
Biosimilars – scientific requirements



Biosimilarity requires thorough comparability studies

The development of a biosimilar requires

- Complete product and process development
  PLUS
- Comparative testing at all stages of development in order to obtain approval by competent authorities (Europe, Canada)



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ICH Definition of Comparability (EU, US, Japan)

ICH HARMONISED TRIPARTITE GUIDELINE
COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS
Q5E

Comparable:

A conclusion that products have **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, nonclinical or clinical data might contribute to the conclusion.

Federal Register, Vol. 70, No. 125, June 30, 2005, pages 37861-37862

Agenda

- Biosimilars – general considerations and EMEA pathway
- **Biosimilars – SANDOZ approach**
- Biosimilars – Looking Forward

Biosimilars – Why Sandoz?

	1946	Entry into pharmaceutical biotechnology
	1980	First production of Interferon alfa in Kundl facility for R&D purpose
since	1987	Production of Bovine Somatropin for Monsanto
	1994	Production of IL-3 and IL-6 for Sandoz Pharma
since	1997	Production of a recombinant BNP for an external pharmaceutical company
since	2002	Production of Fab antibodies for an external pharmaceutical company
up to	today	Production of 25+ different recombinant human proteins for Sandoz, Novartis Pharma and numerous well known pharmaceutical and biotechnology companies at clinical and commercial scale using microbial and cell culture technologies

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Biosimilars Approved In Europe as of to Date

Trade Name	Common Name (INN)	Biosimilar Sponsor	Reference Product	Decision	Date Decision
Omnitrope	Somatropin	Sandoz	Genotropin	Approved	April 12, 2006
Valtropin	Somatropin	BioPartners	Humatrope	Approved	April 24, 2006
Biferonex	Interferon beta-1a	BioPartners	Avonex	Rejected	Feb. 19, 2009
Alpheon	Interferon alfa-2a	BioPartners	Roferon-A	Rejected	June 28, 2006
Binocrit	Epoetin alfa	Sandoz	Eprex	Approved	Aug. 28, 2007
Epoetin alfa Hexal	Epoetin alfa	Hexal	Eprex	Approved	Aug. 28, 2007
Abseamed	Epoetin alfa	Medice	Eprex	Approved	Aug. 28, 2007
Retacrit	Epoetin zeta	Hospira	Eprex	Approved	Dec. 18, 2007
Silapo	Epoetin zeta	STADA	Eprex	Approved	Dec. 18, 2007
Insulin Rapid Marvel	Insulin	Marvel	Humulin	Withdrawn	Jan. 16, 2008
Insulin Long Marvel	Insulin	Marvel	Humulin	Withdrawn	Jan. 16, 2008
Insulin 30/70 Marvel	Insulin	Marvel	Humulin	Withdrawn	Jan. 16, 2008
Biograstim	Filgrastim	CT Arzneimittel GmbH	Neupogen	Approved	Sep. 16, 2008
Filgrastim Ratiopharm	Filgrastim	Ratiopharm GmbH	Neupogen	Approved	Sep. 16, 2008
Ratiograstim	Filgrastim	Ratiopharm GmbH	Neupogen	Approved	Sep. 16, 2008
Tevagrastim	Filgrastim	Teva Generics GmbH	Neupogen	Approved	Sep. 16, 2008
Zarzio	Filgrastim	Sandoz	Neupogen	Approved	Feb. 6, 2009
Filgrastim Hexal	Filgrastim	Hexal	Neupogen	Approved	Feb. 6, 2009

Sandoz - the only company having three biosimilars approved in Europe

- **Omnitrope® (Somatropin),** the first biosimilar ever approved
  - ➢ Approved in **2006**, marketed in **Europe, US,** and **Australia**
  - ➢ Approved for treatment of **growth hormone deficiency** in children and adults

- **Binocrit® (Epoetin alfa),** the world's first biosimilar ESA (Erythropoiesis Stimulating Agent) and the first biosimilar glycoprotein
  - ➢ Approved **2007**, marketed in **Europe**
  - ➢ Approved for the treatment of renal anaemia and chemotherapy induced anaemia

- **Zarzio® (Filgrastim),** a non-glycosylated G-CSF, the company's third biosimilar product,
  - ➢ Approved **February 2009,** marketed in **Europe**
  - ➢ Approved for treatment of neutropenia, severe chronic neutropenia, neutropenia in advanced HIV patients and for stem cell mobilisation

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Omnitrope® approvals details

Country/ Region	Approval date	Procedure	Formulations	Indications
Australia	29 Sept 2004	Stand-alone, full dossier	Powder and Liquid	•GHD children •Turner syndrome •CRI in children
Europe	12 April 2006	Biosimilar to Genotropin (first biosimilar!)	1. Powder ('06) 2. Liquid ('07)	•GHD children •Turner syndrome •CRI in children •PWS •GHD adult
USA	30 May 2006	505b(2)	1. Powder ('06) 2. Liquid ('07)	•GHD children •GHD adult

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Quality by Design: Definition of the Target for Development

Objective of development

- Similarity and equivalence to the reference product with respect to quality, safety & efficacy

Assessment of quality

- Extensive characterization of reference product
- Use of orthogonal analytical tools
- Multiple batches of different ages of reference product
- Accounting for formulation during characterization

Focus: Gaining of knowledge

- Utilize all available public knowledge by original sponsor as well as independent third parties

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Analytical characterization: Objectives

Physicochemical and biological characterization

- Define quality of the reference product
- Provide continuous feedback to steer process development of the biosimilar product
- Gain and extend understanding of product and process
- Assess and ascertain quality of the biosimilar product
- Confirm comparability with the reference product

The extent of studies at the subsequent levels (preclinical, clinical) should ideally be determined by the level of understanding gained from the initial physicochemical and biological analyses.

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Analytical methods used in comparability studies with the reference product

Molecular parameter	Method	Omnitrope®	Reference product
Primary structure	Edman sequencing	x	x
	Peptide map LC-MS	x	x
Mass	MALDI-TOF, ESI-MS	x	x
Spatial structure (secondary and tertiary)	CD spectroscopy	x	x
	NMR spectroscopy	x	x
Polarity	Reversed phase chromatography	x	x
Charge	Capillary electrophoresis	x	x
	Isoelectric focusing	x	x
Size	Size exclusion chromatography	x	x
	Gel electrophoresis	x	x
Immunological tests	Immunoblotting	x	x
Biological activity	In-vivo bioassays	x	x
	Cell proliferation assay	x	x

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How Close is Close Enough? ...Demonstrating Comparability

The criteria for the comparison of the biosimilar and the reference product are based on:

- Understanding batch-to-batch variability of the reference medicinal product
- Classification of the product variants into product-related substances or impurities (ICH Q6B)
- Level of understanding the relevance of subtle differences on safety/efficacy (ICH Q5E)

The manufacturing process for the biosimilar is systematically designed to meet the established criteria applied to comparability

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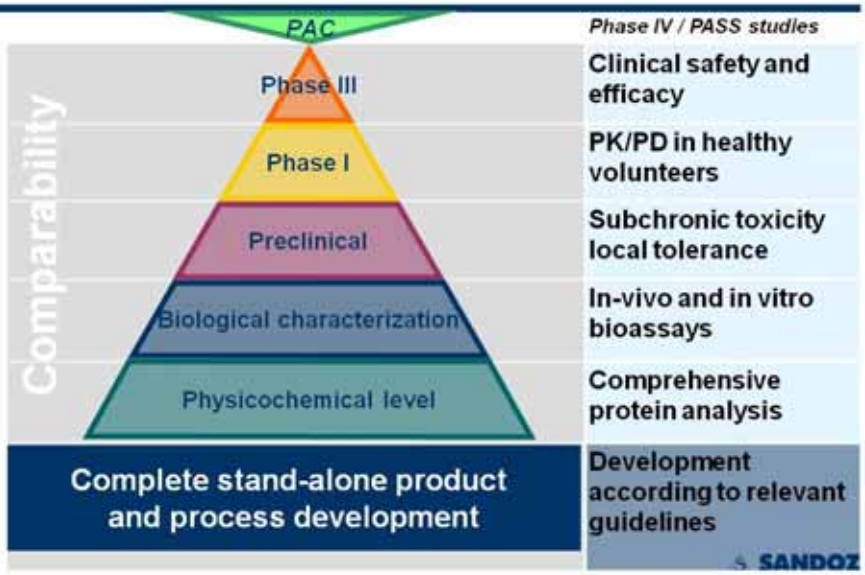
Defining biosimilars - "Quality by Design"

- Biosimilars are developed and manufactured according to the same quality standards as the reference product
- Manufacturing process, including cell lines / production strains, developed to guarantee comparability with the reference product
- Comprehensive analytical tests at all stages of manufacturing process ensure quality remains unchanged
- Preclinical and clinical studies complement and validate tests on comparability, efficacy and safety
- Post Marketing Surveillance (PMS / PASS) to demonstrate long-term safety

Post-marketing surveillance (PMS)

- Upon granting of the marketing authorisation in the EU, Sandoz has been obliged by EMEA to conduct numerous PMS activities in order to further investigate safety and immunogenicity
- Depending on product complexity, EMEA commonly requests such PMS activities for innovator products after approval as well. In this respect, EMEA subjects biosimilar products to the same scrutiny
- Sandoz has set-up several Phase IV/ Non Interventional Studies (NIS) to meet all obligations posed by EMEA

Sandoz Biosimilars – Fully comparable with reference



Agenda

- Biosimilars – general considerations and EMEA pathway
- Biosimilars – SANDOZ approach
- **Biosimilars – Looking Forward**

Biosimilars – cui bono?

A steadily aging population being treated with ever more sophisticated and expensive biopharmaceuticals is driving pharmaceutical costs to unprecedented levels

"Competition is not only the basis of protection to the consumer, but is the incentive to progress" (Herbert Hoover)

Supporting a viable biosimilars industry is a key strategy for any government that is serious about solving this problem, and is good for the biopharmaceutical industry as it frees up health care dollars for innovative premium-priced products

Conclusion of the EGA, February 2008

UK NHS' Allan Karr concludes with the EGA that he can see no problems to use biosimilars widely...

Conclusions of the EGA

- Current analytical technology enables physico-chemical characterisation which along with preclinical and clinical studies provide data to demonstrate comparability.
- Manufacturing and characterisation of biosimilars, like all other biologics, will comply with established high scientific and regulatory standards.
- Current EU biosimilar guidelines in place.

So what **IS** the problem?

The Safety and Efficacy of EU Biosimilars

Nicolas Rossignol, Administrator of the EC's pharmaceuticals on questions of safety for EU biosimilars:

"I don't judge case by case, but I have a message: we have promoted and developed with the European Medicines Agency a special Biosimilars framework. So we are confident that if a product meets all the requirements and gets a marketing authorisation from the commission, it means that the product is as safe and effective as any other product authorized by the commission"

SCRIP World Pharmaceutical News 24 April 2008, reporting on EGA Meeting, London

Adviesgroep Groeihormoon van de Nederlandse Vereniging van Kindergeneeskunde

Gerust groeien:

Sommige kinderen zijn gebaat bij een groeihormoonbehandeling. Alleen de kinderarts-endocrinoloog is dan gemachtigd om medicatie voor te schrijven. Veiligheid en effectiviteit staan daarbij voorop.

*En dus **is de tijd nog niet rijp voor biosimilar groeihormoonpreparaten**, aldus de Adviesgroep Groeihormoon van de Nederlandse Vereniging van Kindergeneeskunde.*

324 | Medisch Contact | 19 februari 2009 | 64 nr. 8

http://www.cbg-meb.nl/cgn/
4 maart
Biosimilar groeihormonen

Forward looking statement

- Biosimilars are a reality and provide a high quality and cost-effective access to critical therapies –however " you have to do them right"
- Biosimilars are products that have been subjected to a very thorough comparability exercise on all development stages
- Various draft guidance documents (BRA, ARG, Malaysia) support this concept, and all such initiatives should aim for global consistency
- Global biosimilar development, including the use of a reference product from respected jurisdictions, will become a necessity to avoid duplication of efforts and to maintain cost-effectiveness

Conclusions : Challenges to bring Biosimilars to the clinic ?

Demonstrate confidence with the clinician through...

Backup

SANDOZ

Thank you

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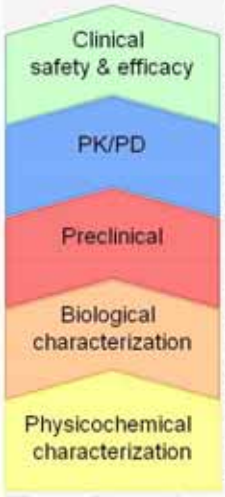
Comparability of Omnitrope® with the reference product Genotropin® was established at all stages

Prescribing information for Omnitrope available on request or at www.fda.gov



Clinical safety & efficacy	PhV and RMP: registry and Phase IV study in SGA indication Efficacy and safety evaluated in 5 Phase III studies in one representative indication: GHD in children, 266 patients, conducted in Europe
PK/PD	5 PK/PD studies in several phase I studies in 120 healthy volunteers using surrogate markers
Preclinical	14-day Subchronic toxicity studies in rats, Tibia width assay in rats, local tolerance in rabbits
Biological characterization	In-vivo (rat weight gain assay) and in-vitro (cell proliferation) bioassay
Physicochemical characterization	Comprehensive analysis of the protein with a wide array of state-of-the-art analytical methods

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Clinical phase III studies with Omnitrope

- 8 Phase III studies in GHD children (4 of which are ongoing)
- 5 European countries (France, Spain, UK, Poland, Hungary)
- Over 250 patients treated with Omnitrope
- Over 600 patient-years exposure

Combined results of Phase III studies demonstrate that Genotropin can be substituted with Omnitrope without any loss of efficacy or change in risk-benefit ratio for patient.

Omnitrope and Genotropin satisfy criteria for therapeutic equivalence.

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Pharmacovigilance Omnitrope®

- Post-Marketing Surveillance to monitor the long-term safety and efficacy of Omnitrope® in children, adolescents and adults

  Observational, multi-centre, open, longitudinal, non-interventional trial

  2.100 patients treated according to the SmPC
- Long-term phase IV multicentre study on the safety and efficacy of Omnitrope® (rhGH) in short children born Small for Gestational Age (SGA)

  240 patients

  LPO: (401) expected in 2021, (402) expected in 2031

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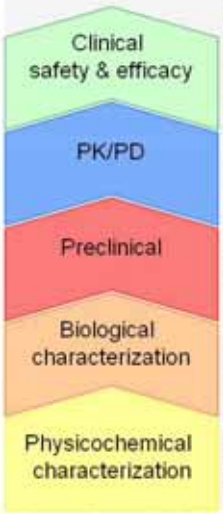
Comparability of Binocrit® with the reference product Eprex®/Erypo® was established at all stages



PhV and RMP:

Phase III study in kidney patients (s.c.) as well as PASS in i.v. patients and in s.c. following approval of s.c.

Efficacy and safety evaluated in 2 Phase III studies in 479 haemodialysis (i.v.) and chemotherapy (s.c.) 114 patients

5 PK/PD studies phase I studies 237 healthy volunteers demonstrating bioequivalence

Note: Binocrit is not approved for marketing in the U.S.; there is no FDPP pathway in the U.S. for biologics licensed under the Public Health Service Act

4-weeks subchronic toxicity in dogs
PK/PD in dogs
local tolerance in rabbits

In-vivo bioassay (normocythaemic mouse assay) in-vitro bioassay

Comprehensive analysis with a wide array of state-of-the-art analytical methods on drug substance and drug product level

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Binocrit®: Overall Clinical Study Program

Phase I Studies

INJ-4: Pilot PK/PD study in volunteers

- single i.v. or s.c. application, reference Erypo®, n =40

⇒ proof of concept, i.v/s.c. comparable PK profiles, same reticulocyte response

INJ-5: Pivotal PK/PD i.v. study in volunteers

- i.v application over 4 weeks, reference Erypo®, n =40

⇒ bioequivalent after multiple applications for AUC and Cmax, equivalent Hb response

INJ-6: Supportive PK/PD study in volunteers

- s.c. application over 4 weeks, reference NeoRecormon®, n =40

⇒ comparable in PK and Hb response

INJ-12: Pivotal PK/PD s.c. study in volunteers

- s.c. application over 4 weeks, reference Erypo®, n =40

⇒ bioequivalent after multiple applications for AUC and Cmax, equivalent Hb response

Phase III Studies

INJ-9: Haemodialysis patients - i.v. application

- double-blind, parallel group, randomized (2:1 - test : reference), n = 462 randomized patients

⇒ HX575 is therapeutically equivalent to Erypo® with respect to hemoglobin response.

⇒ Safety profile of the two products is comparable and no relevant differences in epoetin dose were found.

INJ-11: Cancer patients - s.c. application

- double-blind, parallel, randomized, n = 114

⇒ HX575 is efficacious and safe in the treatment of anaemia associated with chemotherapy

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HX575 : Treatment in patient years in Europe

Treatment experience with marketed HX575

Treatment with HX575 comprises 1,885 patient years from October 2007 to September 2008.

This relates to 3,770 patients treated during 12 months since introduction into the European market in 2007.

Treatment experience with HX575 in PAC trials

To date ~1650 patients have been enrolled on HX575 in the ongoing phase IV program

Treatment experience with HX575 in PMS trials

To date ~1300 patients have been enrolled on HX575 in local PMS programs

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- Session II: Regulatory Issues for Biosimilars

From recombinant proteins to LMWHs the EU regulatory expectations

Speaker:
Eric Bigaud (France)
Head of Regulatory & Technical support
Asia Pacific & Russia
Sanofi-Aventis

Abstract

In Europe, a biological medicine is a medicine whose active substance is produced by or extracted from a biological source. Due to their specificities the generic approach is scientifically not appropriate to register copies of biological medicinal product. A specific regulatory framework has been developed by EMEA [Committee for medicinal products for human use (CHMP)] for copies of biological medicinal products or biosimilars during the last 5 years. Most guidelines that have been released during this period were focussed on similar of Biotechnology derived proteins.

LMWHs are prepared by various depolymerisation processes from unfractionated heparin that is of animal origin. LMWH shave been definitively confirmed in 2006 as biological product in the European Union. Therefore the biosimilar concept applies in Europe to register copies of a reference LMWH Medicinal product. In 2009 the CHMP has published a Guideline relative to the "non-clinical and clinical development of similar biological medicinal products containing low-molecular -weight-heparins (date for coming into effect is October 2009) in which it is considered that the major challenge of demonstrating two LMWHs being similar biological medicinal products is within a comparative clinical efficacy trial. The regulatory paradigm in place in Europe to register similars of biotech proteins also applies to register similars of LMWHs with detailed requirements.

From recombinant proteins to LMWHs (Low Molecular Weight Heparins) the EU regulatory expectations

E. BIGAUD
Regulatory & Technical Support
Asia Pacific & Russia
sanofi aventis

Biological products

⇒ Hormones

⇒⇒ Cytokines

⇒⇒⇒ Monoclonal antibodies

⇒⇒⇒⇒ Blood or Plasma Derived

⇒⇒⇒⇒⇒ Clotting factors

⇒⇒⇒⇒⇒⇒ Gene & Cell Therapy

..... Vaccines

EU Biological Medicinal Product definition

- A biological medicinal product is a product the active substance of which is a biological substance. (Directive 2003/63/EC)
- A biological substance is a substance that
  - is produced by or extracted from a biological source and
  - that needs for its characterisation and the determination of its quality a combination
    - **of physicochemical- biological testing,**
    - **together with the production process and its control.**

3

Biotech derived products

⇒ **Complex structure**

⇒⇒ **Characterization by combination of analytical testing**

⇒⇒⇒ **Complex manufacturing process**

⇒⇒⇒⇒ **"The process is the product "**

⇒⇒⇒⇒⇒ **Immunogenicity**

⇒⇒⇒⇒⇒⇒⇒ The regulatory framework of generics cannot be applied to copies of biopharmaceuticals

⇒⇒⇒⇒⇒ *Biosimilar concept & definition*

4

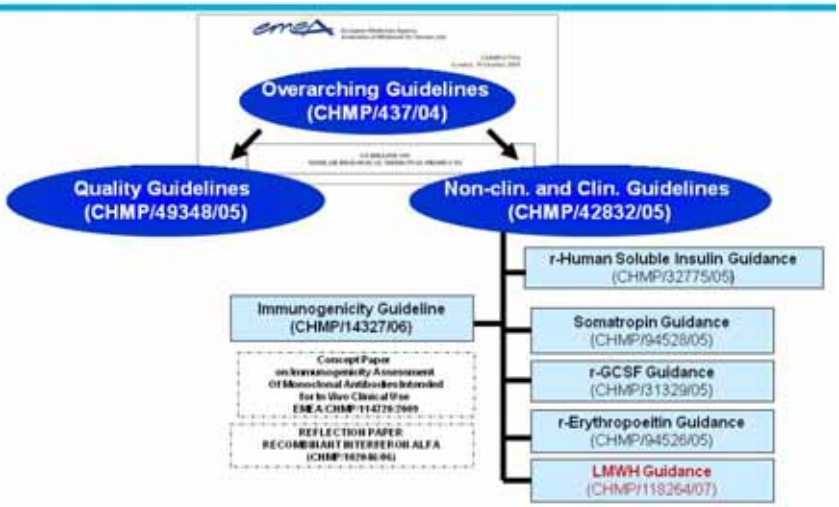
EMEA Biosimilar definition & concept

- A biosimilar medication is a medication which is similar to a biological medication that has already been authorized (the "biological reference medicine"). The active substance of a biosimilar medication is similar to the biological reference medicine.
- Biosimilar principle applies to all Biological products in practice, ...
- Whether a medicinal product would be acceptable using the 'similar biological medicinal product' approach depends on the state of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experience.

5

Guideline On Similar Biological Medicinal Products (CHMP/437/04)

EU Biosimilar Regulatory landscape (Sept. 2009)



Updated June 2009, EMEA website

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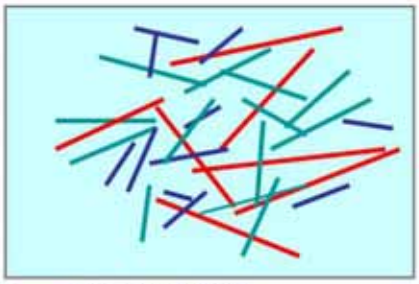
LMWHs : Collection of oligosaccharides chains



- Glycosaminoglycans extracted from animal tissue & fractionated
- Collection of oligosaccharides with distribution of different molecular weight chains
- Different chains exhibit different pharmacological and pharmacokinetic profiles

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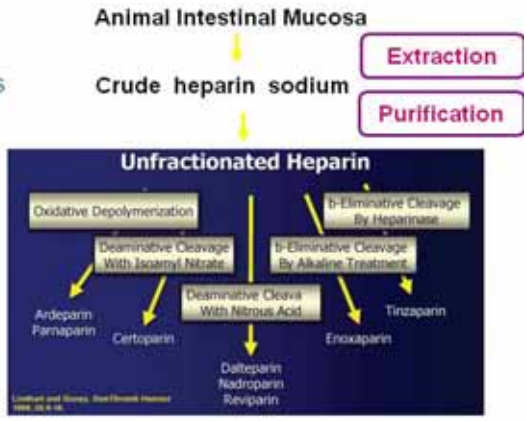
LMWHs Preparation

The starting material of LMWHs is of biological origin and the manufacturing process defines the characteristics of the drug substance.

LMWHs are prepared from unfractionated heparin by various chemical or enzymatic depolymerisation processes



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LMWHs status

- **Different classification for LMWHs**
  - Biological product : EU, AU, SA,…
  - Drug : TW
  - Drugs : USA (as for insulins, hormones,..)
- **Independently of the classification the key question is:**
  - **What should be the regulatory paradigm and the regulatory requirements to register copies of a reference LMWH that ensure the therapeutic equivalence with the reference medicinal product from Quality, Efficacy and Safety standpoints ?**

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EU Approach

CMDh

Report from the CMD(h) meeting held on 26th and 27th June 2006

LMMHs have been classified as Biological medicinal products
in June2006

The CMD(h) has agreed the view of the BWP that low molecular mass heparins and pancreatins should be considered biological medicinal products. Therefore, applications for marketing authorisation as generic medicinal products will not be accepted and should be submitted in accordance with Article 10 (4) of Dir. 2001/83/EC, as amended - 'Similar biological application', with additional physico-chemical characterisation and clinical data.

Active substance master files (ASMF) are not applicable to biological medicinal products and while Certificates of Suitability (CEP) may be considered for these substances, they are not sufficient to replace Module 3S of the MAA dossier.

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http://heads.medagencies.org/index.html

European Medicines Agency

London, 19 March 2009
EMEA/CHMP/BMWP/118264/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON NON-CLINICAL AND CLINICAL DEVELOPMENT OF SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING LOW-MOLECULAR-WEIGHT-HEPARINS

DRAFT AGREED BY BIOSIMILAR MEDICINAL PRODUCTS WORKING PARTY (BMWP)	April 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	April 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	October 2008
AGREED BY BMWP	February 2009
ADOPTION BY CHMP	March 2009
DATE FOR COMING INTO EFFECT	October 2009

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Quality aspects

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LMWHs Specificities

Animal Intestinal Mucosa

Extraction

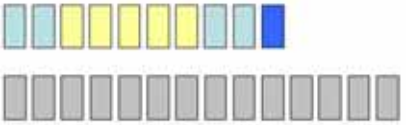
Crude heparin sodium

Purification

Unfractionated heparin

Depolymerisation

LMWH



Unique collection of oligossacharides with different molecular weight distribution

Distinct fingerprints have been identified

Technical limits exist to identify correctly fingerprints & structure

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Complex structure : molecular weight profile

Therapeutic Agent	Molecular Structure	Molecular Weight
Acetylsalicylic Acid *(Aspirin)*	$C_9H_8O_4$	*180 Daltons*
Low Molecular Weight Heparins		
Fragmin		*< 3000 Daltons 3-15%* *3000-8000 Daltons 65-78%* *>8000 Daltons 14-26%*
Lovenox		*< 2000 Daltons ≤ 10%* *2000-8000 Daltons > 68%* *>8000 Daltons ≤ 18%*
Tinzaparin		*< 2000 Daltons 10%* *2000-8000 Daltons 60-72%* *> 8000 Daltons 22-36%*

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Technological limits for characterization

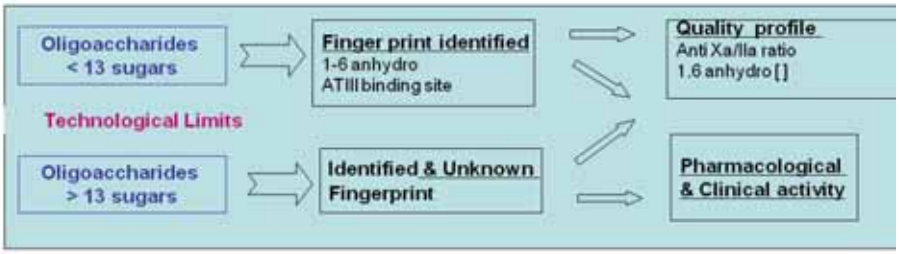
Despite progresses in biochemistry of the complex sugars, LMWH remain not fully characterized

Enoxaparin ⇒⇒ Complex set of polysaccharides that have not yet been completely characterised

European Pharmacopoeia N° 1097

DEFINITION

Enoxaparin sodium is the sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin consists of a complex set of oligosaccharides that have not yet been completely characterised. Based on current knowledge, the majority of the components have a 4-enopyranuronic acid structure at the non-reducing end of their chain. 15 per cent to 25 per cent of the components have a 1,6-anhydro structure at the reducing end of their chain.



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Unique collection of oligosaccharides

Manufacturing Process → Chemical Structure → Pharmacological Activity → Clinical Profile

- The process creates a distinct drug product with a unique chemical structure that is sensitive to Manufacturing conditions (specified temperature, base concentration, duration factors in the reaction.....)

⇒⇒ For LMWHs : the process is the Product

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Quality regulatory framework applicable

- **Quality guidelines for rDNA derived Biosimilar proteins;**
  - Principles also apply to LMWH (as stated CHMP guideline on biosimilar LMWH (CHMP/118264/2007))
  - Full quality dossier (CTD Model 3) + comparability exercise
- **Key points**
  - Comparison to EU Pharmacopoiea Monograph as reference is not sufficient
  - Drug substance/Product Comparability
  - State-of-art analytical methods to be used for characterisation purpose
  - API Process validation
  - Viral safety
  - Cross contamination
  - History of the development Biosimilar batches

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Efficacy & Safety aspects

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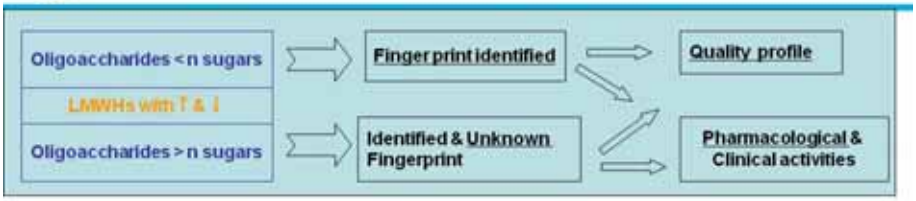
Efficacy /safety issues



- It is **impossible to characterize the quality attributes of LMWHs completely** by physico-chemical analysis alone and to fully **predict the impact of differences** on clinical efficacy and safety.
- A clear correlation between identified surrogate PD marker and clinical outcome has not been established
  - **PD/PK comparative study is not sufficient to predict the Quality difference**
- Position endorsed by Academia : SASAT (2009)/ ISTH (2009),....
- Position endorsed by Health Agencies : EMEA/TGA/...

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Clinical & Safety regulatory framework

- **Nonclinical studies**
  - **Comparative before clinical devt**
- **Clinical studies**
  - **Comparative PD/PK study**
    - By SC & by IV if reference product is licensed for IV or IA route
  - **Comparative clinical efficacy**
    - **One adequately powered, randomised, double blind, parallel group clinical trial**
  - **Extrapolation**
    - Demonstration of comparable efficacy and safety in surgical patients at high risk for VTE as recommended may allow extrapolation to other indications of the reference medicinal product if **appropriately justified** by the applicant.

Non clinical studies		Clinical studies		
PD	Toxicology	PK/PD	Clinical efficacy	Clinical safety
A number of in vitro tests (aXa, alla) Animal models for compara-bility studies	At least 1 repeat dose toxicity study for at least 4 weeks	Double blind randomized single dose two way crossover in healthy volunteers (aXa, alla, TFPI,...)	Double blind randomized parallel group study (prevention of venous or arterial thrombo-embolism	Data from efficacy trial (adverse events, HIT Type II, liver function, osteoporosis)

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Adapted from W.Raake, NATF, 2009

LMWH & Immunogenicity

- Differences in the immunogenic responses (ability to generate A-HPF4-Ab , & antibody subtypes) among different branded LMWHs have been noted due to
  - structural composition of the LMWH
  - interactions with endogenous platelet factor 4 (PF4) and other proteins.
- Assessment of the Immunogenic responses of LMWH biosimilar/copies is part of the regulatory requirements

The Immunogenic Potential of Generic Version of Low-Molecular-Weight Heparins May Not be the Same as the Branded Products

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J Farrell Sat Clin Appl Thromb Hemost 2008; 14, 5
J Walenga Sat Poster, ISTH, 2009

Immunogenicity (CHMP/118264/2007)

- **Comparative safety trial**
  - For the detection of the immune-mediated type of Heparin-induced Thrombocytopenia (HIT Type II) monitoring of platelet count and an adequate diagnostic procedure in patients developing thrombocytopenia and/or thromboembolism (HITT) during the trial has to be performed.
- **Immunogenicity testing framework**
  - Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (CHMP/BMWP/14327/06)
- **Special focus expected in the Risk Management Plan**
  - The risk management plan should particularly focus on rare serious adverse events known to be associated with LMWHs such as Heparin-induced Thrombocytopenia Type II (HIT II, HITT) as well as anaphylactoid and anaphylactic reaction

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Other key regulatory points

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Other key regulatory points

- **PMS traceability:** Important to identify the specific product causing ADR
- **CMC post-approval changes**
- **Interchangeability /substitution :** EU current status
  - Interchangeability : responsibility of the Qualified Healthcare professional [**ref: EMEA Q&A document, EMEA/74562/2006 Rev. 1 (22 Oct. 2008)].**
  - Substitution : rules under the direct supervision of EU member states. Some states have implemented specific rules preventing automatic substitution.

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Comparative complexity between Proteins & Complex sugars

Comparative regulatory framework

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Comparative complexity between Proteins & Complex sugars

	Proteins	Complex Sugars (i.e. LMWHs)
Starting Material	Amino Acid Chain +/- Glycosylation	Heteropolymer of Disaccharides with 48 theoretical variants
Direct Characterization of I^{ary} Structure	Possible for amino acids chain	Partial
~~Impact of II^{ary} or III^{ary}~~ Structure	Critical	Not fully elucidated
Size in Daltons	> 5000 (Insulin) > 19 000 (interferon)	< 18 000 for largest sugars
Active Ingredients	Unique or with Isoforms	Multiple (thousands)
Process Dependent	Highly for Impurities/Glycosylation	Highly for final Active Ingredients composition
Structure Activity Relationship	Usually well known	Not fully elucidated
Immunogenicity Issue	High and Direct when heterolog	Significant and Indirect (HIT)

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Comparative Safety and Efficacy Requirements

Product class	Efficacy requirements	Safety requirements
EPO	Clinical efficacy studies are required (2 clinical trials of at least 12 weeks)	Safety data from patients during clinical trials, as well as at least 12 months of immunogenicity data
HGH	clinical efficacy studies are required (6-12 months)	Data from patients in the efficacy trials, as well as at least 12 months of immunogenicity data
G-CSF	Clinical efficacy studies in recommended clinical models is preferred	Data collected from patients after repeated dosing, with a 6-month follow-up of a "sufficient" number of patients
rh Insulin (Short acting)	Efficacy studies are not required if PK/PD profile is comparable	12 months of immunogenicity data using subcutaneous administration
2009		
LMWHs	Clinical study conducted in major orthopaedic surgery	Immune response in comparative study

EPO=erythropoietins; G-CSF=granulocyte-colony stimulating factor; HGH=human growth hormone; LMWH Low Molecular Weight Heparin

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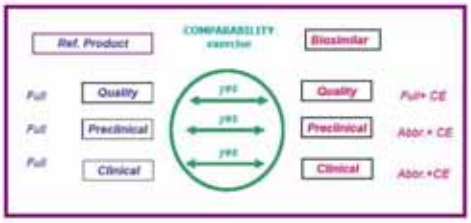
EU Regulatory paradigm of LMWH is identical to the "Biotech derived products" recombinant proteins

- Development + Comparability exercise versus a reference product
  - Quality (Full development)
  - Preclinical
  - Clinical
- The reference product should be authorised in the European Community
- The same reference product throughout the comparability program for quality, safety and efficacy



28

Conclusion

- The definition of Biological product includes LMWhs in EU.
- LMWHs share common characteristics with Biotech products .
- The generic route is not applicable for LMWHs - Only the biosimilar one.
- The principle is supported by Academia.
- A regulatory paradigm including comparability exercise by EMEA has been specifically developed to register biosimilars of a reference LMWH medicinal product.

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THANK YOU

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- Session II: Regulatory Issues for Biosimilars

Biosimilars - Industry Perspective

Speaker:
Estelle Michael (Belgium)
Senior Manager
Regulatory Policy
GSK Biologicals

Contents

- Overview - global landscape of biosimilars
  - In EU, Asia Pacific, Latin America, Middle East, North America, Other

- Fundamental Principles of Biosimilars Guidelines
  - The safety of patients must be central to any regulatory pathway and must be reflected in the guidelines
  - Full quality package and full quality comparison
  - Interchangeability is not interchangeable with automatic substitution

- Reference Product
  - The reference product should have been registered based on full quality, full non-clinical and full clinical data

- Conclusions
  - Some areas where there needs strong emphasis
  - Interchangeability, automatic substitution, naming/labelling, reference product issues


GlaxoSmithKline
Biosimilars – Industry Perspective
Estelle Michael BSc Hons, Batchelor of Law (LLB) Hons
Senior Manager, GlaxoSmithKline Biologicals


Agenda
Overview - global landscape of biosimilars
Fundamental Principles of Biosimilars Guidelines
Reference Product
Conclusion

Overview - global landscape of biosimilars

European Union

Asia Pacific: Australia, Japan, Malaysia,Singapore, South Korea, Taiwan

Latin America: Colombia, Mexico

Middle East: Jordan, Kuwait, Turkiye

North America: Canada, USA

Other: WHO

Agenda

- Overview - global landscape of biosimilars
- Fundamental Principles of Biosimilars Guidelines
- Reference Product
- Conclusion

Fundamental Principles

- A *full comparison* of the quality, safety and efficacy of the biosimilar against the reference product should always be undertaken and must include assessment of physical/chemical, biological, pre-clinical and clinical similarity
- There should be a clear requirement for substantial pharmacovigilance data
- Vaccines are unique compared with other biologicals because of their mode of use and mode of action
  - Vaccines should probably be excluded from biosimilar guidelines

The **safety** of patients must be central to any regulatory pathway and must be reflected in the guidelines.

Fundamental Principles

- Misleading and inappropriate terms such as "bio-generics" must be avoided
  - Biosimilars are similar but not identical to the original innovative biologic
- A biosi
- All b uld have
  uniq ribing, in
  dispe
- The labe idance for
  healthcare pr in which indication
  the biosimilar product has been tested in humans
- At the point of dispensing biosimilars should not be automatically substitutable with the reference product
- The data exclusivity period should be adequate so as to protect innovation in the development of biologicals

The **safety** of patients must be central to any regulatory pathway and must be reflected in the guidelines.

Full quality package and full quality comparison

- Biosimilars guidelines should incorporate the principle that the "process is the product"
  - The way the product is made will impact significantly on efficacy and safety (e.g. immunogenicity)
- Guidelines should account for the fact that biological medicines are produced using a living system or organism known as a cell line
  - No two cell lines are the same, so each biological medicine uses a unique cell line as its starting material
  - As a consequence, each biological medicine is individually unique
- A full quality package for each unique biological medicine should be required
- For a biosimilar, a full comparability package is needed to demonstrate comparability between the reference and biosimilar product

Interchangability is not interchangable with automatic substitution!

Interchangability

The practice by which a physician prescribes one product in place of another

- It is in the hands of the physician in a given clinical setting to determine if one product is interchangable with another and to determine which product is the most safe and efficacious for his/her patients
- In the EU, biosimilar products are being prescribed by physicians in place of the reference product
- Serious consideration should be given to the appropriateness of switching a patient from the reference product to the biosimilar during the course of treatment

Automatic Substitution

The practice by which a product is automatically substituted for another product at the point of dispensing

- Several EU Member States have already enacted either legislation or administrative provisions to advise against or prohibit substitution:
  - These countries are: Spain, France, Sweden, UK and Netherlands; substitution between biological products is already prohibited in Germany; substitutability is currently under discussion in Belgium

Agenda

- Overview - global landscape of biosimilars
- Fundamental Principles of Biosimilars Guidelines
- Reference Product
- Conclusion

Reference Product

- The reference product should have been registered based on full quality, full non-clinical and full clinical data
- The reference product should not have been registered via an abbreviated pathway
  - It would preclude a biosimilar being used as a reference product
- In some territories, it is required that the reference product be registered in that country/region,e.g. EU; in other territories there is an option to cite a reference product, which is registered in another country, e.g. Canada
- If the reference product is not registered in the target country:
  - May be more difficult to register the biosimilar product because the Regulatory Authority does not have experience of the reference product
  - Alternative options? Register the biosimilar product in a country where the reference product is registered

Agenda

- Overview - global landscape of biosimilars
- Fundamental Principles of Biosimilars Guidelines
- Reference Product
- Conclusion

Conclusion

- Overall common global approach to biosimilar guidelines
- Some areas where there needs strong emphasis:
  - Full quality package and full comparability exercise required
- Areas where further discussion required:
  - Interchangability
  - Automatic substitution
  - Naming/labelling
  - Reference Product

- **Session III: Regulatory Landscape on Biosimilars**

Health Canada Perspective on Biosimilars: Some Salient Points and Lingering Issues regarding the Canadian Regulatory Approach

Speaker:
Anthony Ridgway (Canada)
Senior Regulatory Scientist
Biologics and Genetic Therapies Directorate
Health Canada

Abstract

Health Canada has maintained an approach that regulatory decisions regarding the quality, safety and efficacy of medicinal products should be based on scientific evidence and accepts that copies of biologics originally licensed by innovator companies will have a role in health care. Such products should not be considered as generics; however, information in the public domain regarding safety and efficacy of an innovator product over many years of use can be considered relevant if suitable data is provided demonstrating comparability / similarity to that specific reference product. Health Canada is in the late stages of developing a guideline addressing the regulatory process for subsequent-entry biologics (biosimilars, follow-on protein products). The basis for the Canadian approach, important elements in establishing comparability / similarity, and various challenges to the industry and to regulators, will be presented. In addition, the Canadian perspective on important issues such as choice of reference product, access to clinical indications and product substitution / interchange will be discussed.

Health Canada Perspective on Biosimilars:

Some Salient Points and Lingering Issues regarding the Canadian Regulatory Approach

Anthony Ridgway, Ph.D.
Senior Regulatory Scientist
Biologics & Genetic Therapies Directorate
Health Canada

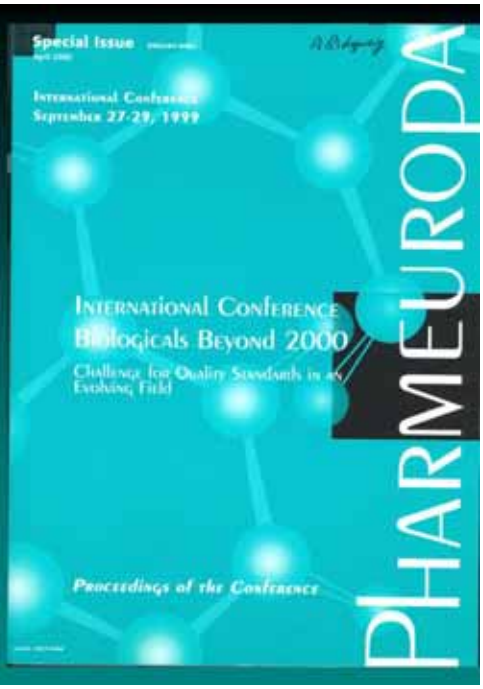
APEC Harmonization Center Workshop on Biosimilars
Seoul, September 17, 2009

Presentation Outline

- Canadian approach and background
  - Comparability and ICH guidance
  - Scientific and regulatory challenges
  - Key elements and considerations
- Some wording from the draft Canadian guidance reflecting specific issues
- Major issue for globalization of biosimilars: choice of reference biologic product and regulatory acceptability
- Update on the WHO guidance on Biosimilars

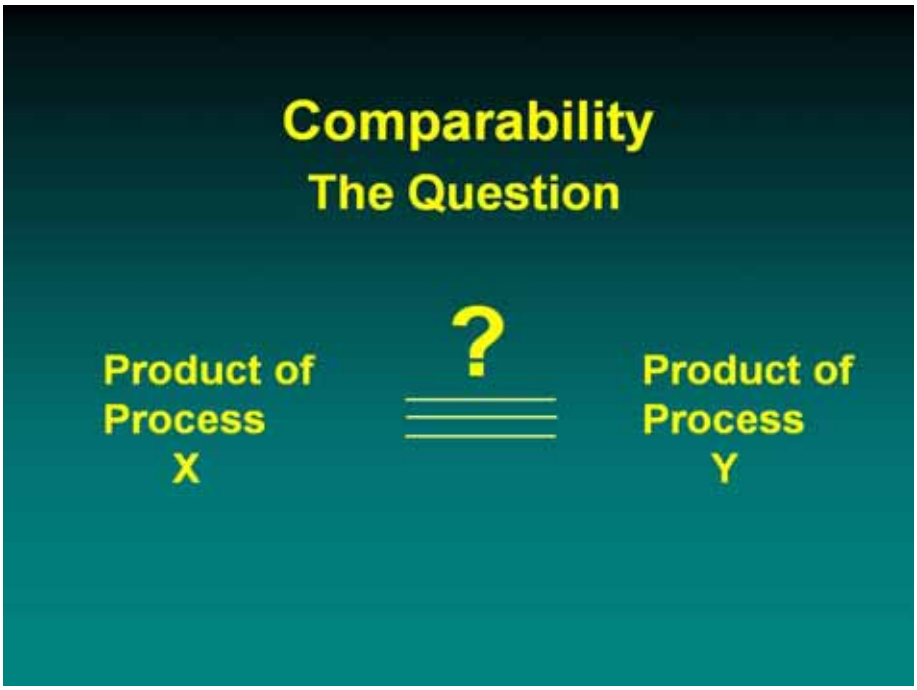
Biologicals Beyond 2000
September, 1999

From a photo by Dr. Wendy Mooney



Specific & Related Activities at Health Canada

- Regulation of SEBs is possible within the scope of current regulations
  - "Outline Document" on the Canadian regulatory approach to SEBs has been made available since 1999
  - "Fact Sheet" on SEBs posted to HC website, July, 2006
- Work is ongoing to address any impediments to a clearer and more fully described regulatory framework for SEBs and to develop or adopt more detailed scientific/clinical guidance
  - External Consultation/Workshop held June 5-6, 2008. (Revised discussion document posted on HC website)
- New authorities & product-life-cycle approaches relevant to SEBs are captured within the broader initiative on "Legislative and Regulatory Modernization"


Comparability
The Question
Product of Process X
?
Product of Process Y


Comparability
Extent of Studies
• Stage/extent of changes
• Impact on the product
• Analytical capability
• Link between quality criteria and safety and efficacy

ICH Quality - Biotechnology

Q5 A Viral Safety

Q5 B Genetic Stability

Q5 C Product Stability

Q5 D Cell Substrates

Q6 B Product Specifications

Q5 E Comparability

(S6 Safety Studies)

Q5E - General Principles

The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change products are identical; but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

Comparability
Key Elements

- Characterization
- Specifications
- Validation
  - changes to materials or process

Characterization
ICH Q6B

- Chemical structure
- Physicochemical properties
- Biological activity
- Purity
- Impurities
- Quantity

Characterization
Purity/Impurity Profile

Drug substance = Multiple entities

- Desired product (microheterogeneity)
- Product-related substances

- Product-related impurities
- Process-related impurities

- Contaminants

Comparability
Clinical Considerations
bridging study vs larger trial

- Indication
  - mode of action
  - outcome measures

- Dosing and Patient Response
  - units of activity
  - route of administration
  - narrow therapeutic index

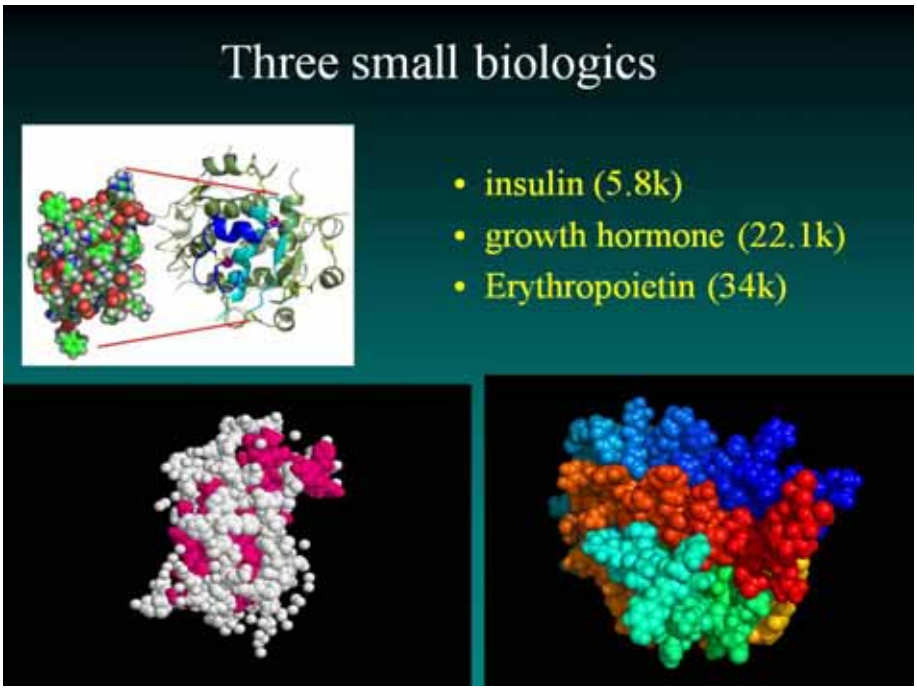
- Safety Versus Efficacy
  - immunogenicity
  - active ingredient vs impurities

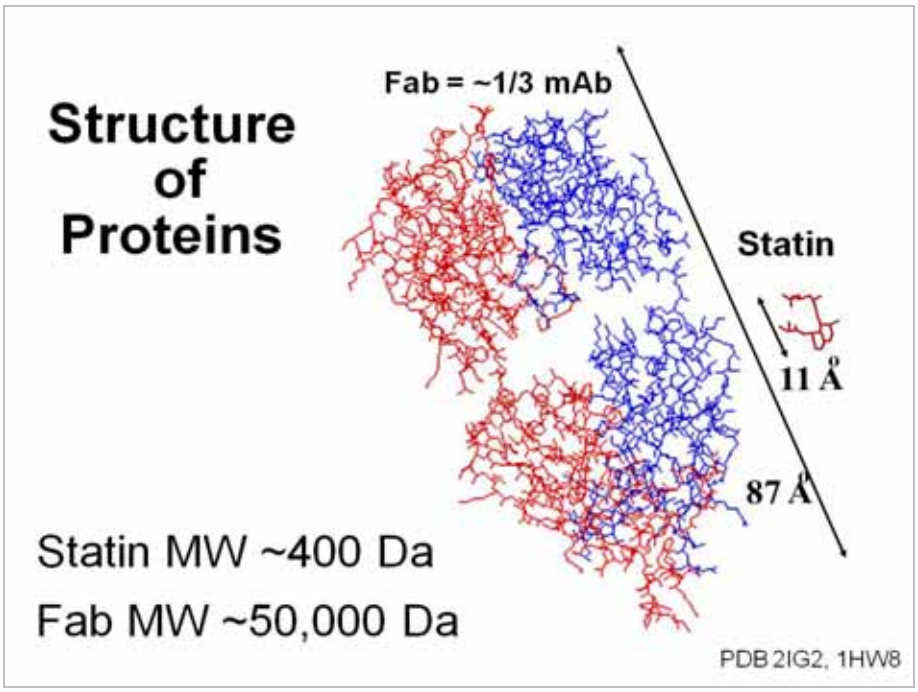
Immunogenicity Issues

- Most biopharmaceuticals induce antibodies
- Manufacturing changes can cause unexpected changes in immunogenicity
- Current analytical methods cannot fully predict biological properties
- Immunogenicity of biopharmaceuticals may have serious clinical consequences

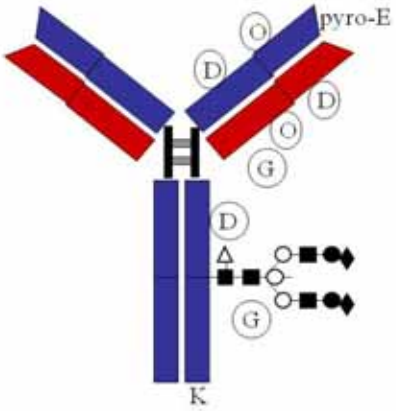
Comparability Challenges: Biologic vs Chemical Drug

- Size and complexity of the "desired product"
- Heterogeneity (inherent, process-related, etc.) and the purity/impurity profile of drug product
- Adventitious agents
- Limitations of methods for characterization
- Immunogenicity


Three small biologics
• insulin (5.8k)
• growth hormone (22.1k)
• Erythropoietin (34k)


Structure of Proteins
Fab = ~1/3 mAb
Statin
11 Å
87 Å
Statin MW ~400 Da
Fab MW ~50,000 Da
PDB 2IG2, 1HW8

Modifications



- Pyro-Glu (2)
- Deamidation (3 x 2)
- Methionine oxidation (2 x 2)
- Glycation (2 x 2)
- High mannose, G0, G1, G1, G2 (5)
- Sialylation (5)
- C-term Lys (2)

Courtesy of Steve Kozlowski, FDA

Innovator Advantages for Demonstration of Comparability for a Biologic

- Broad experience with product and process
- Availability of drug substance
- Linkages between quality attributes of product and clinical safety and efficacy are known
- Ability to examine any observed change in the context of the range of historical values for clinical trial materials

The Regulatory Pathway Dilemma

- Approach and set of requirements for less complex products will be inadequate for complex products
- Approach and set of requirements for complex products may be excessive for less complex products

Furthermore, clinical parameters (indication, posology, therapeutic index, etc.) influence data requirements

Therefore:

- Detailed guidance must be specific to product or class
- Regulatory approach must be case-by-case

Conclusions

- Health Canada is moving forward with a regulatory approach to SEBs (Biosimilars) that is science-based
- Where possible, principles and guidance from ICH documents are applied
- Opportunities for collaborative regulatory approaches are being actively pursued and relevant guidance from regulatory partners will be referenced or adopted

Subsequent-Entry Biologics
Current Canadian Perspective

- Examined on a case-by-case basis
- Full chemistry & manufacturing data required
  - plus comparability study with "reference product"
- Clinical data is required
  - extent is negotiable (influenced by several factors)
  - Same reference product throughout development program
- One indication will not support all indications
  - However - same mechanism of action + rationale ..... ?
- "Stand-alone" products
  - Approval does not imply automatically substitution
    - Scientific & pharmacovigilance issues (not generics!)

Presentation Outline

- Canadian approach and background
  - Comparability and ICH guidance
  - Scientific and regulatory challenges
  - Key elements and considerations
- Some wording from the draft Canadian guidance reflecting specific issues
- Major issue for globalization of biosimilars: choice of reference biologic product and regulatory acceptability
- Update on the WHO guidance on Biosimilars

Elements of the Draft Guidance:
Choice of reference biologic (comparator)

- ".. Health Canada will, in appropriate and special circumstances, permit the use of a reference biologic drug that is not authorized for sale in Canada. However ... must explain the link .. (to) .. the product authorized for sale in Canada"
- "The reference biologic drug should have significant safety and efficacy data accumulated such that the demonstration of similarity will bring into relevance a substantial body of reliable data"
- ".. a SEB cannot be used as a reference biologic product"

Elements of the Draft Guidance:
Choice of reference biologic (comparator)

- "Products employing clearly different approaches to manufacture than the reference biologic drug will not be eligible ...."
- "the product can be well characterized by a set of modern analytical methods"
- "..... through extensive characterization and analysis, the biologic drug can be judged similar to the reference biologic drug by meeting an appropriate set of pre-determined criteria"
- "The chosen reference biologic product should be used throughout the studies supporting the safety, quality and efficacy of the product"

Elements of the Draft Guidance:
Issues surrounding comparability/similarity

- "If the reference drug substance used for characterization is isolated from a formulated reference drug product, additional studies must demonstrate that the drug substance is not changed by the isolation process."

- "A final determination of similarity can be based on a combination of analytical testing, biological assays, and non-clinical and clinical data. However, to be considered a SEB, the weight of evidence should be provided by the analytical and biological characterization."

Elements of the Draft Guidance:
Issues surrounding comparability/similarity

- "Once granted a NOC, a SEB is considered to be a new (stand-alone) product with all of the associated regulatory requirements. For any changes to the manufacturing process that warrant a demonstration of comparability, the products to be compared will be the pre-change and post-change versions of the SEB. Comparisons with the original reference biologic drug are not required."

(N.B., This has implications regarding "substitution")

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Choice of Reference Product

Considerations for the sponsor include:

- Satisfy registration requirements (multi-national?)
- Similarity of host cells & manufacturing process
- Ability to derive DS, i.e. to de-formulate DP
- Extent of clinical use (and where?)
- Desired indications

Similarity of Host Cells & Manufacturing process

Major influence on determination of biosimilarity:

- Isoforms of desired product and product-related substances
- Product- and process-related impurities
- Relevance & capability of chosen analytical methods

Ability to Derive Drug Substance from Drug Product

De-formulating DP may be a significant challenge:

- If the reference DS used for characterization is isolated from a formulated reference DP, additional studies must demonstrate that the DS is not changed by the isolation process
- May need to formulate the SEB in a manor similar to the Reference DP, then de-formulate in parallel with Reference DP, then show de-formulated SEB is comparable to SEB DS

Extent of clinical use
(and where?)

How much supportive clinical data becomes relevant through the demonstration of biosimilarity?:

- What is the real-world experience with the Reference Product?
  - How long has it been registered?
  - How many patients have been treated?
- What relevant clinical studies are in the public domain and available to be referenced?
- (Is data from an acceptable regulatory jurisdiction?)

Desired Indications

- Which clinical indications are held by different potential Reference Products?
- What are national rules regarding extent of permissible indications?
- What are the data requirements for extrapolation to additional indications?

Regulatory Aspects Relevant to Reference Biologic Product

Factors possibly affecting the consideration of a non-national RBP:

- Comparability is assessed and maintained following manufacturing changes to Reference Product
  - Because data in the public domain is collected at different times over registration period
- Adverse event reporting system(s)
- ICH guidance is part of regulatory framework
- Existence of MOU for exchange of regulatory information (especially r.e. safety)

Regulatory Aspects Relevant to Reference Biologic Product

Factors possibly affecting the relative value of a national RBP:

- Despite regulatory experience, there may be legal barriers to using data in the innovator's files
- The original submission may be significantly dated and/or the original review report may be of poor quality
- Recent review experience may be limited (if no recent manufacturing changes or product not marketed)
- The data in the public domain brought into relevance through biosimilarity may be less than for a non-national reference product

Canadian Perspective and Implications

Non-Canadian reference product may be acceptable

- Clinical data for SEB (Biosimilar) is required
- Data made relevant by biosimilarity is supportive
  - So what/where is the best supportive data?
- Once approved, SEB (Biosimilar) is a "stand-alone" product which has implications for:
  - Post-approval changes and comparability
  - Additional strengths, presentations, indications
  - Substitution/interchange

Presentation Outline

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IABS/HC/WHO - July, 2009

- IABS/HC Workshop on Biologicals: Scientific Basis for Regulatory Approval of Similar Biotherapeutic Products: Key considerations to ensure Quality, Safety and Efficacy; Ottawa, July 13-14, 2009
- WHO/HC Consultation on Regulatory Considerations in Evaluating Similar Biotherapeutic Products; Ottawa, July 15-16, 2009
- APEC participation (Malaysia, Republic of Korea, USA, Canada, Peoples Republic of China, and Thailand) but also representatives from outside APEC, and from industry

Issues Identified As Important That May Warrant Further Discussion Amongst APEC Countries

- Appropriate choice of reference biologic products
  - # RBPs & variable submission requirements will influence access & cost
- Scope of products eligible as biosimilars (e.g. mAb, vaccines)
- Whether "biobetters" should be included
- Degree of similarity required and extent of reliance upon quality comparisons versus non-clinical and clinical comparisons
- Ability to extrapolate indications
- Post-market use of biosimilars
  - Interchange/substitution
  - Off-label use
  - Vigilance

Update on WHO Guideline

- Restructured following comments & input from WHO ECBS October/08 Meeting
- July 13-14/09, HC & IABS hosted a meeting in Ottawa on the scientific basis for Similar Biotherapeutic Products (SBPs); followed July 15-16 by meeting of NRAs on issues r.e. the WHO guideline
- Comments from a public consultation in June/09, from the meetings in July, and from invited reviewers have been incorporated and will be presented at the ECBS meeting in October, 2009
- Following adoption by the ECBS, it is anticipated that there will be training sessions for implementation

- Session III: Regulatory Landscape on Biosimilars

Similar Biotherapeutics Products - A Malaysian Regulatory Overview

Speaker:
Arpah Abas (Malaysia)
Head of Biotech Section
National Pharmaceutical Control Bureau
Ministry of Health Malaysia

Abstract

Over the last 20 years a new class of drugs has been developed and produced – safe and effective therapeutic proteins/biotech drugs. The biotechnology industry is maturing rapidly but faces increasing scrutiny over the high cost of biotherapeutics and that often limits their use. Global prescription sales of biotech drugs increased 12.5% to more than $75 billion in 2007 *(IMS).* Reducing healthcare costs is a hot political issue in many countries, so the introduction and use of generic drugs is stimulated.

Based on the current analytical techniques, two biologicals produced by different manufacturing processes cannot be shown to be identical, but similar at best. Thus, the term 'biosimilar' is coined Given the notable differences between biosimilars and traditional small molecule drugs, it is only fitting that the regulations to govern biosimilars account for such disparities, hence the generic approach is scientifically inappropriate for these products.

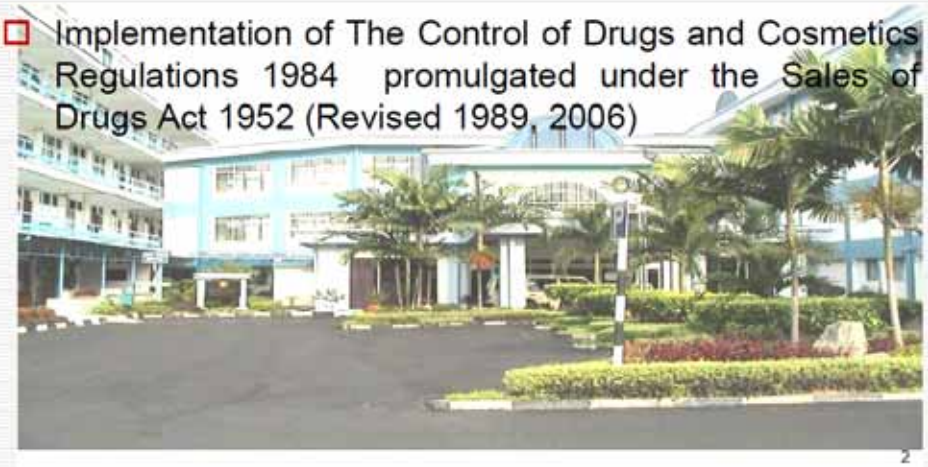
Patient safety is a key concern and guiding principle for both manufacturers and regulators. Worldwide, varying degrees of regulatory preparedness and divergent approaches to the regulatory oversight of biosimilars exist. Biosimilars are controversial and delivering these products to the patient involves complex technical and regulatory challenges. Whilst there are arguments for slightly less stringent regulatory requirements, a deliberated approach of proactive identification and management of proven and possible risks, and devotion of

sufficient time to the comprehensive development programme, are key factors to success.

It is important that appropriate legal guidelines are used to regulate their use. The rapidly expanding field of biosimilars calls for awareness, alertness and education to all stakeholders. Biosimilars will likely forge ahead and become a reality in the near future.

National Pharmaceutical Control Bureau

- Government agency (NRA) under the Ministry of Health
- Implementation of The Control of Drugs and Cosmetics Regulations 1984 promulgated under the Sales of Drugs Act 1952 (Revised 1989, 2006)



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BIOTECH
Where are we now ?

- Biotechnological products are now well established as key therapeutic modality: targeted therapies and providing treatments for hitherto incurable diseases. Cancer treatment (40%), auto-immune diseases etc.
- Exponential growing share of prescription pharmaceutical spending, global biotech sales grew 12.5% in 2007. Today, more than $70 billion business worldwide, accounting 20% of total pharma market.
- By 2010, nearly 50% of new drugs are biodrugs/biotech-derived. More than 500 are in various stages of clinical trials
- Next 5 years, global biotech market closely parallel traditional pharma marketplace, reflecting – changing industry dynamics. "Charmed life" – facing a new reality (loss of exclusivity, competition from biosimilars, crowded therapy, price scrutiny, safety concerns …. moderate growth rate 2012.

Source: IMS 2008

3

Why Biosimilars – and why now ?

- **Patent Expiry**
  The imminent patent expiration of many biotechnological products, potentially opening the market for so-called "copycat" version termed biosimilars.

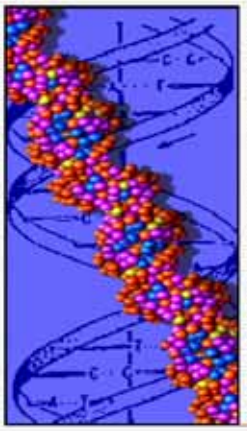
- **Cost containment**
  Biotech products are expensive to develop, manufacture and administer. In most countries healthcare costs are out of control. Cheaper biosimilars could ease the pain!

- Available in Asian, Eastern European, Latin American markets for many years. Until recently, activity (in Asia) was driven by China and India, but there is now a surge in the rest of Asia as well.

4

Biologicals – are they special ?

- Biotech-derived products:



Highly diverse molecular structures

Highly diverse mechanism of action

Highly diverse clinical indications

Recombinant…….

- Hormones: Insulins, Growth hormone
- Cytokines: Epoetin, G-CSF
- Interferons
- Enzymes
- Monoclonal antibodies

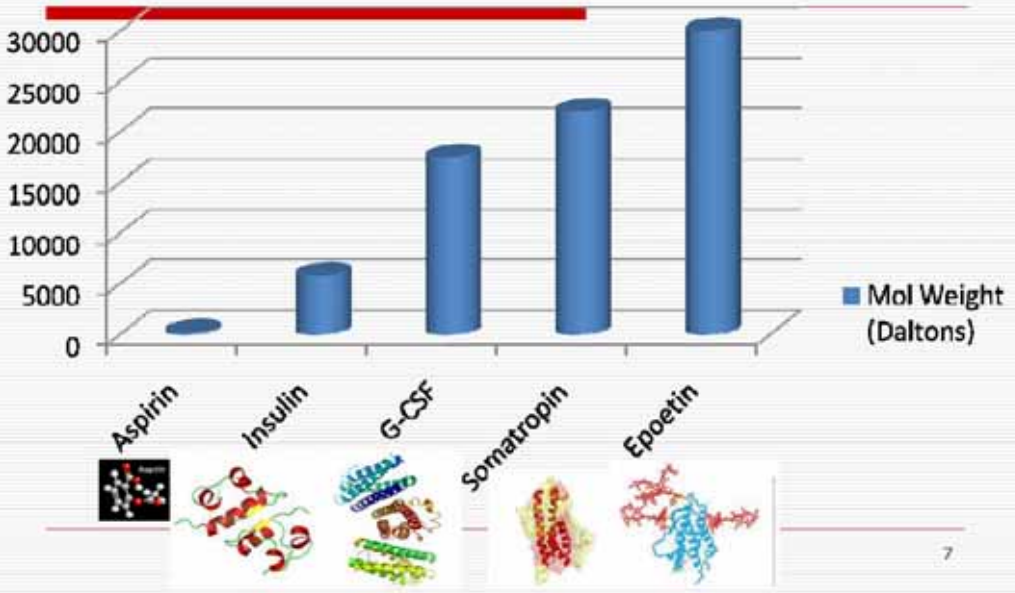
5

Biologicals vs Chemical Pharmaceutical Products

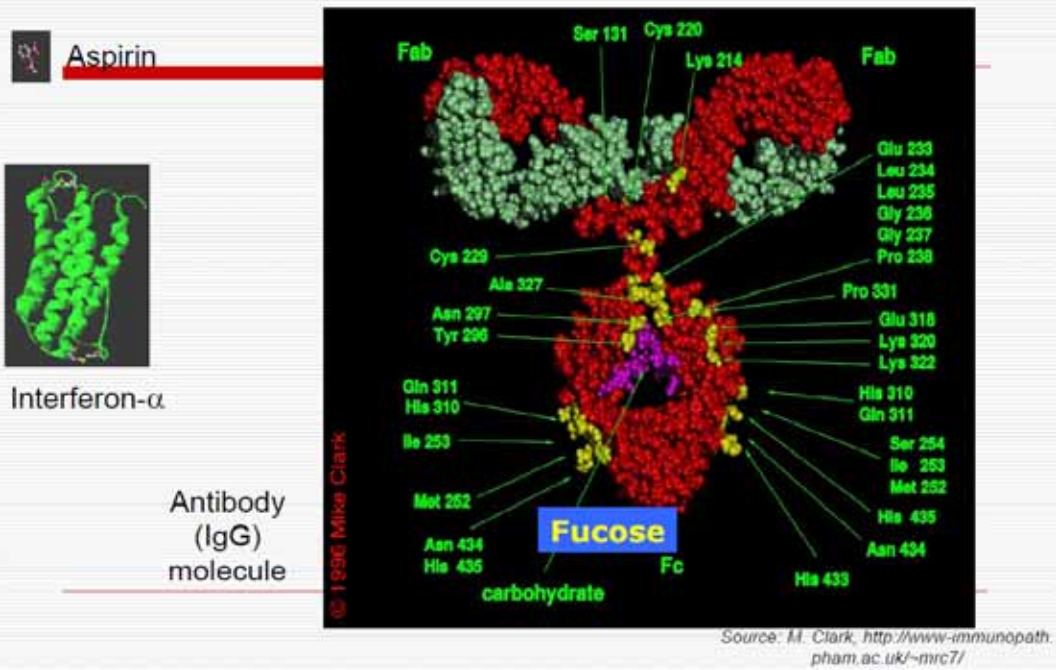
- ✓ High molecular weight
- ✓ Complexicity
- ✓ Heterogenous
- ✓ Production processes
- ✓ Physicochemical characteristics
- ✓ Formulation
- ✓ Analytics
- ✓ Stability profile
- ✓ Storage and handling conditions
- ✓ Expiration dating
- ✓ Immunogenicity

6

Molecular Weight of Aspirin vs. Biopharmaceuticals

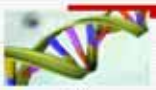


Complexity of Monoclonal Antibodies (mAb)



Source: M. Clark, http://www-immunopath.pham.ac.uk/~mrc7/

Manufacturing Process: Producing a Biopharmaceutical



Establishment of genetically engineered cells that produce the desired product

Scale-up and production of large quantities

Downstream processing and purification

Human gene

DNA Vector

Transfer into host cell

Cloning into DNA vector

Bacterial or mammalian cell produces protein

Fermentation

Formulation

The process makes the product

9

Regulators face up to 'Biosimilar' complexity

- The generic paradigm does not work, hence biosimilar a new regulatory pathway.
- How far should we regulate this sector ?
- How much information should we demand from the manufacturers of biosimilars ?
- How many tests should we request to prove that the copies of biopharmaceuticals are as safe and efficacious as the original product ?
- How much clinical data to show equivalent efficacy and safety as the original product ?
- Ensure regulatory position adequately reflects scientific advances/expertise, multidisciplinary resources. Establish international collaboration & cooperation (WHO & other DRAs)

10

Guidance Document and Guidelines for Registration of Biosimilars in Malaysia

FORMATION OF TWG,(Biotech)	25 February 2008
PREPARATION OF DRAFT DOCUMENT	1 March 2008
DISCUSSION/DISSEMINATION OF DRAFT GUIDANCE	23 April 2008
COLLATION OF FEEDBACK AND COMMENTS	23 May 2008 2 July 2008 25 July 2008
FINAL GUIDANCE	30 July 2008
CONSIDERATION FOR ADOPTION	4 August 2008

11

Innovators *Versus* Generic Manufacturers

- **Innovators**
  - Biological products can not be characterised
  - An identical process is needed. Lacks expertise
  - Safety cannot be assured and immunogenicity is a concern
  - Preclinical and clinical studies required
  - It is unethical to subject patients to any incremental risk when safe and efficacious protein biologics are available

- **Generic Industry**
  - Advanced analytical techniques are available for product comparative characterisation
  - Producing biologic is not easy. Reject the notion that complexity = impossibility
  - Additional confirmatory pre-clinical or clinical studies should be determined case-by-case
  - Overstating the complexity and bioequivalence issues, money matters

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Biosimilars and NRA: Guiding Principles

- Patient safety first. Other considerations: cost containment - inexpensive drugs/cost saving. More accessible to patients.
- Regulatory requirements must reflect scientific progress not define pathways. Maintain the rigorous standards of ensuring product safety and efficacy while at the same time allowing competition.
- Regulations based on state-of-the-art science, fair and feasible, not too onerous, avoiding over-regulation, 'win-win' objective.
- Regulatory transparency and open dialogue with all stakeholders: key to put in place a robust regulatory framework in this emerging field.

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Principles of Licensing of Biosimilars

1. The principles within the existing regulatory framework for biologics, biotechnology drugs: the basis for the regulatory framework for biosimilars with the new element of comparability to prove similarity in quality, safety and efficacy.
2. Scope: well characterised proteins such as recombinant DNA derived therapeutic proteins.
3. GMP Audit of manufacturer which is from non-PIC/S countries is mandatory, unless the manufacturer has been inspected by PIC/S member countries or reference countries, the inspection reports will be considered.
4. Demonstration of consistent and robust manufacturing process.
5. Robust pharmacovigilance including Risk Management Plan and traceability are essential. PSURs of biosimilar should be submitted with evaluation of benefit/risk of the biosimilar post-market.
6. Labelling/Package insert must be transparent and clear – distinct name, reference product, overview of clinical data, clear guidance of interchangeability/substitutability based on data.

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Reference Product

- Suitable duration and volume of marketed use
- A product already approved / registered in Malaysia on the basis of a complete dossier (quality, safety and efficacy)
- Alternatively, a product registered in the reference countries Australia, Canada, EU (via centralised procedure), United Kingdom, France, Japan, Sweden, Switzerland and USA is considered acceptable
- A biosimilar product in the country of origin cannot be used as a reference product.
- Published data/standard as a reference (eg. Pharmacopeia monograph, WHO etc.) can be used for basic comparisons, however this is often insufficient to establish all aspects of comparability.

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Development of a Biosimilar

Define and characterise the reference product → Complete product & process development of biosimilar → Confirm comparability of the biosimilar with the reference product.

Physicochemical characterisation
Biological characterisation

Non-Clinical	Pre-clinical tests PK/PD tests
Clinical	PK/PD in men All clinical trials for efficacy and safety (indications, immonogenicity, post-market monitoring)

Courtesy: EGA Handbook

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Scientific Considerations: Comparability Exercises

Molecular complexibility
Manufacturing process
Degree of characterisation
Clinical indications
Availability of safety data
Availability of clinical data

- **Quality Studies:**
  - Physicochemical tests
  - Bioactivity/Potency tests
  - Purity
  - Stability
- **Non-Clinical Studies:**
  - PK/PD
  - Toxicology
- **Clinical Studies:**
  - Efficacy/Therapeutic Equivalence
  - Immunogenicity

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Characterisation: Comprehensive and orthogonal analytical analysis

- ☐ Physicochemical characterisation and
- ☐ Bioanalytical characterisation

Note:

a) The arsenal of advanced protein analytics may show an absence of differences more and more precisely. But the absence of detectable difference is no evidence for identity – and the relevance of small differences for clinical properties usually cannot be predicted

b) Issue like big molecules, such as antibodies, are difficult to characterise fully with the current range of analytical technologies. "When it comes characterising proteins there is not one test and one answer. It is more a case of doing 20 different tests and getting an answer that does necessarily describe all the characteristics of the protein – *Andrew Fox*

c) Analytics do not allow complete characterisation.

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Immunogenicity – A unique Safety Issue For Biotech Medicines

- Immunogenicity cannot be predicted with pre-clinical or non-human studies
- No comprehensive guidelines on the approaches required for immunogenicity testing during product development.
- A risk-based approach/strategy is advocated
- A risk profile should be formulated, and a battery of clinical and non-clinical tests/assays should be adopted that appropriately reflects level of risk.

➢ A risk-based bioanalytical strategy for the assessment of antibody immune responses against biological drugs

Shankar G, Pendley.C, Stein K.E (2007) Nat Biotechnol, 25(5):555-56

19

Drug Safety: Proactive Risk Management

- Pharmacovigilance plan
  - Routine pharmacovigilance (milestones, PSURs)
  - Additional parmacovigilance
    - important potential risks – immunogenicity
    - important missing safety information – additional patient group, indications
- Risk management plan (RMP)
  - Risk identification & Characterisation (e.g assays)
  - Risk monitoring (framework to associate risk with product)
  - Risk minimization & mitigation strategies
  - Risk communication (information to prescribers, patients, traceability plan, patient registry, surveillance, tracking)

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Challenging issues: Interchangeability/Substitution/INN

- For a designation of interchangeable, applicant must provide evidence that, in any given patient, the biosimilar product yields the same clinical result as the comparator and that it presents no risk to safety or efficacy if the patient alternates or is switched between products.
- No automatic substitution. Repeated substitution will prevent accurate pharmacovigilance.
- INN should not be relied upon as the only means of product identification, nor as the sole indicator of product interchangeability.

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Dossier Requirements for Biosimilars (ACTD)

Part 1 – Normal Requirements

Integrated Comparability Exercise

Quality, Part II – FULL	+ CE
Non-clinical, Part III – Reduced	+ CE
Clinical, Part IV – Reduced	+ CE

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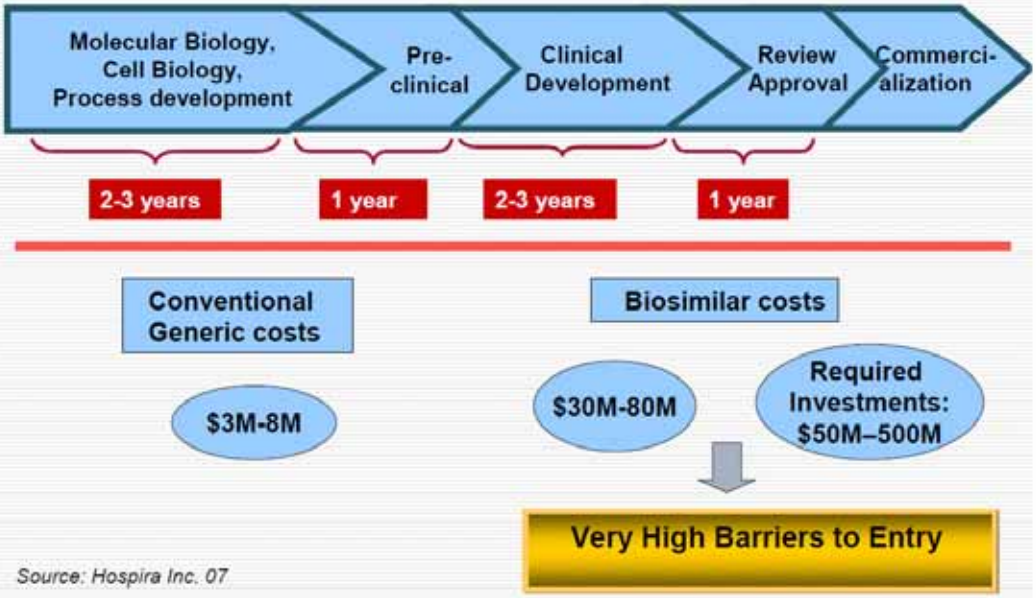
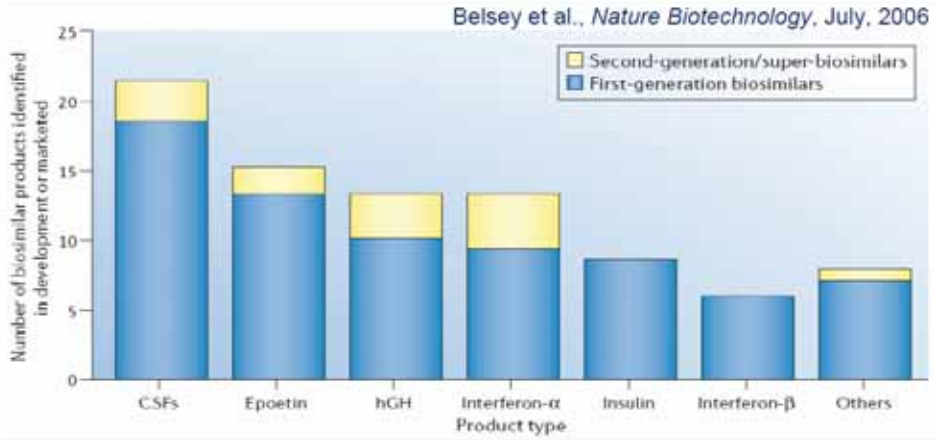
It is Not the Generics We Know



Source: Hospira Inc. 07

Biosimilar suitability depends on drug class



- Market potential of biosimilars affected by:
  - Existing competition
  - Ease of product development and characterisation
  - Required level of patient support

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Typical Pitfalls in Application for MA of Biosimilar in Malaysia

- Generally paucity of data on development, manufacture and control for both DS and DP and validation of infectious agents elimination. No comparability studies.
- Batch-to-batch consistency not demonstrated
- Biosimilarity not addressed in terms of formulation, specifications, stability.
- Quality control: Inadequate assay formats and incomplete assay validation.
- Non comprehensive and inadequate characterisation
- Inadequate clinical studies, poor designs (non-comparative, observational, small number)
- Safety: lack of risk management strategies, incomplete PSUR
- Lack of information on handling and storage

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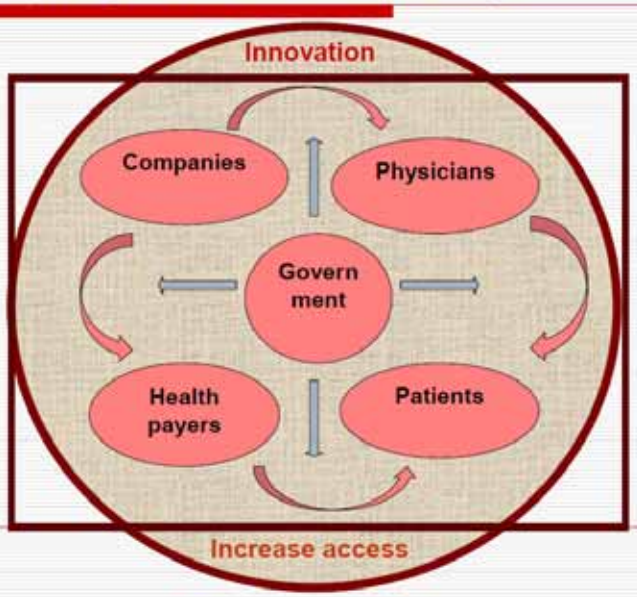
The biosimilar sector continues to attract huge interest and controversy. Companies want profit, health payers want cost reductions, clinicians want efficacy, safety and patients want drugs. Squaring the circle will take some doing.



26

Views evolved .....

- What can be considered to be biosimilar is also not perfectly clear at present!
- Many regulators had expressed : Monoclonals are too complex to develop as biosimilar
- " What constitutes a biosimilar monoclonal antibody is going to open up a completely new discussion "
- " In my view you always need to consider them as a unique protein" *Nature Reviews Drug Discovery 5, 445 (June 2006)*
- " It remains to be seen whether the development of a biosimilar mAb is possible and feasible " Glycosylation patterns are likely to be among the most crucial issues for biosimilar mAb

Schneider & Kalinke, Nature Biotech 26, 2008

At the EMEA Workshop on Biosimilars mAbs 2 July 2009 – the consensus appeared to be that biosimilars monoclonals are feasible.

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Looking forward .....

- Despite of obstacles to biosimilars heavy costs and complexity in development, and new and uncharted territory, the future for biosimilars appears inevitable.
- With a large market share and rapidly growing market segment adding economic incentive for manufacturers, and patents using biopharmaceuticals running out, the future has already begun
- Supporting a viable biosimilars industry is a key for any government that is serious about solving the hard-pressed healthcare budgets.
- Various guidance documents are in the making, and all such initiatives should aim for global consistency and harmonisation.

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Conclusion

- Biosimilars is an important issue for all parties – patients, generic and innovative industries, healthcare authorities, researchers & academicians.
- Regulation of biosimilars and availability of safe biosimilars will be a major challenge for NRAs for years to come.
- A well-defined regulatory framework that can be built up based on experience and increasing scientific knowledge is essential.
- Evolving and rapidly expanding field following different rules and dynamics than generic drugs.

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- Session III: Regulatory Landscape on Biosimilars

Regulatory Landscape on Biosimilar Current Status of laws and Regulations in Thailand

Presenter
Prapassorn Thanaphollert (Thailand)
Senior Pharmacist
Biological Products Group
Drug Control Division
Thai FDA

Contents

- Key Issues
- Current status of laws and regulations in Thailand
- Safety and Efficacy: Dogma of Generics does not apply to Biological therapeutic products
- Careful Evaluation
- Unpredictable security profile
- Necessary to consider the implementation of the appropriate guideline
- Physicians should be fully informed about the Biological therapeutic products and their followed on products
- Real time situation
- Need a more practical guideline
- WHO guideline is needed

- Lessons learned
  - Stand-alone approach
  - Facing safety issues
  - Thai EPO Registry
  - Need of an extensive investigation and risk mitigation plans

- Conclusion

Regulatory Landscape on Biosimilar

Current Status of Laws and Regulations in Thailand

Prapassorn Thanaphollert
Thai Food and Drug Administration
17 September, 2009

Outline of presentation

- Key issues
- Lesson learned

Key issues (1)

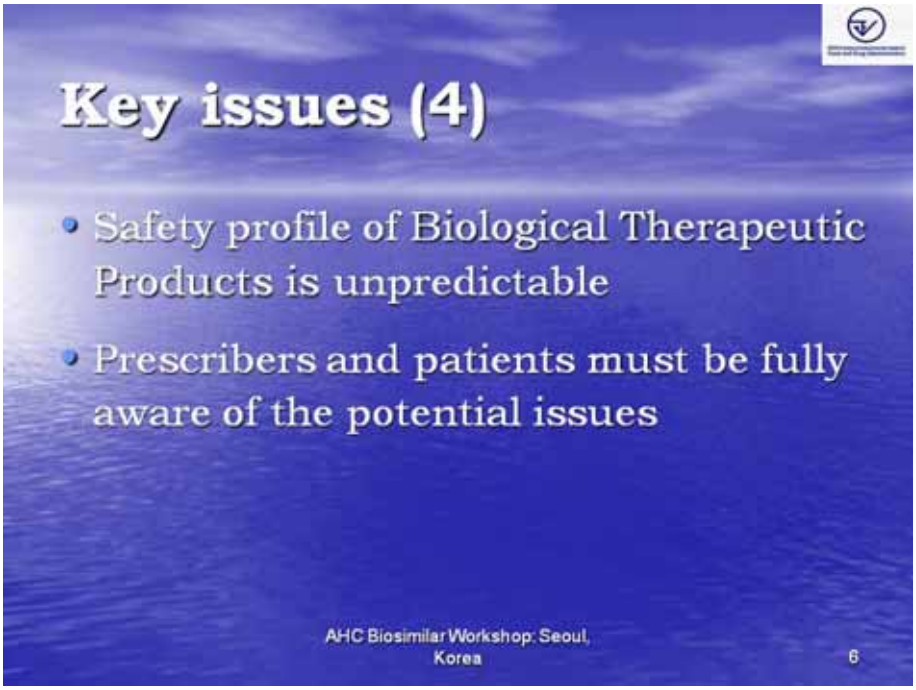
- Current Status of Laws and Regulations in Thailand
  - -Drug Act B.E.2510 (1967)
  - -No specific Biosimilar Guideline
  - -Apply stand alone approach to approve **Biological Therapeutic Products** AND **their followed on products** OR **Biogeneric Products**

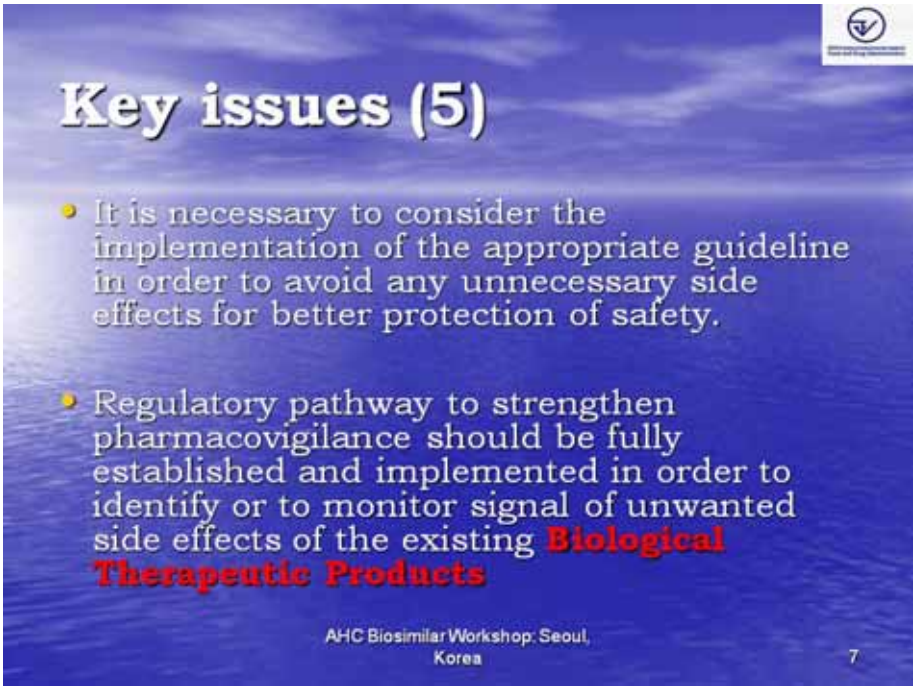
Key issues (2)

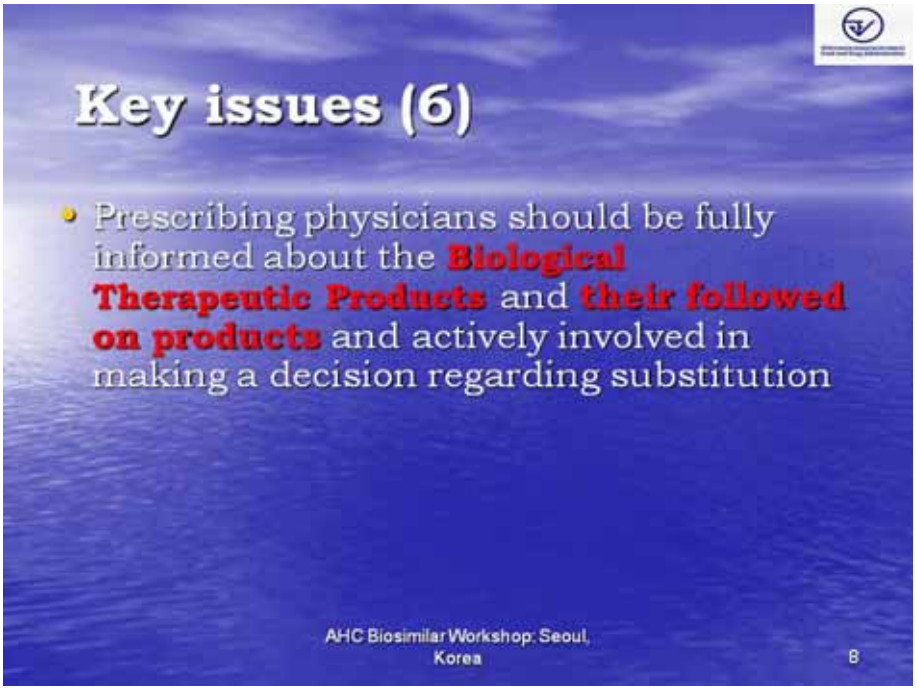
Safety And Efficacy: Dogma of Generics does NOT apply to Biological Therapeutic Products

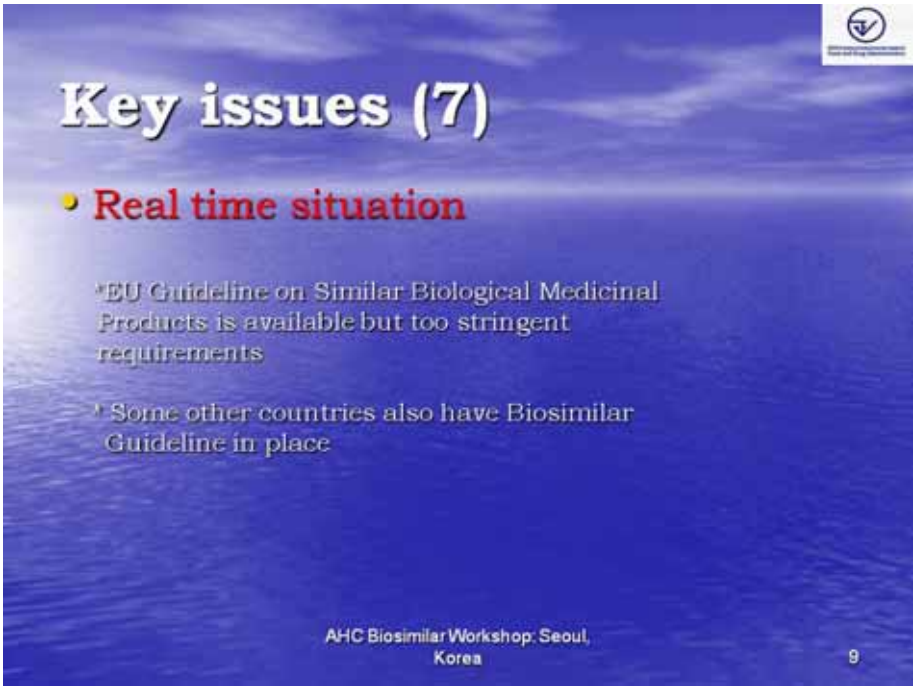
Generics	✓ Bioavailability	→	✓ Safety ✓ Efficacy
Biological Therapeutic Products	✓ Bioavailability	→ (crossed out)	X Safety X Efficacy


Key issues (3)
• Biological Therapeutic Products need careful evaluation by Regulatory bodies to ensure quality, safety, and efficacy
• Regulatory requirements should be transparent, science based, predictable and product specific
AHC Biosimilar Workshop: Seoul, Korea
5


Key issues (4)
• Safety profile of Biological Therapeutic Products is unpredictable
• Prescribers and patients must be fully aware of the potential issues
AHC Biosimilar Workshop: Seoul, Korea
6


Key issues (5)
• It is necessary to consider the implementation of the appropriate guideline in order to avoid any unnecessary side effects for better protection of safety.
• Regulatory pathway to strengthen pharmacovigilance should be fully established and implemented in order to identify or to monitor signal of unwanted side effects of the existing Biological Therapeutic Products
AHC Biosimilar Workshop: Seoul, Korea
7


Key issues (6)
• Prescribing physicians should be fully informed about the Biological Therapeutic Products and their followed on products and actively involved in making a decision regarding substitution
AHC Biosimilar Workshop: Seoul, Korea
8


Key issues (7)
• Real time situation
*EU Guideline on Similar Biological Medicinal Products is available but too stringent requirements
* Some other countries also have Biosimilar Guideline in place
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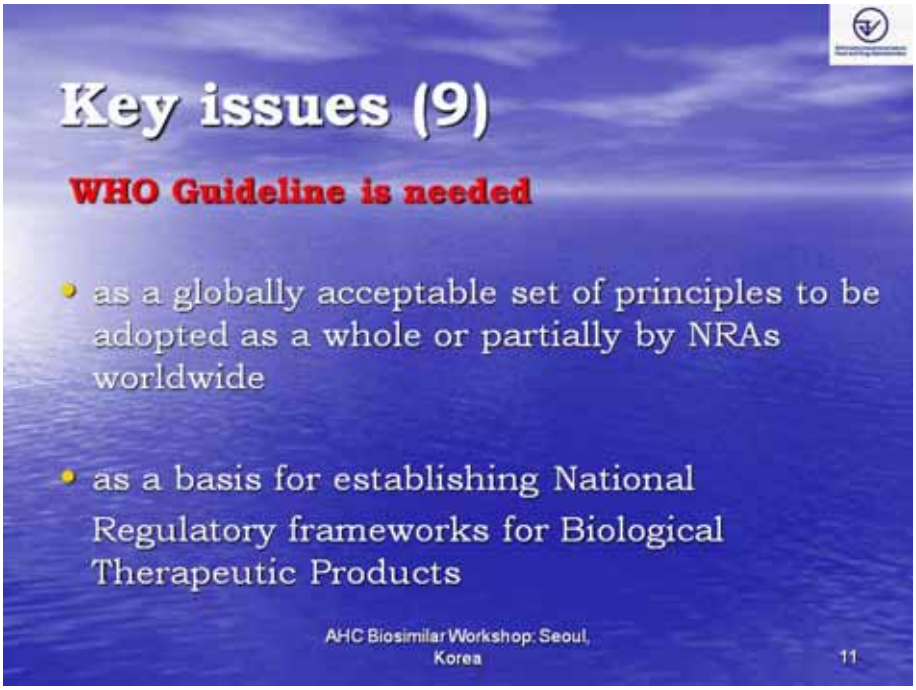
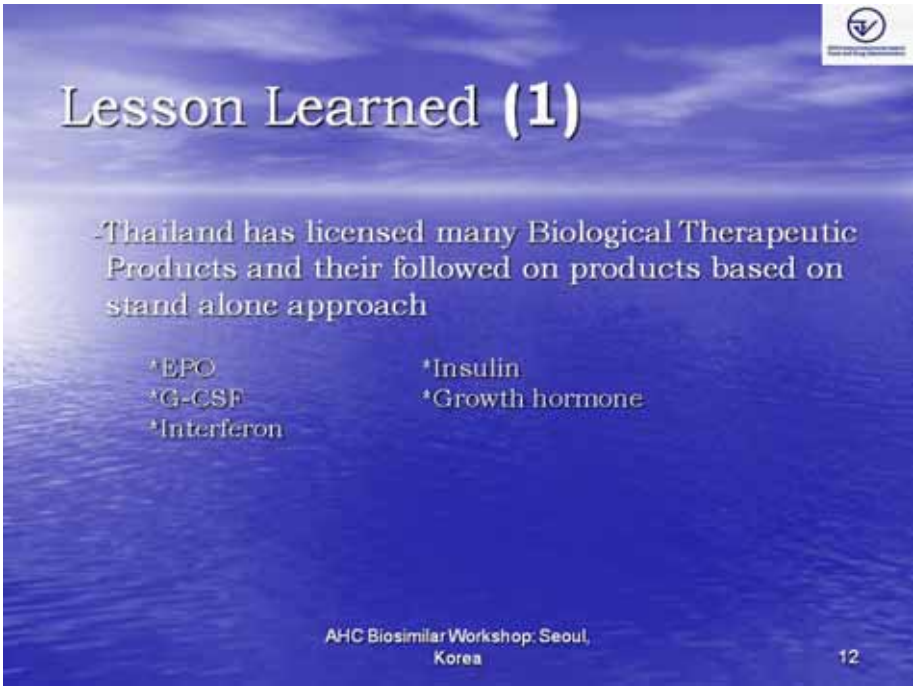
Key issues (8)
*Thailand and many other developing countries need a more practical Guideline on Biological Therapeutic Products that can be fully implemented without compromising the quality, safety and efficacy in order to allow access to Biological Therapeutic Products at affordable price
AHC Biosimilar Workshop: Seoul, Korea
10


Key issues (9)
WHO Guideline is needed
as a globally acceptable set of principles to be adopted as a whole or partially by NRAs worldwide
as a basis for establishing National Regulatory frameworks for Biological Therapeutic Products
AHC Biosimilar Workshop: Seoul, Korea
11


Lesson Learned (1)
-Thailand has licensed many Biological Therapeutic Products and their followed on products based on stand alone approach
*EPO
*G-CSF
*Interferon
*Insulin
*Growth hormone
AHC Biosimilar Workshop: Seoul, Korea
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Lesson Learned (2)

*Thailand is facing safety issues especially PRCA cases resulting from widely automatic substitution of EPO (Biological Therapeutic Products)

*Introduction of Thai EPO Registry to address the possible root cause of PRCA in Thailand has underway since July 08

Lesson Learned (3)

Thai EPO Registry (3 years follow up period)

*Prospective surveillance registry to monitor and minimize EPO - PRCA risk in Thai patients with transparency, reliable and ethical care

*Observational but defined approach if loss of effect detected

*Can serve as a model for assessment of the immunogenicity profiles of currently marketed and future ESAs (Biological Therapeutic Products)

Lesson Learned (4)

- Minor differences can impact the immunogenicity profile of Biological Therapeutic Products.
- Effective pharmacovigilance and traceability are very important to detect and investigate any safety signals.
- An extensive investigation and Risk Mitigation plans are necessary to manage such problems.

Conclusion

WHO Guideline on Biosimilar is needed ASAP through the assistance from APEC Harmonization Center

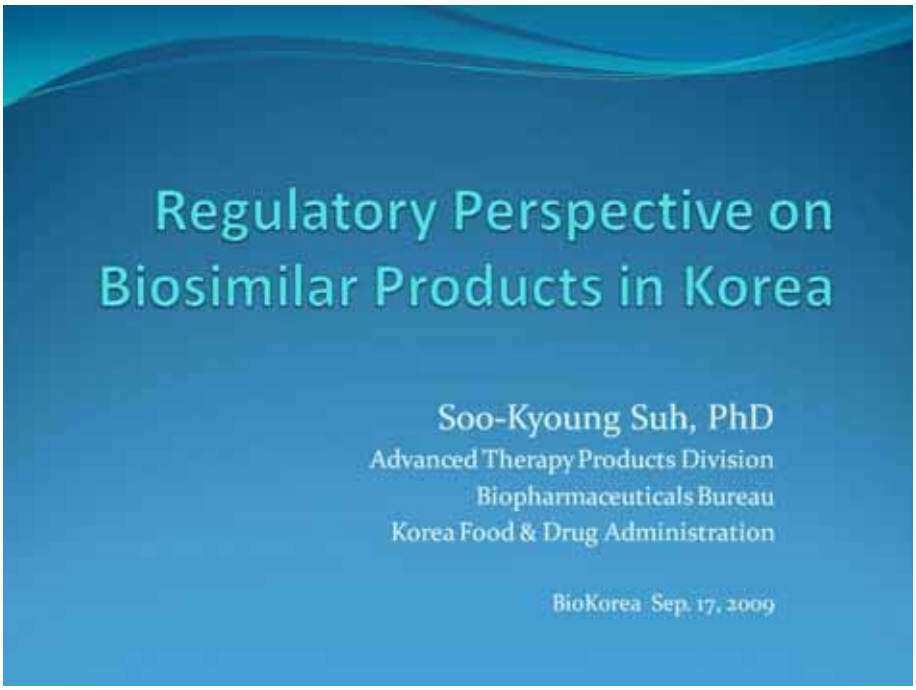
- Session III: Regulatory Landscape on Biosimilars

Regulatory Perspective on Biosimilar Products in Korea

Presenter
Soo-kyoung Suh (Korea)
Senior Scientific Officer
Advanced Therapy Products Division
Biopharmaceuticals and Herbal Medicine Bureau
KFDA

Abstract

A biosimilar drug is a medicine that is not identical, but similar to a biological medicine that has already been approved. There have been much discussion and debate about the scientific considerations related to biosimilar products Because of the molecular complexity of protein drugs and the differences between protein drugs and small molecule drugs, existing regulatory pathway is not applied to the biosimilar products. Recently, the regulatory structures have been adapted to approve the biosimilar products based on reduced data packages and the biosimilar guideline has been issued in Korea. New regulatory framework is based on scientific rationale and experience. This presentation will give an overview of the Korean regulatory process of biosimilar products, focusing on regulatory guideline.



Outline

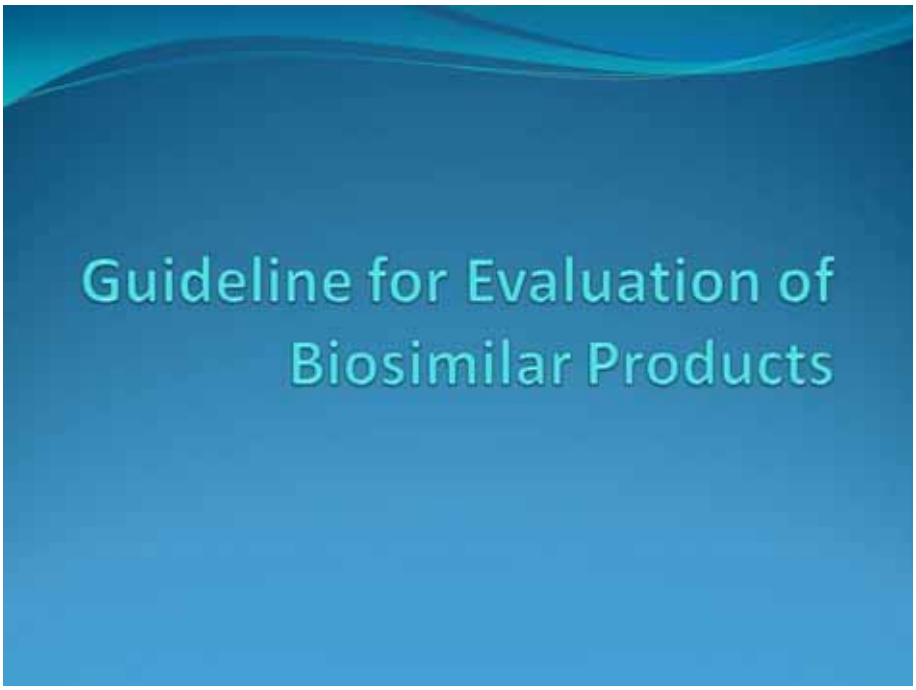
- Regulatory Pathway for Biosimilar products
- Korean Biosimilar Guideline
  - Scope & Definition
  - Principles of Biosimilar Approach
  - Reference Drug
  - Requirements for Quality studies
  - Requirements for Non-clinical studies
  - Requirements for Clinical studies
- Conclusion

Regulatory Pathway for Biosimilar

- **Existing Regulatory Framework - NOT a best fit to approve biosimilar products**
  - r-DNA products of which host cell or vector system or acquisition of DNA are different from that of the products already approved in Korea
- **Regulation for Review and Approval of Biologics**
  - New Drug Application
  - non-New Drug Application
    - New dosage form/ indication/ route of administration, Variation
    - Biosimilar Products (amended, July 2009)
- **Guideline**
  - Guideline for Evaluation of Biosimilar Products (July 2009)

Regulatory perspective for Biosimilar

- Existing generic definition is not appropriate for biosimilar
- Regulatory decision making regarding the biosimilar product shall be based on science and regulatory principles existing within the Korean Pharmaceutical Affairs Act and Regulations
- Approval of the biosimilar product shall be based on the demonstration of similarity to a suitable reference drug with comprehensive comparative data
- **Abridged Data Package for Application**
  - Quality ⇨ Full package + Comparabilty exercise
  - Non-clinical ⇨ Reduced + Comparabilty exercise
  - Clinical ⇨ Reduced + Comparabilty exercise



Scope & Definition

- **Name**
  - Biosimilar Product
- **Definition**
  - a biotechnological product that is proved to be comparable to an already approved reference products in quality, non-clinical and clinical evaluation
- **Scope**
  - well-characterized recombinant protein products

Principles of Biosimilar Approach

- Development of biosimilar products requires a complete independent product and process development
- Comprehensive characterization and comparison at quality level shall provide a basis for a reduction in the non-clinical and clinical data
- Development of biosimilar products involves a stepwise approach of comparability exercise beginning with quality studies and followed by non-clinical and clinical studies
- A final determination of similarity can be based on a combination of quality, non-clinical and clinical evaluation

Reference Drug

- The reference drug should be already approved on the basis of a complete dossier package in Korea
- The reference drug should be used throughout the studies supporting the quality, safety, and efficacy of the product
- The dosage form, strength, and route of administration of the biosimilar product should be the same as that of the reference product
- The biosimilar product should not be used as a reference drug

Requirements for Quality studies

- Full CMC and comparability exercise data between biosimilar product and reference product are required
  - Extensive side by side characterization
  - Physicochemical properties
  - Biological activity
  - Immunochemical properties
  - Impurities
- Analytical techniques should be the state of art to detect slight differences in quality attributes
- Comparability of the biosimilar product with the reference product should be addressed for product and active substance.

Requirements for Quality studies

- Stability Testing
  - Long term, real time, stability test are required
  - Accelerated degradation studies and stress-condition stability studies should be conducted to detect possible impurities
- Specification
  - Product-specific tests should be selected
  - Acceptance criteria should be established and justified based on the results of a number of representative lot analyses

Requirements for Non-clinical studies

- Comparative non-clinical studies should be designed to detect significant differences between the biosimilar product and the reference product
  - In vitro study
    - Receptor binding study, Cell proliferation assay
  - In vivo study
    - Biological/Pharmacodynamic studies relevant to the clinical application
    - Toxicity
      - At least one repeat dose toxicity study in a relevant species, including toxicokinetic study, Ab measurement
      - Local tolerance study

Requirements for Clinical studies

- Comparative clinical trials are required to demonstrate the similarity in efficacy and safety profiles between the biosimilar product and the reference product
- Clinical comparability exercise is a stepwise procedure that should begin with PK and PD studies followed by the pivotal clinical trials
  - Pharmacokinetic Studies/Pharmacodynamic Studies
  - Clinical Efficacy & Safety trials
  - Confirmatory PK/PD studies
    - Clinical comparability margins should be pre-specified and justified

Requirements for Clinical studies

- In some cases, confirmatory PK/PD studies may be sufficient
  - PK and PD properties of reference product are well characterized
  - At least one PD marker is an accepted surrogate maker for efficacy
  - Relationship between dose/exposure and response/efficacy of reference product is established

Requirements for Clinical studies

- Extrapolation to other indications of the reference drug may be possible if similar efficacy and safety has been demonstrated for a particular clinical indication

  if all of the following conditions should be satisfied :
  - Sensitive clinical model to detect potential differences are used
  - Clinically relevant mechanism of action and involved receptor are same in different indications
  - Safety and immunogenicity have been sufficiently characterized

Requirements for Clinical Safety

- Even if comparable efficacy is shown, there may be differences in safety
  - Pre-approval safety data from sufficient number of patients and study duration should be provided to compare the nature, severity, and frequency of adverse reactions
  - Pharmacovigilance plan should be presented
- Immunogenicity of a biosimilar product must always be investigated, separately in different indications
  - Long-term data are required due to unpredictibility of onset and incidence of immunogenicity
  - Neutralising potential of detected antibodies should be assayed

Conclusion

- Regulatory framework introduced in "Regulation for Review and Approval of Biologics " as amended
  - Biosimilar approach
    - a full dossier + comparability exercise
    - in principle, comparative quality, safety, and efficacy
  - Applicant may choose to file as stand-alone application
- Development of biosimilar products involves a stepwise approach of comparability exercise beginning with quality studies and followed by non-clinical and clinical studies
- Establishing a high degree of similarity in quality between the biosimilar product and the original product is a crucial key in the regulatory approval process

Annexes

I. Messages - Opening Remarks / Welcoming Address

Opening Remarks by the Director of the APEC Harmonization Center

Distinguished Guests, and Ladies and Gentlemen,

In this beautiful September with warm sunshine and fresh breeze, I extend my heartfelt welcome to all of you to the second APEC Harmonization Center Workshop on Biosimilars.

In particular, I would like to offer my sincere appreciation to distinguished participants who traveled long distances from abroad for this workshop.

On behalf of the APEC Harmonization Center, it's my great pleasure to declare the 2nd APEC Harmonization Center Workshop open today, following the great success of the previous inaugural Workshop of the AHC in last June.

Distinguished Participants, Biosimilars have drawn the global attention with their great potential as an emerging area in the healthcare field.

In this regards, I am very pleased that this second workshop will offer a timely opportunity to gain basic knowledge on biosimilars as well as the latest information of their global trends and current regulatory policies among APEC economies.

I hope that insightful presentations and networking opportunities that help participants to build clear idea and vision on the future of biosimilars.

Ladies and gentlemen from home and abroad,

I have no doubt that experts from Government, Industry, and Academia here today will not only provide their wisdom and insights on biosimilars but also make an effort to build cooperative networking for regulatory harmonization in this field.

I am also confident that this Workshop serves as an important milestone to address how we can cooperate to promote the healthcare economy among APEC region.

Ladies and gentlemen, now I would like to conclude my remarks with our promise that AHC is committed to provide valuable educational programs continuously.

I sincerely hope that the series of our commemorative workshops will strengthen our cooperation and promote sustainable development in the Asia-Pacific region with further prosperity.

September is the beginning of Autumn in Korea and thus it is regarded as the most fruitful season.

I hope all of you have a pleasant time during your stay in Seoul.

Thank you very much for your attention.

Seung Hee Kim
Director of the APEC Harmonization Center
President of NIFDS

Welcoming Address by Deputy Commissioner of KFDA

Distinguished government officials, industry leaders, academic professionals from home and abroad, and ladies and gentlemen,

I would like to extend my sincere welcome to all of you to APEC Harmonization Center Biosimilar Workshop in Seoul, the historic capital city of Korea.

With international attention being brought to biosimilars than ever, world's leading pharmaceutical companies are rushing to develop these promising, cost-saving products. The rapid advancing biosimilars market prompts many countries to feel the need to establish concrete strategies.

In this respect, today's AHC Biosimilar Workshop is timely and meaningful as it will serve as a forum for enthusiastic discussions and presentations to establish the vision and strategies for the biosimilars market.

Distinguished ladies and gentlemen,

In this globalized world, the importance of international exchanges cannot be overstated. At a time when coexistence and cooperation are urgently required, I believe the current global issues should be tackled through mutual assistance and international collaboration.

This Workshop's programs will offer clear ideas and visions to develop practical and reasonable regulatory framework by gathering expertise and wisdom of the professionals from government, industry, and academia in the Asia-pacific region.

And I am confident that today's landmark event will also help grow the biosimilars market in the region and will play a pivotal role in inducing collaboration to create new markets.

Lastly, your keen interest and support for this second Workshop following the successful previous one will be highly appreciated. I wish you a fruitful and memorable experience during your stay in Korea. Thank you very much.

Sang Yong Lee
Deputy Commissioner of KFDA

Welcoming Address by President of Korea Health Industry Development Institute

Honorable Deputy Commissioner Sang Yong Lee of Korea Food and Drug Administration, Dr. Anthony Ridgway, and distinguished 9 Speakers, and government officials from APEC member economies, and participants from industry and academic professionals from Korea and abroad,

I welcome you all to the APEC Harmonization Center Biosimilar Workshop in Seoul and would like to thank all distinguished speakers and guests here today.

Ladies and Gentlemen,

In this gathering, distinguished speakers and participants will engage in discussions of potential development and provide a vision of future on biosimilars as it is represented as one of the most evolving areas of product development in the bio-pharmaceutical industry.

I hope all the speakers and participants will put forth constructive advice for biosimilars in the Asia-pacific region as well as insightful ideas. Through this process, we will eventually support the current landscape regarding the regulatory approval of biosimilars and identify the regulatory approach to biosimlars in the Asia-pacific region.

As a president of KHIDI that organize the whole events of BIO KOREA 2009 including AHC Workshop, I will wholeheartedly support to provide the utmost efforts throughout the workshop for a pleasant and safe stay of all the participants.

Ladies and Gentlemen,

To conclude my remarks, I would like to extend my sincere appreciation once again to all of you for participating in the second workshop of APEC Harmonization Center.

I wish every one of you success and happiness. Thank you.

Bup Wan Kim
President of the Korea Health Industry Development Institute (KHIDI)

III. Articles on the AHC Biosimilar Workshop

APEC Harmonization Center for Life Sciences launches its second workshop on biosimilars

Seoul, 11 August 2009

Following the great success of the first workshop on multi-regional clinical trials, the APEC Harmonization Center (AHC) hosts its second workshop on biosimilars on the 16-18 of September, at COEX, Seoul, Korea. This Workshop will be held in alignment with BIO KOREA 2009, a major bio event in Asia, hosted by the Korea Food and Drug Administration (KFDA) and organized by the Korea Health Industry Development Institute (KHIDI).

As serious and in-depth debates go on biosimilars, therapeutic biological products that are similar to previously approved products, the AHC Biosimilar Workshop is expected to cover overall features of the subject at the right moment. The workshop will address the opportunities and challenges of biosimilars, introduce the details of existing EU guidelines and WHO draft guidelines up to date, and foresee what should be done for the future regulatory landscape on biosimilars. Especially, the workshop will focus on the obstacles that developing economies are facing in current situation and explore the strategies that we can effectively establish for global system. With the fruitful results of the workshop, the APEC Harmonization Center is expected to play a role of a forum that properly and objectively delivers the voices of both developing and developed economies to regulators, academia, and industry stakeholders within the APEC region.

The APEC Harmonization Center hosted its first workshop in last June, 2009 with wide participation of regulatory authorities, industry, and academia from 17 APEC economies. Following the AHC's inaugural ceremony on June 15, the workshop successfully raised awareness and understanding on the key issues on multi-regional clinical trials. AHC Workshop in series will provide the medium towards the sustained and long-term capacity building activities that would contribute to regional economic integration, further leading to the APEC's effective facilitation and liberalization of trade and investment.

About the APEC Harmonization Center:

The APEC Harmonization Center is established under the authority of the APEC Life Sciences Innovation Forum (LSIF) to provide a platform to address and resolve priority concerns of APEC member economies on regulatory harmonization. In 2008, APEC Ministers and Leaders specifically endorsed the AHC in the annual Ministerial Joint Statement:

> *"Recalling our commitment to promoting regulatory reform and harmonization, we welcomed and endorsed the establishment of the APEC LSIF Harmonization Centre in Seoul as a key step forward."*

For more information:

Please visit the APEC Harmonization Center website at www.apec-ahc.org or email to the AHC Secretariat at ahckorea@khidi.or.kr

AHC Workshop discusses issues on research and development related to biosimilars

Singapore, September 24, 2009: The delegates at the APEC Harmonization Center (AHC) Biosimilar Workshop, held on the 16-18 of September at COEX, Seoul, discussed major issues of Biosimilars research and development. This was the second workshop of the APEC Harmonization Center, attracting interests of 434 participants from government authorities, industries, and academia of 13 economies.

In the workshop, speakers from Asia, North America and Europe have delivered their presentations on the present and the future of biosimilars. Beginning with the basic background of biomedicine and biosimilars, each speaker shared his or her insights on the current status of biosimilars in their own economies, explaining the challenges and obstacles that may hinder economies' path toward the regulatory harmonization. The workshop invited many advisors for developing nations as lecturers, leading discussions after discussions on biosimilars. The main objective was to discuss challenges and opportunities of biosimilars in promoting APEC's ideology of regional economic integration, trade facilitation, and trade liberalization.

Both speakers and the participants raised the issue of interchangeability and that safety should be regarded as the major concern for further development of biosimilars. For each of the sessions, the participants and speakers engaged into active discussions, sharing their knowledge on global biosimilars and how harmonized regulations should and would respond to the biosimilars.

Source: BioSpectrum Bureau

III. Major Scenes of the workshop

- **Opening Ceremony**

	
Floor Announcement (*Kyung-Won Jang*)	Opening Remarks (*Seung Hee Kim*)
	
Welcoming Address (*Sang Yong Lee*)	Welcoming Address (*Bup Wan Kim*)

- **Session (The Opportunities and Challenges of Biological Medicines)**

<table>
<tr><td> 
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<tr><td>Moderator
(Chi Young Ahn)</td><td>Presentation (Jacques Turgeon)</td></tr>
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<tr><td>Presentation
(Kum Cheun Wong)</td><td>Panel Discussion</td></tr>
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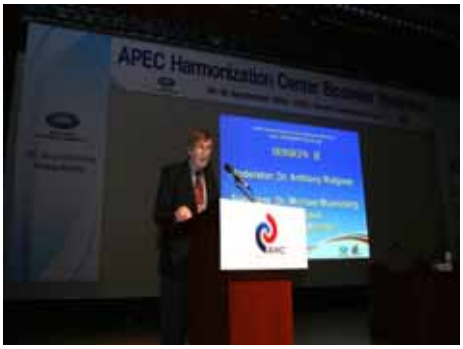
Panel Discussion	Audience

- **Session II (Regulatory Issues for Biosimilars)**

	
Moderator *(Anthony Ridgway)*	Presentation *(Michael Müenzberg)*
	

Presentation *(Eric Bigaud)*	Presentation *(Estelle Michael)*
	
Panel Discussion	Panel Discussion

- **Session □ (Regulatory Landscape on Biosimilars)**

	
Moderator *(Michael Müenzberg)*	Presentation *(Anthony Ridgway)*
	

Presentation *(Arpah Abas)*	Presentation *(Prapassorn Thanaphollert)*
	
Presentation *(Soo-Kyoung Suh)*	Panel Discussion

- **Plenary, Group Photo Session**

	
Plenary *(Feedback from Sessions)*	Group Photo

	
Group Photo *(Speakers)*	Audience
	
Audience	Audience

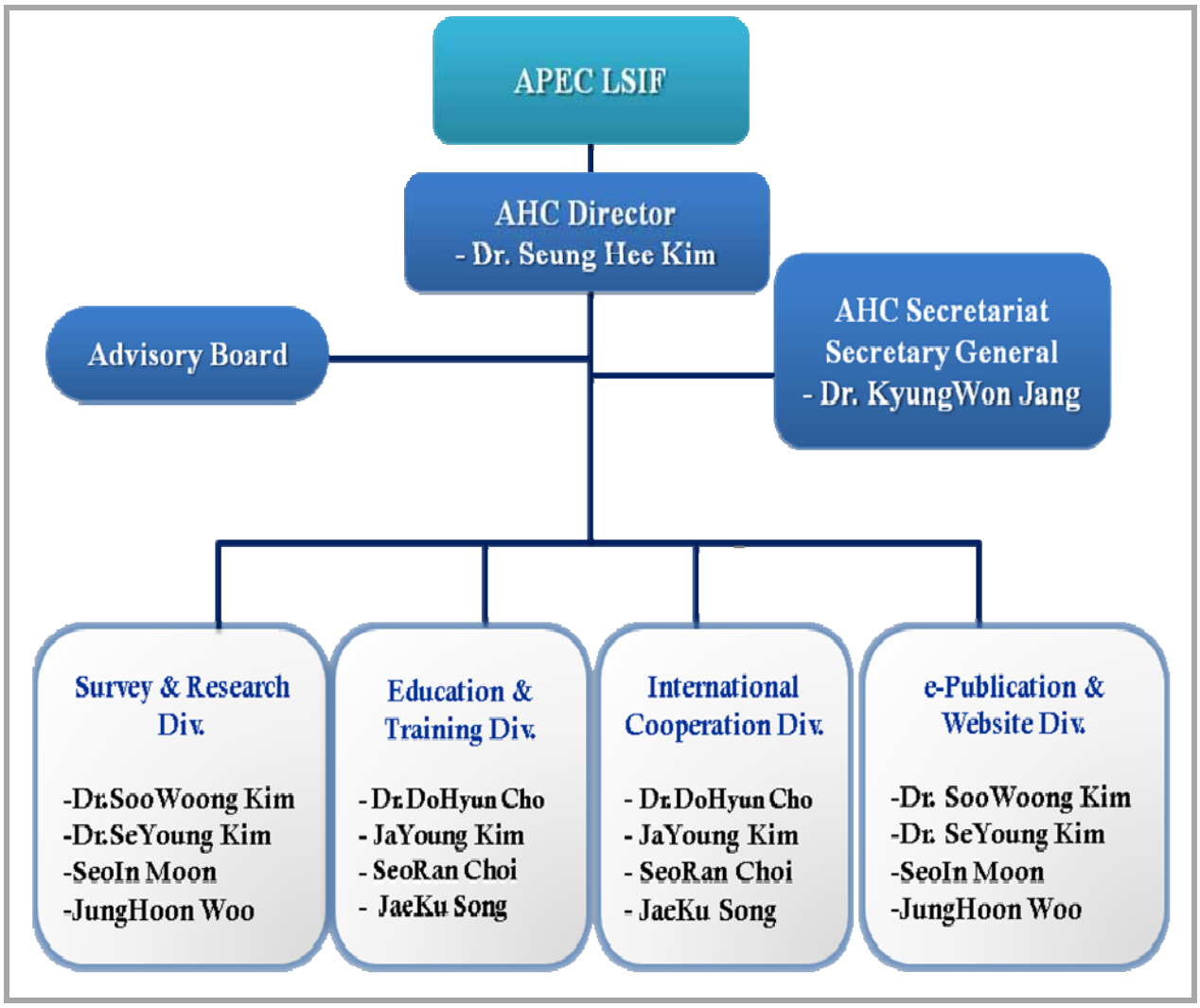
- **GMP Pharmaceutical Ware Visit (Celltrion) & Seoul Tour**

IV. APEC Harmonization Secretariat (KHIDI)

AHC Secretariat is provided by KHIDI (Korea Health Industry Development Institute).KHIDI is a non-profit government affiliated organization, working in cooperation with the government, industry, and academia in policy making, promoting industry, and supporting R&D. The secretariat is in charge of operating the AHC, directed by APEC LSIF and APEC LSIF RHSC, and with support of the AHC Advisory Board.

Organization Structure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Advisory Board
AHC Secretariat
Secretary General
- Dr. KyungWon Jang
Survey & Research Div.
-Dr.SooWoong Kim
-Dr.SeYoung Kim
-SeoIn Moon
-JungHoon Woo
Education & Training Div.
- Dr.DoHyun Cho
- JaYoung Kim
- SeoRan Choi
- JaeKu Song
International Cooperation Div.
- Dr.DoHyun Cho
- JaYoung Kim
- SeoRan Choi
- JaeKu Song
e-Publication & Website Div.
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-Dr. SeYoung Kim
-SeoIn Moon
-JungHoon Woo

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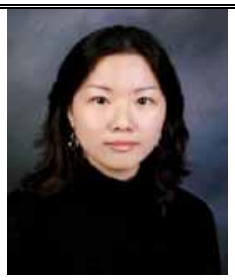
SeoRan (Rachel) Choi		srchoi@khidi.or.kr +82-2-2194-7323 • Support Functions on: - Division of Education & Training - Division of International Cooperation • AHC Communications, Administrative Affairs
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Members:
Front Row (Left to Right): SeoIn (Simon) Moon, SeoRan (Rachel) Choi, Dr. Kyung Won Jang, JaeKu (Jack) Song, Dr. GangYong Park
Second Row (Left to Right): Dr. SeYoung Kim, Dr. SooWoong Kim, HwaSeok (Brian) Suh, JaYoung Kim

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