



**Subsequent Entry Biologics:
Interchangeability/Substitutability, Liability Concerns**

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Laval, June 21, 2010.

Are Biosimilars Generics?

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Subsequent Entry Biologics

PRESENTATION OUTLINE

INTRODUCTION

- Expiration of patents
- Terminology used
- Definitions

FIRST BIOSIMILAR APPROVED IN REGULATED COUNTRIES

HOW ARE BIOSIMILARS DIFFERENT? : Literature review

RECORD OF BIOSIMILARS APPROVAL STATUS WORLDWIDE

SUBSEQUENT ENTRY BIOLOGICS

- Experience of Health Canada with SEB
- Health Canada Approach

SEB IS NOT GENERIC BIOLOGIC!

Flexibility of guidance ~ Controversy

Subsequent Entry Biologics

PRESENTATION Outline

LIABILITY RISK

- SEB is not a <<Generic biologic>>
- Liability sources

INTERCHANGEABILITY /SUBSTITUTABILITY

Definitions /Various Provincial Laws

LIABILITY / INTERCHANGEABILITY ACROSS CANADA

If a patient get injured, what are the legal consequences?

- Ontario, Quebec, British Columbia, Alberta

CONCEPT OF PROCESS IS THE PRODUCT

- Health Canada
- Manufacturer of Biosimilars
- Clinical Development

PHARMACOVIGILANCE AND TRACEABILITY

Requirement of Accumulating Data

CONCLUSION AND THANKS

Biosimilars, SEBs and Follow-on Biologics/Proteins

INTRODUCTION

Expiration of Patents

The history of biologics started with the smallpox vaccine (Edward Jenner's discovery in 1796) but the biotech industry is much younger. The first generation of bio products using recombinant technologies was launched in the 1980s - first recombinant insulin in 1982). Some patents therefore expired and others are nearing the expiration:

☛ In 2010, expiration of 12 patents (US).

☛ "Biosimilars are cheaper than branded biologics by 20%–25%. Based on this estimate, Biosimilars are expected to save approximately:

- \$71 billion in healthcare expenditure in the US between 2007–17

-\$3 billion per year in the EU.

(Source: The World Market for Biosimilars and the Potential for US Follow-on Biologics By: *Kalorama Information*).

☛ As the competition intensifies with the introduction of more biosimilars, prices are expected to decrease further...

(Source: *The Top 10 Biosimilar Players: Positioning, performance and SWOT analyses. 2009, Business Insights Ltd*).

Terminology used

These are terms used to identify officially the products approved following patent expiry of innovator biopharmaceutical products :

☛ **Biosimilars (Europe)**

☛ **Subsequent Entry Biologics (Canada)**

☛ **Follow-on Biologics, Follow-on Proteins, or 'Biogenerics'** applied for simple peptides. **(US)**.

Recognition of need for biologics competition as patents expire in different countries (Europe, Australia, Canada, Japan) and aggressive defense by some Brands, the biosimilars now represent one of the most rapidly evolving areas of pharmaceutical industry.

Among all the products, Biosimilar erythropoietins are expected to emerge as the best product with a market worth \$6.1 billion by 2014, assuming that biosimilars are priced at 70% of the innovator products and selected companies are based in India, Europe, the US, Canada and Israel.

(source: MarketsandMarkets Publisher., Biosimilars 2009 -2014).

Biosimilars, SEBs and Follow-on Biologics/Proteins

INTRODUCTION

Regulators are seeking a balance with respect to how much biosimilars can rely on data from the original drug in applying for their own approval, and with respect to how long to protect the reference drug's data.

- No approval pathway for Follow-on Biologics issued by US-FDA but US Healthcare reform legislation was approved by March 2010. The FDA has already approved several "generic" versions of biologic molecules.
 - India and China: no formal regulatory framework for biosimilars
 - No legal framework for biosimilars currently exists in Japan.
 - The Health Canada Guidance of Subsequent Entry Biologics (SEBs) is effective as of 5 March 2010.
 - The EU has been the initial target of most companies developing biosimilars for the regulated markets.
- The firms have been busy setting up subsidiaries or partnerships focused on biosimilars and linking up with smaller companies. Selected companies are based in India, Europe, the US, Canada and Israel

DEFINITIONS

Biosimilars, Subsequent Entry Biologics or follow-on proteins, are new versions of existing biopharmaceuticals whose patents have expired.

They are produced using the same core genetic material and are approved on the basis that they are equal to the reference product in terms of both safety and efficacy.

Unlike generics which are small molecules and produced by chemical synthesis, Biosimilars are large and complex molecules produced by living organisms, which are highly sensitive to manufacturing changes.

Biosimilars Approval Status Worldwide (2009)

FIRST BIOSIMILAR APPROVED IN FOLLOWING COUNTRIES

Europe: Omnitrope (Sandoz) was approved in late 2004.

In 2005 the European Medicines Agency (EMA) issued a statement declaring that biosimilars are not generic drugs and should therefore be subject to different protocols prior to marketing approval.

In some cases the large expenses involved have prompted drug companies to opt for listing of their product as a new drug rather than a biosimilar.

In addition to the usual requirements for generic drug trials, the EMA requires crossover trials against the innovator product, randomized clinical trials, safety monitoring and submission of a post marketing surveillance plan. Therefore, the cost savings from biosimilar products may not be as expected, and completely different of that seen with traditional generics.

Australia: Omnitrope (Sandoz) was approved in late 2004.

In the National Health Act Amendment (Pharmaceutical Benefits Scheme) Act 2007, a definition of the word 'biosimilars' was omitted. Consequently, the meaning is poorly understood. The registration of biosimilars in Australia is regulated by the Therapeutic Goods Administration (TGA), which determines whether a biosimilar is safe and effective. To evaluate biosimilars, the TGA has adopted the EMEA guidelines.

United States: The US-FDA approved GlucaGen (recombinant Glucagon) of Novo Nordisk in 1998, and the r-HGH, Tev-tropin (Teva Ferring) and Omnitrope (Sandoz) in 2005.

However, there has been much lobbying in the US to have an 'abbreviated' listing process similar to the European model and despite continued lobbying, the FDA is yet to release its own formalised guidelines.

Canada: On April 20, 2009, Health Canada issued a Notice of Compliance to Sandoz Canada Inc. for the drug product Omnitrope.

How are Biosimilars different?

Due to the complicated nature of biologic drugs as compared to traditional small-molecule medicines, even the smallest variation in the manufacturing process can produce toxic results.

	Small molecule generics	Biosimilars
Product characteristics	Small molecules Often very stable Mostly without a device	Large, complex molecules Stability requires special handling Device is often a key differentiator
Production	Produced by chemical synthesis	Produced in living organisms Highly sensitive to manufacturing changes Often comparatively high costs
Development	Very limited clinical trials (often only Phase I PK/PD studies)	Significant R&D (i.e. cell lines) Extensive clinical trials, including Phase I and Phase III studies
Regulation	Abbreviated registration procedures in Europe and US "substitutability"	Regulatory pathway now defined by EMA "Comparability"
Marketing	No or limited detailing to physicians Key role of wholesalers and payers Market substitution in pharmacies High price discounts	No pathway yet in US Detailing to (specialist) physicians required Pharmacists may not substitute Price discounts smaller; price sensitivity is product specific

Source: Sandoz website.

How are Biosimilars different?

LITERATURE REVIEW

- Unlike small molecules produced by chemical synthesis, biologics are made from living cells.
- They are complex and impossible to characterize fully. They typically consist of amino acids to form a protein that may exist in many forms due to its capacity to 'fold' in on itself. It is sensitive to small change in manufacturing, formulation, change of ingredients, etc.
- As pharmaceutical companies do not disclose the information about how they manufacture biological drugs it is almost impossible for the follow on manufacturer to have access to the origin molecular clone and original cell bank, nor to the exact fermentation and purification process. However it is proposed that a difference in critical production steps is the main contributor to variations, nearly undetectable differences in impurities are known to have serious modification to a biologic.
- All biologic medicines have the potential for immunogenicity. Therefore even small changes in how the biologic is made could have a significant impact on its safety and/or efficacy. The example of Ortho Biotech with Eprex (epoetin alfa), in 1998 illustrates it very well. It took about 5 years at a cost of more than \$100 million, before the company could identify that organic compounds (leachates) formed after a stabilizer was added to the formulation, produce an immune reaction in some patients who received the injection and developed a rare anemia.
- Biosimilars cannot be brought to the market using the same procedure applied to generics; and any policies about their development should consider their complexity.

Record of Biosimilars Approval Status Worldwide

Country	Drug class	Drug name	Company	Status	Date
<p>a.: Although no formal pathway exists to approve generic versions of more complex recombinant biologics, the FDA has approved generic versions of simpler biologics via 505(b)(2) of the Food, Drug, and Cosmetic Act. Source: Data collected by Robert Blakie, ERA Consulting, London.</p>					
US ^a	Recombinant glucagon	GlucaGen	Novo Nordisk	Approved	June 25, 1998
US ^a	Recombinant human growth hormone (rhGH)	Tev-tropin	Teva/Ferring	Approved	2005
Australia	rhGH	Omnitrope	Sandoz	Approved	September 2004
US ^a	Hyaluronidase	Amphadase	Amphastar	Approved	October 2004
US ^a	rhGH	Omnitrope	Sandoz	Approved	May 2005
US ^a	Recombinant salmon calcitonin	Fortical Nasal Spray	Upsher-Smith Laboratories, Inc./UNIGENE	Approved	October 2005
US ^a	Hyaluronidase	Hydase	PrimaPharm	Approved	November 2005
US ^a	Recombinant human hyaluronidase	Hylenex	Baxter	Approved	December 2005
EU	rhGH	Omnitrope	Sandoz	Approved	April 12, 2006
EU	rhGH	Valtropin	BioPartners	Approved	April 24, 2006
EU	Interferon alpha	Alpheon	BioPartners	Refusal	June 28, 2006
EU	Recombinant human EPO (rhEPO)	Binocrit (epoetin alfa)	Sandoz	Approved	August 28, 2007
EU	rhEPO	Hexal (epoetin alfa)	Hexal	Approved	August 28, 2007

Table From the article: Who guidelines presage US biosimilars legislation?, John Hodgson, Nature Biotechnology 27, 963 – 965(2009)

Record of Biosimilars Approval Status Worldwide

Country	Drug class	Drug name	Company	Status	Date
EU	rhEPO	Abseamed	Medice	Approved	August 28, 2007
EU	rhEPO	Silapo	Stada	Approved	December 8, 2007
EU	rhEPO	Retacrit	Hospira	Approved	December 18, 2007
EU	rhEPO	Insulin Human Rapid Marvel	Marvel Life Sciences	Application withdrawn	January 24, 2008
EU	Insulin	Insulin Human Long Marvel	Marvel Life Sciences	Application withdrawn	January 24, 2008
EU	Insulin	Insulin Human 30/70 Mix Marvel	Marvel Life Sciences	Application withdrawn	January 24, 2008
EU	Recombinant human granulocyte colony stimulating factor (G-CSF)	Tevagrastim	Teva	Approved	Sept. 15, 2008
EU	G-CSF	Ratiograstim	Ratiopharm	Approved	Sept. 15, 2008
EU	G-CSF	Biograstim	CT Arzneimittel	Approved	Sept. 15, 2008
Japan	EPO	EPO	Nippon Chemical Research	Application pending	Submitted Nov. 2008
EU	G-CSF	Zarzio	Sandoz	Approved	February 6, 2009
EU	G-CSF	Filgrastim Hexal	Hexal	Approved	February 6, 2009
EU	Interferon beta-1a	Biferonex	BioPartners	Withdrawal	May 29, 2009
Japan	rhGH	Somatropin BS	Sandoz	Approved	June 2009
Canada	rhGH	Omnitrope	Sandoz	Approved	April 20, 2009

Subsequent Entry Biologics

EXPERIENCE OF HEALTH CANADA WITH SEB

“ Health Canada has been with SEBs since at least 1999 ” . Everyone felt initially comfortable with the approach of similarity but then suddenly confronted with monoclonal antibodies, issues of interchangeability, reimbursement and market access.

As there are different frameworks and pathways considered for Biosimilars, it is common to refer to the European model, as it adopts flexibility by product class. A commitment was made to look on an individual basis at additional product classes.

It means that Health Canada is aware of the difficulties that a sponsor faces. The manufacture of biosimilars is a labour-intensive process, with different challenging factors: the size and the complexity of the nature of product, heterogeneity factors, required agents that are usually not an issue in evaluation of generics, the limitations to current methods for product characterization and, beyond that, the immunogenicity.

Outcome:

- The key question of interchangeability comes up very early. Eventually when SEBs are approved there will be issues of post-marketing surveillance to address.
- Demonstration of comparability = demonstrating similarity among products.
- Comparability is critical, the major concern is not the efficacy but the safety.
- The immunogenicity concern. The originator biologic drug (reference) should have significant safety and efficacy data accumulated and available.
- The choice of appropriate reference product.
- In the final guidance, Health Canada aligned in its thinking with the EMA, currently considered as the world leader with respect to the SEB approach, Health Canada has retained the flexibility.

Subsequent Entry Biologics

HEALTH CANADA APPROACH

- SEBs are evaluated against a known biologic already used in Canada. The origin biologic product should be marketed in Canada, but a sponsor may be permitted to use a non-Canadian reference for comparative studies.
- Companies are required to use clinical trials to demonstrate similarity to a reference biologic in terms of safety, efficacy and quality.
- After the approval, the SEB will be regarded as a novel drug and will therefore have the potential to be subjected to pricing restrictions by Health Canada's Patented Medicines Prices Review Board (PMPRB) unit.
- The Canadian and non-Canadian versions of the reference must be marketed by the same innovator company in the same dosage form, and the non-Canadian reference product must be from a jurisdiction with an established relationship with Health Canada.
- SEB manufacturers may apply for one or more of the indications for use granted to the reference biologic drug, but in some cases, additional indications may be granted to the SEB in the absence of clinical data if extrapolation to other uses is justified and persuasive.
- In designing clinical trials, manufacturers should note that equivalence trials are generally preferred but if trials show superior efficacy to a reference, or an increase in adverse reactions, the product would not be considered as an SEB.
- Demonstration of non-inferiority between a SEB and its reference would not necessarily permit extrapolation of approval for all indications, especially if the indications include different dosages from those tested in the trial.

Health Canada retained the flexibility of the European model of approval and the concept “the process is the product”.

SEB is not a generic biologic

FLEXIBILITY OF GUIDANCE AND CONTROVERSY_

- The Canadian guidance seems to have 2 fundamentally incompatible statements:
 - (i) authorization of SEBs is not a declaration of pharmaceutical or therapeutic equivalence (but it is considering them as such!...)
 - (ii) accepts a reduced data package for SEB based on "...demonstrated similarity between the SEB and the suitable reference drug".

Health Canada is well aware that SEBs are not really "equivalent". At the February 17, 2009 PMDA Symposium on Biologics, Health Canada said that "interchangeability remains a provincial decision, which puts the burden on CADTH and the provinces.

- CADTH has accepted that SEBs are suitable for consideration for listing on provincial formularies:
- *CDR Update* — Issue 59, released June 30, 2009, announced that submissions for drugs reviewed by Health Canada as subsequent entry biologics (SEBs) should be filed with the Common Drug Review (CDR). Based on its experience reviewing the first SEB submission, CDR has initiated a pilot project. The purpose of the pilot process is to determine the CDR requirements for the SEB submissions; establish the evaluative framework for conducting the CDR review; and through interactions with Health Canada, gain an increased understanding of Health Canada's approach to assessing SEBs.
 - *CDR Update*—Issue 62: New Pilot Project: Subsequent Entry Biologics — Effective Immediately.

CADTH (The Canadian Agency for Drugs and Technologies in Health) is an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision makers).

CDR (The Common Drug Review) is one of the committees of CADTH and conducts objective, rigorous reviews of the clinical and cost effectiveness of drugs, and provides formulary listing recommendations to the publicly funded drug plans in Canada (except Québec, the equivalent of CDR is Comité du Médicament).

Liability Risk

SEB IS NOT A “GENERIC BIOLOGIC”

It has been established from a long time that biologics are different, and it is widely and worldwide accepted that a Biosimilar is not an identical copy of the origin product it aim to take place of (interchangeability, substitutability or replacement).

To date, there is no indication as to whether provincial authorities will consider SEBs as suitable for interchangeable status. In fact:

- Unlike ‘small molecule’ drugs, where bioequivalence is sufficient to show that the active ingredients are identical, with biologicals even minor differences in the “process” can lead to profound differences in clinical activity and side effect profile.
- These differences may not become apparent until the drug is in widespread use, which almost never happens with generics that demonstrated their bioequivalence.
- Accordingly, all parties (doctors, druggists, provincial drug plans and regulator) are concerned.
- The situation concerning liability is highly dependent on the specifics of provincial law. Each province has different definitions of “interchangeability”; and different levels of protection for dispensing an interchangeable product. It means that each province must be specifically examined for liability concerns in respect of SEBs.

Liability Sources:

- Physicians: Negligence in prescribing a SEB when it is reasonably foreseeable that such a product carries greater risks than an existing alternative drug
- Pharmacists: Negligence in interchanging an ‘unproven’ SEB for a safer existing drug.
- Provincial Drug Plans: Negligence in declaring a SEB “interchangeable” with the ‘innovative’ drug, thus encouraging acceptance of the (presumably) less expensive but less well-characterized drug.
- Health Canada: approving the SEB for sale in Canada that is not equivalent to the reference biologic product.

Interchangeability / substitutability

DEFINITIONS / VARIOUS PROVINCIAL LAWS

The terms of interchangeability and substitutability refer to the ability of a pharmacist to provide a drug other than the 'original' drug prescribed to a patient (usually because the 'substituted' drug is cheaper).

The terms are defined under various provincial laws.

- "Interchangeability" because of lower cost generic version drug (a 'financial' decision).
- "Therapeutic substitution" - substituting a different drug as considered equivalent to a prescribed drug for treating the same condition (a medical decision).

- The EMA has a categorical view of interchangeability: it is not possible to guarantee that two biological products are the same. There are many member countries in the EU forbidding substitution.

The issue with substitution and interchangeability goes beyond concerns about whether these products are the same. It goes back to the basic issue in pharmacovigilance and traceability of AEs which one is related to SEB. For example, it has been recommended that marketed erythropoietins be prescribed by brand name in order to support traceability.

- The FDA is quite clear that there is no basis on which to conclude that two compounds of a similar biologic nature can be considered identical.

- In the Health Canada Guidance for SEB, March 10, 2010, there is safety concerns:

- Approval is not a declaration of pharmaceutical or therapeutic equivalence.
- Clinical trials required as part of an approval pathway, while less costly than that for an innovator product, it is not an abbreviated NDS.
- A regimen of post-marketing requirements such as periodic safety update reports.

Liability / Interchangeability across Canada

If a patient get injured, what are the legal consequences?

In Ontario

☛ The “interchangeability” is defined in the *Drug Interchangeability and Dispensing Fee Act* as:
“interchangeable product” means a drug or combination of drugs in a particular dosage form and strength identified by a specific product name or manufacturer and designated as interchangeable with one or more other such products’. A condition of “interchangeability” is that the drugs must be bioequivalent.

☛ “Therapeutic substitution” means the substitution of a drug that contains chemically different active ingredients that are considered to be therapeutically equivalent, without authorization from a person authorized to prescribe drugs within the scope of his/her health profession.

It is unclear whether or not an SEB may be declared “interchangeable” under Ontario legislation. Assuming it is, all parties are protected from liability for interchanging such a product by legislation. Section 8 of the *Drug Interchangeability and Dispensing Fee Act* states as follows:

☛ “8. If an interchangeable product is dispensed in accordance with this Act, no action or other proceeding lies or shall be instituted against the person who issued the prescription, the dispenser or any person who is responsible in law for the acts of either of them on the grounds that an interchangeable product other than the one prescribed was dispensed.”

☛ This section has not yet been judicially challenged. It is unclear whether it could withstand a *Charter* challenge (as in *Chaoulli report in Quebec*, infringement s.7 rights). The right to sue would not be subject to the same degree of protection as for generics

Liability / Interchangeability across Canada

In Quebec

No definition or standard for “interchangeability”.

- Under the “15 year rule” the full cost of an innovative product is reimbursed for 15 years; thereafter, only the cost of the lowest cost alternative is reimbursed.
- Pharmacists may provide a medicine with the same generic name (unless the physician indicates otherwise) under s. 21 of the Quebec *Pharmacy Act*. In general, this does not apply to SEBs.
- There are no provisions insulating the pharmacist from liability for the ‘interchange. In June 2010, “Conseil du médicament” listed Omnitrope as medication of exception. The CM said: En conclusion, d’après les données d’efficacité obtenues chez des enfants atteints de déficit en hormone de croissance, les avantages du traitement avec OmnitropeMC sont les mêmes que ceux du produit de référence retenu. Par ailleurs, les études ont montré qu’OmnitropeMC est bien toléré et qu’il présente un profil d’innocuité acceptable. C’est pourquoi le Conseil reconnaît la valeur thérapeutique d’OmnitropeMC, au même titre que les autres somatotrophines inscrites sur les listes, pour le traitement du déficit en hormone de croissance chez l’enfant. Par ailleurs, il juge que son utilisation pour les indications actuellement reconnues s’applique aussi.

In British Columbia

- British Columbia permits pharmacists to “adapt” a prescription by policy approved by the College of Pharmacists (March 2009). The Policy states: “A pharmacist may dispense a drug contrary to the terms of a prescription (adapt a prescription) if the action is intended to optimize the therapeutic outcome of treatment with the prescribed drug and meets all of the following elements of a protocol to adapt a prescription ...”
- Permits “therapeutic” substitution.
- No statutory protections: Pharmacist remains liable for “adaptation”.

In Alberta

- In Alberta, “interchangeability” is simply a designation of purposes of determining reimbursement under the provincial drug plan. Like British Columbia, Alberta has by policy authorized pharmacists to “adapt” prescriptions and described by the College as follows: “prescription modification—modifying a prescription written by another prescriber to alter dosage, formulation, regimen or duration of the prescribed drug, or provide a therapeutic alternative to improve drug therapy or provide continuity of therapy.”
- No statutory protections: Pharmacist remains liable for “adaptation”.

Concept of Process is the Product

Health Canada

First Pair: [(specific process of approval ↔ specific product)]

It was made by Regulatory agencies: case-by-case evaluation.

Manufacturer of Biosimilars

Second Pair : [(specific manufacturing facility ↔ specific product)]

Based on the fact that it is unlikely, if not impossible, that 2 biological products produced by different manufactures would have the same immunogenicity profile, sponsors are considering the concept of the process is the product for manufacturing the product (when outsourcing).

Its makes no sense to assume that some in vitro tests, and testing SEB on a small size of population, one can have sufficient data of toxicity and figure out about the risk when the product will be used in large population.

Clinical Development

Third Pair : [(clinical facility ↔ product nature)]

Being a decade with BA/BE Clinical Research Organizations in Europe and then in Canada, followed by 6 years in Phase 1 CPU clinic, it let me to understand that clinical development of new products require different skills and approach when comparing to generics.

It is understood that the reason of developing generic products is that they are cheaper, because their development is much less. It happens, that some BA/BE studies are complex and require specific design, that most of the time is covered by the guidance, however when it comes to innovator product, it always deserves specific plan of clinical development, studies adapted to the medication profile and the target population. The expertise and the experience enable to gauge how trial protocols manifest in real life, it shorts the delays and the cost consequently and substantially.

Pharmacovigilance (Post Marketing Surveillance)

REQUIREMENT OF ACCUMULATING DATA

If for some small molecules the variability is problematic, SEBs adds another level of complexity. The immunogenicity is the principal concern and in the first instance we think about Antibodies that cause or enhance hypersensitivity.

The cost of SEBs development is not that far from the originator biologic product, and because of the challenges that a sponsor faces, and beyond, the immunogenicity, we must be cautious about introducing a SEBs aimed to replace existing validated therapies.

When a decision is made to produce a SEB, the 2nd and the 3rd pairs apply. In fact, Biosimilar development requires a highly specialized, cross-disciplinary team. It is critical for potential biosimilar manufacturers to access a depth of medical, clinical, and regulatory expertise to help support and guide their decision-making. When not sufficient safety data are available, post surveillance studies should take place and good risk management programs to ensure that SEBs are equivalent or even better.

Given the complexity of serious adverse events, the liability issue that Health Professionals and Regulators may face when a patient get injured with a SEB, permission for substitution of SEBs might be not a good idea.

Biosimilars are not Generics?

CONCLUSION

- Simple and flexible regulations allow the rapid introduction of regulatory framework.
- A well-planned program development is critical for success (Chemistry manufacturing, non-clinical and clinical).
- Manufacturers must be aware of batch-to-batch variability in the reference product.
- Comparative trials need to be performed in a sensitive population.
- Any differences in impurities between the biosimilar and the reference product must be explained and clinically justified.
- A safety database is necessary, but the size can be variable depending on the indication and the type of biologic.
- Despite the progress that has been made in the EU in setting the groundwork for biosimilar development, despite Health Canada Guidance is flexible, evolving well and le tspace to the scientific judgment, many questions remain:
 - Which products will qualify as biosimilars,
 - What degree of similarity will be required biosimilars.
 - How will the legislation work?

The challenge for Regulators and the biopharmaceutical industry in this constantly changing environment is to maintain the approach demonstrated by the EU and resolve the issues in a way that keeps the science of biosimilars moving forward for the benefit of patients.

THANK YOU