

# CARE



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## CONGRESS ON BIOSIMILARS

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### CONGRESS REPORT

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CARE CONGRESS ON BIOSIMILARS - TORONTO, CANADA - JANUARY 13, 2017

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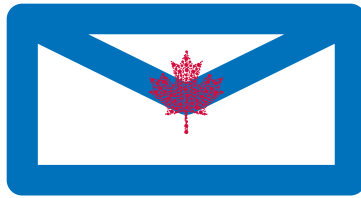
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# CARE CONGRESS ON BIOSIMILARS

## JANUARY 13<sup>TH</sup>, 2017, TORONTO, ONTARIO

### TORONTO MARRIOTT DOWNTOWN EATON CENTRE HOTEL

## OVERVIEW

CARE (Community, Academic, Research, Education) believes in: optimization of current therapy, innovation with new treatments, and competition to help deliver savings and accessibility; considered in ways that deliver better healthcare solutions to Canadians.

On January 13<sup>th</sup>, 2017, a pan-Canadian group of more than 100 stakeholders along the patient pathway gathered in Toronto for a discussion about how biosimilars are being used appropriately in the Canadian landscape. Among these thought leaders were the CEOs of advocacy groups, leading allied health care professionals and organizations, legal representatives, and leading specialists from across Canada.

This report summarizes presentations given by a variety of stakeholders. The Congress was chaired by Dr. John Kuruvilla from Princess Margaret Cancer Centre, and Dr. John Marshall from McMaster University. Dr. Hartmut Grasmann from SickKids Hospital facilitated the meeting.

The message from the event was clear: stakeholders need to address what the patient wants/needs and health care professionals, payers, and government need to work together to ensure high quality of care and patient satisfaction/safety is being delivered, in regards to the use of biosimilars.

## MEETING CHAIRS

John Kuruvilla, MD  
Princess Margaret Cancer Centre

John Marshall, MD  
McMaster University

## MEETING FACILITATOR

Hartmut Grasmann, MD  
SickKids Hospital

*The content that follows is a summary of each of the presentations made at the CARE Congress, followed by additional discussion points from the panelists. Images are drawn from the presentation of each speaker. Presentations can be found at [www.CAREeducation.ca](http://www.CAREeducation.ca).*

Presented by:

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## CARE FACULTY PANELISTS

NAME	SPECIALTY	CENTRE
Vipul Jairath, MD	Gastroenterology	Western University
John Marshall, MD*	Gastroenterology	McMaster University
Anthony Otley, MD	Gastroenterology	Dalhousie University
Thomas Walters, MD	Gastroenterology	The Hospital for Sick Children
Ted Xenodemetropoulos, MD	Gastroenterology	McMaster University
Stephen Chia, MD	Oncology	BC Cancer Agency
Rob El-Maraghi, MD	Oncology	Royal Victoria Regional Health Centre
Denis Soulières, MD	Oncology/Hematology	Centre hospitalier de l'Université de Montréal
Peter Anglin, MD	Hematology	Southlake Regional Health Centre
John Kuruvilla, MD*	Hematology	Princess Margaret Cancer Centre
Darrell White, MD	Hematology	Dalhousie University
Philip Baer, MD	Rheumatology	Ontario Medical Association
Vinod Chandran, MD	Rheumatology	Toronto Western Hospital
Denis Choquette, MD	Rheumatology	Centre hospitalier de l'Université de Montréal
Hartmut Grasmann, MD**	Respirology	The Hospital for Sick Children

\*Chair

\*\*Facilitator

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Vipul Jairath, MD	Gastroenterology	Western University
Jing (Jenny) Ning, MD	Government	Health Canada
Sherry O'Quinn, B.Sc. (Pharm)	Public Payer	PDCI Market Access
Laureen Rance, PharmD & Kim MacFarlane	Private Payer	Manulife
Eric Thomson, BA, MA	Advocacy	Crohn's & Colitis Canada
Elizabeth Lye, B.Sc.	Advocacy	Lymphoma Canada
Martine Elias, B.Sc., M.Sc.	Advocacy	Myeloma Canada
Usha Chauhan, NP	Gastroenterology	McMaster University
Diana Incekol, Advanced Practice Nurse Educator	Oncology	University Health Network
Ruth Turner, RN	Hematology	Princess Margaret Cancer Centre
Scott Edwards, PharmD	Pharmacy	Dr H Bliss Murphy Cancer Centre
Eileen McMahon	Legal	Torys Law Firm
Durhane Wong-Reiger, PhD	Patients/Ethics	Consumer AdvoCare Network
Paul Grootendorst, PhD	Economist	University of Toronto
Candice Munroe, PharmD	Private Payer	ClaimSecure

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# SCIENTIFIC REVIEW OF BIOSIMILARS

ROB LAISTER, PHD IN BIO-CHEMISTRY, TRANSLATIONAL MEDICINE - PRINCESS MARGARET CANCER CENTRE

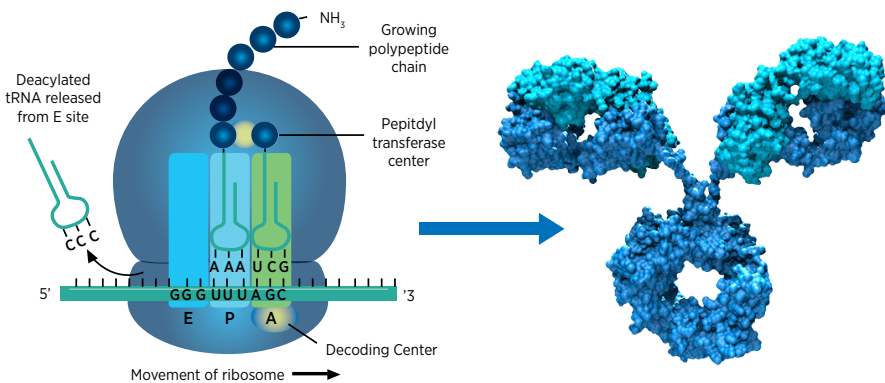
Small molecule pharmaceuticals are inherently different from protein based drugs on a number of levels. The focus of this presentation was aimed at differentiating small molecules from biologics, exploring the complexity of biologics and identifying how manufacturing processes influence the final product that is administered to patients. Immunogenicity was also discussed as an important consideration for biologics and biosimilars.

## Differences Between Small Molecules and Biologics

In the 1970s before the molecular biology revolution, organic chemists were dominating the pharmaceutical product development. They synthesized molecules of interest via chemical synthesis *in vitro* and potentially via different synthetic routes. Importantly, irrespective of the synthetic route used, the exact same molecule was obtained (i.e. same chemical formula, molecular weight and stereochemistry). Therefore, the development goal was to faithfully reproduce small organic molecules. Consequently, all generic small molecules, irrespective of their source, have identical chemical formulas, molecular structures and stereochemistry.

The synthesis of biologics uses a different route entirely. A host organisms' cellular machinery translates RNA from a gene blueprint into a protein. Here, the ribosome is used as the manufacturer, taking a piece of RNA and integrating amino acids in a desired sequence, to obtain a specific protein (Figure 1).

Figure 1: Protein Synthesis via a Ribosome to Produce Identical Copies of a Folded Polypeptide

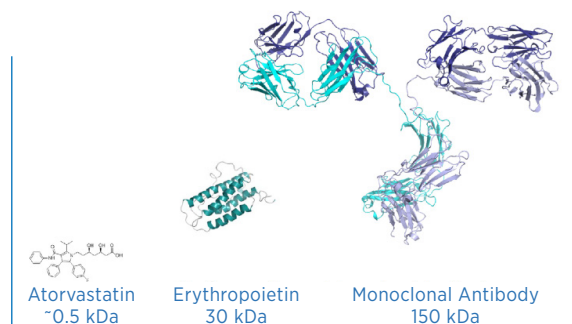


Irrespective of the host organism, the final protein product may be subject to numerous post-translational modifications that can alter the chemistry of the molecule. These modifications can have several important implications from a clinical perspective.

## Biologics and Their Inherent Complexity

Biologics are far more complex than small molecules. In terms of size, what is considered a small to a medium size protein, such as erythropoietin (30 kDa), or a larger protein, such as a monoclonal antibody (up to 150 kDa), are significantly larger than an organic small molecule, such as atorvastatin (~0.5 kDa; Figure 2).

Figure 2: Mass, Heterogeneity, Potential for Modification, Molecular Complexity



“BIOLOGICS ARE FAR MORE COMPLEX  
THAN SMALL MOLECULES.”

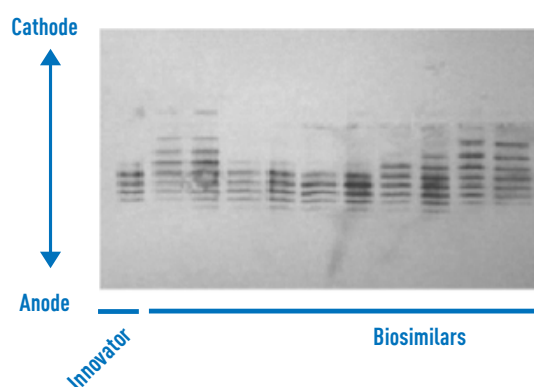
The mass of biologics increases the number of potential sites for chemical modification following translation (e.g., glycosylation, oxidation, proteolysis, or acetylation/methylation). These modifications can affect both innovator and biosimilar molecules. Such an increase in complexity and heterogeneity will influence the final product and make it more difficult to accurately characterize the active pharmaceutical mixture.

It is important to realize that:

1. Identical genes will not necessarily result in the same protein product.
2. Different protein products may have different properties in terms of efficacy and immunogenicity.

To illustrate this, an innovator biologic (Eprex [erythropoietin]) and a panel of biosimilars were run through an isoelectric focusing gel (Figure 3).<sup>1</sup> An electric field was applied to the gel, and depending on the charge distribution ratio of the molecules, the molecules migrated towards the cathode or the anode (where the center of the gel was more neutral).

Figure 3: Isoelectric Focusing Gel/Western Blot Showing Differences in Heterogeneity Between the Innovator Biologic and a Panel of Biosimilars



The innovator, shown on the far left, has multiple bands (5), showing its heterogeneity. Importantly, this indicates that even innovator biologics occur as multiple species. When looking at the panel of biosimilars, additional bands are showing, with each band representing a different molecular species. Notably, the biosimilars are different from the innovator compound, and furthermore, the biosimilars are different from each other. Tested in an *in vivo* assay, four of these biosimilars showed higher activity and two of them had lower activity compared to specifications of the reference compound (Eprex).

Glycosylation – a post-translational modification whereby branched carbohydrates (sugar molecules) are attached to the surface of a protein – is another aspect of the complexity of biologics. When proteins come off the ribosome, there are a number of different enzymes that achieve modifications (i.e. adding complex branched/antennary sugar molecules onto an asparagine residue of the target protein). These sugar modifications on their own are even larger and more complex than most small molecule synthetic drugs.

In addition, there are many different sites where biologics can be modified (e.g., on a monoclonal antibody: pyro-glutamate, deamidation, methionine oxidation, glycation, C-term lysine processing). For instance, on a monoclonal antibody, over 147,000 potential molecules can be obtained from these modifications. Though not all of these modifications will necessarily occur, this certainly speaks to the capacity for multiple species, a phenomenon that does not occur with small molecules.

## How Manufacturing Processes Influence Biologics

Beyond the production of these biologics, manufacturing processes can influence the differences between these molecules. The details of the manufacturing process are proprietary and could affect the final product. These include: the choice of host organism, the type of media, the temperature, and the purification process. There are several types of host organisms (Table 1).

Table 1. Examples of Host Organisms

Host Organism	Characteristics
<i>E. coli</i>	High yields, easy to grow, no PTMs, no folding machinery. Contaminating <i>E. coli</i> proteins or metabolites can be immunogenic
Mammalian cells	Gold standard, folding+glycosylation, high protein production, construction of strains can be difficult, IP issues, media expensive
Yeast	Cheap, existing vectors, PTMs, cell disruption to harvest proteins can be difficult
Insect cells	Eukaryotic, PTMs, low growth rate, difficult to scale up, currently more suited to laboratory research vs. industrial applications
Microalgae	Can be grown on a very large scale, no regulatory experience, currently better suited to non-pharma biologic production
Duckweed	Grown cheaply, economical, little to no regulatory experience



How might these modifications affect the efficacy of biologic pharmaceuticals? The Fc domain (e.g. the tail region of an antibody that interacts with cell surface receptors - Fc receptors) can be affected by the glycosylation by modifying the affinity for the Fc receptors, and that directly affects efficacy. Furthermore, different organisms will have different sugar modifications on the Fc region, which will impact their binding capacity, and as a consequence the biologics' efficacy.

## Immunogenicity

Perhaps the most important consideration in terms of differences between innovator biologics and biosimilars is related to immunogenicity. When using molecular techniques to characterize these molecules, such as mass spectrometry, it is very difficult to predict how the physicochemical differences will behave from a biological standpoint. The demonstration of immunogenetic differences between reference molecules and biosimilars has to be done *in vivo*.

Adding to this complexity, the patient's immune response to a biologic can impact both the efficacy and the safety of treatment. Indeed, administered biologics are seen as foreign bodies and can trigger immune responses in patients. The immune reaction itself can be toxic, and the development of anti-drug antibodies (ADAs) can affect the efficacy, stability, and safety of a biologic. These ADA responses can be broken down into 4 categories:

1. Patient related
2. Treatment related (acute vs. chronic)
3. Dependent on the chemistry and manufacturing of the biologic
4. Potential epitope content

Neutralizing and non-neutralizing ADAs are both important, as the neutralizing ADA will prevent the biologic from binding to the target site. The non-neutralizing ADA, although allowing the biologics to bind to the target site, can affect the biologics' clearance, half-life, and exposure (ie. the PK and PD of the molecule).

How are assays developed to measure immunogenicity? These assays are often developed not during clinical trials but as part of pre-clinical development, where an organism is immunized. The caveat is that in all cases, the test sample is not from human serum. A relevant question at this point is: does the assay have the capacity to detect all types of antibodies (IgG, IgA, IgM and IgE)?

Another layer of complexity resides in the post-production: the propensity of these therapeutic proteins to aggregate (unlike small molecules) during manufacturing, shipping, and storage. When proteins aggregate, even if they are the same molecular structure, they are processed differently by the immune system. Protein aggregation can happen for instance when a product is frozen, agitated, or when impurities are present.

## Conclusions

In summary:

- Biologics are inherently complex molecules.
- Physicochemical characterization is difficult, requiring a range of methodologies/techniques.
- Industrial production of biologics has many layers, all of which influence the activity of the final product.
- Methods to predict immunogenic potential before clinical trials are not ideal.
- Much diligence is required to produce safe and effective biologics.
- Monitoring systems may be required (e.g., at the institutional level) to track which biosimilars are being used and when.

# CLINICAL DATA REVIEW

VIPUL JAIRATH, MD, MBCHB, PHD, MRCP (UK) - GASTROENTEROLOGIST, WESTERN UNIVERSITY

The goal of this session was to highlight the data of a biosimilar switching study (NOR-SWITCH study), and to critically analyze it.

## NOR-SWITCH Study

Underlying this study is a question often raised by practicing physicians: If patients are stable and doing well using an innovator biologic, can these patients be switched to a biosimilar? Subsequently, what are the implications of such a switch? Is it effective and, importantly, is it safe? While there is observational data available that suggests the practice of switching being safe and effective, these data have limitations. Robust data is needed.

The NOR-SWITCH study was funded by the Norwegian government. It is a pragmatic study where patients who were stable on innovator infliximab were randomized 50% to biosimilar infliximab (CT-P13, Inflectra) and 50% to continue treatment on innovator infliximab (Remicade). Many conditions using infliximab were observed: ulcerative colitis, Crohn's disease, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis. The same dose and frequency as prior to inclusion in the study were continued (ClinicalTrials.gov identifier: NCT02148640).

## Objectives, Inclusion, Endpoints, and Design

The main objective of the study was to show whether switching to the biosimilar (CT-P13) was non-inferior to continuing with the innovator (infliximab [IFX]) with regards to disease worsening in patients who have been stable on infliximab for more than 6 months. Therefore, this study was designed to show that the switch was no worse than the existing intervention.

The secondary objectives were to:

- Assess safety and immunogenicity of CT-P13 compared to IFX in patients who have been stable on IFX for > 6 months.
- Compare efficacy of CT-P13 to IFX in patients who have been stable on IFX treatment for > 6 months applying generic and disease specific outcome measures.
- Compare cost-effectiveness of CT-P13 to IFX in patients who have been stable on IFX for > 6 months

To be included in the study, the patients had to have a clinical diagnosis of one of the conditions listed above and had to be stable on IFX during the past 6 months.

The primary endpoint was to measure disease worsening during a 52-week follow up, based on specific efficacy assessments. Generic and disease-specific measures were used as secondary endpoints (Table 2).

*Table 2. Generic and Disease-Specific Measures*

Generic	Disease Specific
<ul style="list-style-type: none"> <li>• Time to disease worsening</li> <li>• Occurrence of drug discontinuation</li> <li>• Time to drug discontinuation</li> </ul>	<ul style="list-style-type: none"> <li>• RA and PsA: DAS28, MHAQ, RAID, PsAID</li> <li>• SpA: ASDAS, MHAQ, BASDAI</li> <li>• Psoriasis: PASI, DLQI</li> <li>• UC: Partial Mayo, IBD-Q</li> <li>• CD: HBI, IBD-Q</li> <li>• Inflammatory markers</li> <li>• Other: EQ-5D, SF-36, Healthcare resource use</li> </ul>

The study was a randomized, double-blind, parallel-group, multicenter, non-inferior study (1:1 randomisation); stratification by disease, concomitant medication). It was estimated that the primary endpoint would occur in 30% of patients during 52 weeks (e.g. 30% would have their disease worsening of the year).

The margin of non-inferiority was 15%, therefore half of the difference (compared to expected worsening) was acceptable. Five hundred patients were randomized. The data are not fully published yet; however, some data were presented at the UEGW (United European Gastroenterology Week, October 15 - 19, 2016) and ACR (American College of Rheumatology - November 6 - 11, 2016), finding that CT-P13 is non-inferior to infliximab.

## Results

Between October 6, 2014 and July 8, 2016, 481 patients (IFX 241 patients and CT-P13 240 patients) at 40 Norwegian study centres were randomized, received treatment, and were followed for 52 weeks.

Disease worsening occurred in 26.2% and 29.6% of patients in the IFX and CT-P13 arms, respectively, which was not detected as being significantly different. The 95% confidence interval of the adjusted treatment difference (-4.4%) was -12.7 - 3.9, which was within the pre-specified non-inferiority margin (Table 3).

Table 3. Results of the Primary Endpoint of the NOR-SWITCH Study

Disease Worsening	Infliximab (IFX)	Inflectra (CT-P13)	Non-Inferiority Margin
All	53 (26.2%)	61 (29.6%)	-12.7 - 3.9%
Crohn's disease	14 (21.2%)	23 (36.5%)	-29.3 - 0.7%
Ulcerative colitis	3 (9.1%)	5 (11.9%)	-15.2 - 10.0%
Spondyloarthritis	17 (39.5%)	14 (33.3%)	-14.5 - 27.2%
Psoriatic arthritis	7 (53.8%)	8 (61.5%)	-45.4 - 28.1%
Psoriasis	1 (5.9%)	2 (12.5%)	-26.9 - 13.2%

On the right-hand side column, each result that is smaller than -15 means that the biosimilar was not non-inferior (e.g. did not meet the non-inferiority margin objective). Although the study was exploratory, the difference in worsening between IFX and CT-P13 raises a point of discussion.

The incidence of anti-drug antibodies detected during the study was 17 (7.1%) and 19 (7.9%) in the IFX and CT-P13 patients, respectively. Trough drug levels and the frequencies of reported adverse events including infusion reactions were also similar. With regards to the other endpoints such as the quality of life measures, there were no differences observed overall.

The conclusion from the NOR-SWITCH study is that switching stable patients from IFX to CT-P13 was not inferior to continued treatment with IFX.

### Strengths and Weaknesses

One strength of the NOR-SWITCH study was that this pragmatic study reported real-life data (randomized, real-world, non-inferiority trial). It was funded by the Norwegian government agency.<sup>2</sup>

One of the weaknesses was the large non-inferiority margin of 15%. This could represent a clinically meaningful difference. This trial was a trade-off between what is feasible and affordable; in this case a relatively small sample size (n=481) across 6 disease categories.

Additionally, this study only looked at a one-way switch. There is a concern that as more manufacturers release biosimilars, physicians may be forced to switch multiple times; potentially causing stress to immune system and patient sensitivity. The question that arose was, what would happen with multiple switches? Future studies will need to investigate the potential effects of switching to different biosimilars several times.

Another concern that was identified, was the large non-inferiority margin. The subset analysis within this trial showed what could be interpreted as a clinically meaningful difference between the innovator and biosimilar in Crohn's disease in terms of disease worsening (-14.3%). This should be addressed in trials moving forward.

The question of interchangeability (accepting an innovator biologic and a biosimilar as the same) is also of concern; government needs to apply pressure on biosimilar companies and ensure that post-marketing studies are done if they want interchangeability.

### Conclusions

NOR-SWITCH is an important landmark study. Moving forward, larger-scale, randomized trials need to be developed to look at specific disease categories with a smaller non-inferiority margin in order to determine whether switching from an innovator to a biosimilar is safe.

In conclusion, physicians are ultimately advocates for their patients. Cost-effectiveness is essential; however, clinical effectiveness and safety is paramount.

## HEALTH CANADA: CLINICAL ASSESSMENT OF BIOSIMILARS

JING (JENNY) NING, MD - SENIOR CLINICAL EVALUATOR/BIOLOGIST, HEALTH CANADA

On November 14, 2016, Health Canada published a revised “Guidance Document Information and Submission Requirement for Biosimilar Biologic Drugs”.

This presentation aimed to share the key considerations for the clinical assessment of biosimilars. The information presented is in the public domain and contains no proprietary information or trade secrets.

### Highlights of Revised Guidance

The changes from the previous version are highlighted as follows:

- Change in terminology:
  - The term subsequent entry biologic (SEB) is changed to *biosimilar biologic* drug and its internationally accepted abbreviation *biosimilar*.
- Clarification of the requirement for the use of a non-Canadian reference biologic drug.
- The guidance was updated to further assist sponsors in selecting sensitive populations and endpoints for clinical comparability assessments.
- Further details were provided on the process and requirements for “indication authorization”.
- Clarification of the status of a biosimilar once it has received authorization:
  - A biosimilar is a new drug with all of the associated regulatory requirement under the Food and Drugs Act and Regulations.
  - Biosimilars are not generic biologics. Authorization of a biosimilar is not a declaration of pharmaceutical equivalence, bioequivalence or clinical equivalence to the reference biologic drug.

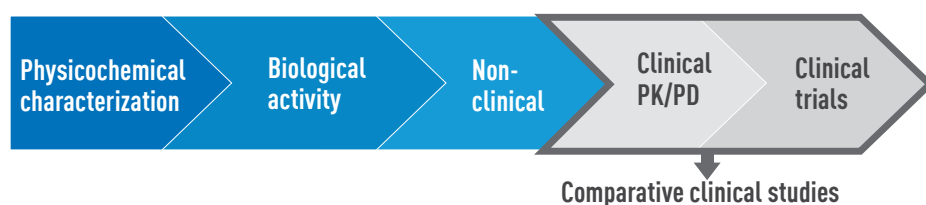
The Guidance also indicates that “Designation of a drug as interchangeable is under the purview of the provinces and territories, and is thus outside the scope of the Guidance Document for Biosimilars”.

Biosimilars currently authorized in Canada since 2009 are: Omnitrope (somatotropin), Remsima (infliximab), Inflectra (infliximab), Basaglar (insulin glargine), Grastofil (filgrastim) and Brenzys (etanercept).

### Approach for Similarity Evaluation and Difference in Data Requirement

The evaluation for biosimilars is a step-wise approach, evaluating residual uncertainty at each step. It is a case-by-case based approach that is tailored to each individual product (Figure 4).

Figure 4. Case-by-case Approach



“THE GUIDANCE INDICATES THAT ‘DESIGNATION OF A DRUG AS INTERCHANGEABLE IS UNDER THE PURVIEW OF THE PROVINCES AND TERRITORIES.’”

The regulatory pathway for both biologics and biosimilars is a New Drug Submission (NDS); there is no different pathway for biosimilars. There are differences in submission data requirement between originators and biosimilars (Table 4).

Table 4. Submission Data Requirement: Originators vs. Biosimilars

	Originator Biologics	Biosimilars
Regulatory Pathway	• New Drug Submission (NDS)	• NDS
Chemistry & Manufacturing (C&M) Studies	• Full package	• Full package • Extensive comparative analytical studies between biosimilar and RBD
Non-Clinical Study	• Full data package as per ICH S6(R1)	• Reduced and comparative to RBD
PK/PD Study	• Standard PK/PD studies	• Comparative PK/PD profile to RBD
Clinical Efficacy	• Required for all indications	• In most cases, comparative to RBD for at least one indications in a representative indication and sensitive population
• Clinical trial design	• Superiority, non-inferiority or equivalence trial design	• Equivalence trial preferred over non-inferiority design • Adequately sensitive to rule out clinically meaningful differences within predefined comparability margins
• Study endpoint	• Clinical outcomes or validated surrogates	• Sensitive and clinically relevant
Efficacy/Safety	• Establishing evidence of efficacy and safety/Acceptable risk and benefit profile	• No clinically meaningful difference to RBD • Safety must be assessed in a sufficient number of patients treated for an acceptable period of time
Immunogenicity	• Acceptable immunogenicity profile	• No meaningful difference to RBD
Post market	• Risk management plan	• Risk management plan

## Demonstration of Similarity and Purpose of the Clinical Program

How is similarity demonstrated?

- The quality attributes should be highly similar.
- Any differences in quality attributes should have no adverse impact upon safety or efficacy of the biosimilar.
- Non-clinical and clinical data previously generated with the reference biologic drug are relevant to the biosimilar.
- The degree of similarity at the quality level will determine the scope and the breadth of the required non-clinical and clinical data.

The purpose of the clinical program is not to demonstrate the safety and efficacy of the biosimilar since these have been established with the reference biologic drug, but to show that there are no clinically meaningful differences between the biosimilar and the reference biologic drug.

The clinical program includes:

- Comparative Pharmacokinetic (PK) studies: Comparative bioavailability.
- Comparative Pharmacodynamic (PD) studies: Parameters investigated in PD studies should be clinically relevant.
- A clinical efficacy trial may not always be necessary (e.g. where there is a validated and clinically relevant PD endpoint). In such cases, a scientific justification is needed and safety as well as comparative immunogenicity data are still required. Safety and Immunogenicity
  - Safety in sufficient number of patients for sufficient length of time.

## Comparative PK Studies

In designing clinical PK studies for biosimilars:

- Comparative clinical PK data are required.
- The comparative PK studies should be conducted in a setting that is reflective of the clinical situation and/or is sensitive to detect differences between the biosimilar and the reference.
- The most sensitive PK study design to detect potential differences is the single dose cross-over design (short half-life).
- The cross-over, single dose design can be limited by the properties of the biologics. Alternatively, parallel and/or multiple-dose design could be considered.

The factors should be taken into consideration for PK study design: half life of the biologics, linearity of PK parameter, endogenous levels and diurnal variation of the protein under study and conditions and diseases to be treated, route of administration, and indications for which the biosimilar sponsor is applying.

### Comparative PD Studies

The PD studies should be comparative in nature and combined with PK studies. The PD parameters should be clinically relevant, scientifically justified and relevant to the mechanism of action of the drug (e.g. absolute neutrophil count for a biosimilar G-CSF is an established surrogate PD marker to predict clinical outcome - febrile neutropenia-infection). The assay/dosing sensitivity has to be considered. Dose in the steep part of the dose-response curve should be considered; it must be sensitive enough to detect any differences.

### Comparative Clinical Study

The comparative clinical study should be conducted in a **sufficiently sensitive population** that is representative of the authorized indications to detect differences between the biosimilar and the drug reference.

A comparative clinical study should consider:

- A homogeneous population (e.g. same disease stage, monotherapy with immunosuppressant) would give a better chance to detect potential differences between a biosimilar and its originator biologic.
- Observed clinical effects are the direct action by the biosimilar or the reference without interference of other drugs.
- A large body of historical data is available for validation of study outcomes.
- Mechanism of action is well-understood and representative.
- Large effect size.

### Endpoints and Equivalence Margins

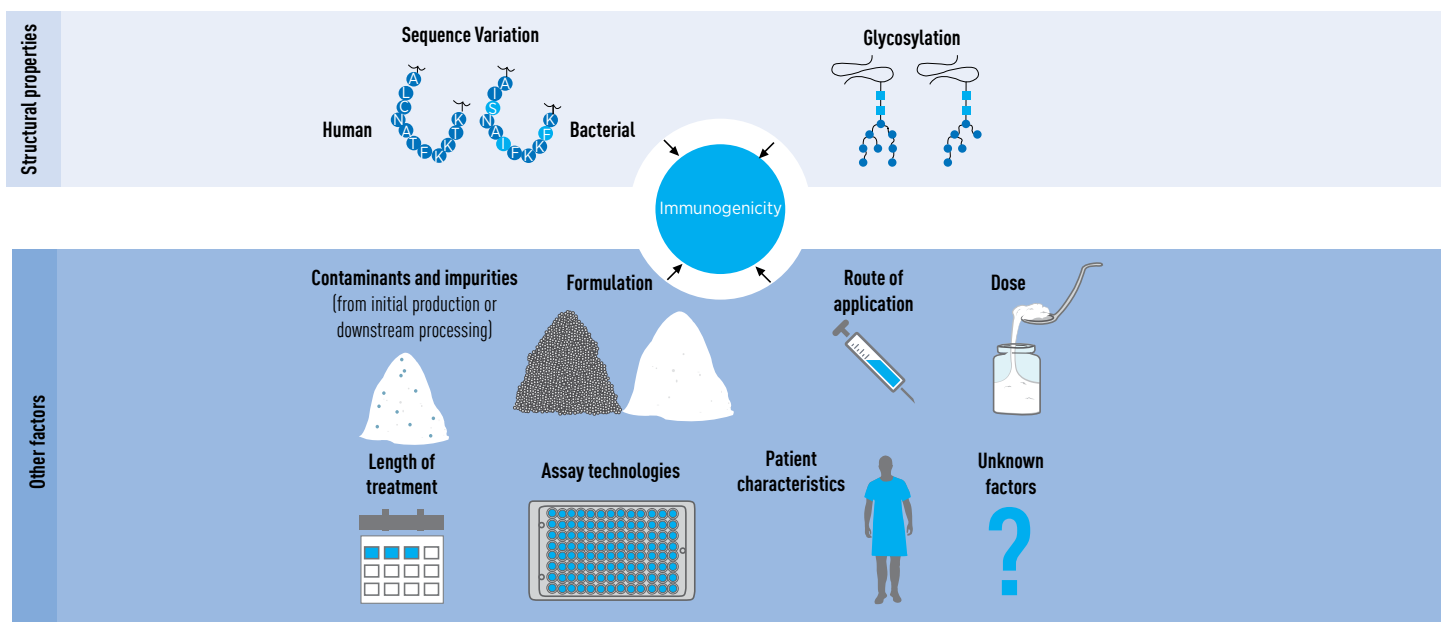
Equivalence trials are preferred over non-inferiority trials. A sensitive primary study endpoint should be considered to improve the detection of potential differences between the biosimilar and the reference within the sensitive population. Also:

- A study endpoint different from the innovator’s original study endpoint(s) may be used, e.g., ORR or PFS as primary endpoint instead of OS in oncology trials for biosimilars.
- The equivalence margin should be the largest difference that can be judged as clinically acceptable for the biosimilar and smaller than differences observed in superiority trials of the reference biologic drug.

### Immunogenicity

Most biologics induce some level of anti-drug antibodies (ADAs) and these ADAs may have undesirable clinical effect on pharmacokinetics, efficacy and/or safety, including immunogenicity<sup>4</sup> (See [Rob Laister’s presentation](#); Scientific Review of Biosimilars for additional information on immunogenicity). There are several factors that can affect immunogenicity (Figure 5).

Figure 5. Factors Affecting Immunogenicity



Immunogenicity should be compared between the biosimilar and the reference in at least one clinical study that enrolled a sufficient number of patients for a sufficient period of time in an appropriate population (immunocompetence, use of immunosuppressant and immunogenicity data from the reference biologic drug. Health Canada insists that a biosimilar should not be more immunogenic than its reference in terms of ADA incidence and ADA concentration.

## Conclusions

Overall, biosimilars can receive all indications held by the reference based on the totality of evidence obtained from all comparative analyses.

- A biosimilar has to demonstrate that its structure and function(s) are (highly) similar to the reference biologic product.
- Clinical studies should be conducted in a sufficiently sensitive population that is representative of the authorized therapeutic indications and should use a sensitive clinical endpoint to demonstrate that residual uncertainty from quality assessment does not cause clinically meaningful differences in efficacy, safety and/or immunogenicity.
- Immunogenicity is a key concern in the context of biosimilar development, and its clinical relevance and potential risk should be thoroughly assessed.
- Therapeutic indications held by the reference product can be granted to its biosimilars when appropriate data and rationales are provided based on the totality of evidence.



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A BIOSIMILAR HAS TO DEMONSTRATE THAT ITS STRUCTURE AND FUNCTION(S) ARE (HIGHLY) SIMILAR TO THE REFERENCE BIOLOGIC PRODUCT.

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## PUBLIC REIMBURSEMENT OF BIOSIMILARS IN CANADA

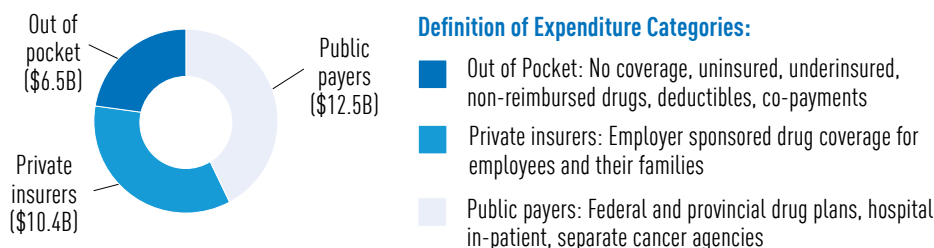
SHERRY O'QUINN, BSC (PHARM) - PDCI MARKET ACCESS

The objective of this presentation was to provide an overview of the Canadian reimbursement landscape and the public payer biosimilar experience in Canada to date.

### Who Funds Prescription Drugs in Canada?

In Canada, prescription drugs are funded through 3 major categories: public plans cover 42%, 36% comes from private insurers, and a significant amount (22%) was paid by patients out-of-pocket (Figure 6).

Figure 6. Distribution of Rx Drug Expenditures Canada 2014 (Total Spend = \$29.4B)



#### PUBLIC PAYERS

2 of the top 10 classes are biologic drugs: anti-TNF and anti-neovascularization agents

Source: Canadian Institute for Health Information (CIHI), Prescribed Drug Spending in Canada, 2016: Focus on Public Drug Programs (Published, 2016)

Many of the decisions made today around biologics and biosimilars are in the context of a fairly strained fiscal situation. Drug plan managers are dealing with budgets that are growing at about 2% per year so they must decide whether to fund a product when they have no budget to do so.

Biologics have been revolutionary for patients and have become the focus of a lot of development by drug companies, however they are one of the highest expenditure categories for payers. The traditional equilibrium in the system is changing, where small molecule drugs are funded with a defined life cycle as they come off-patent, bringing a relief to drug programs. As more biologics are being developed, this life cycle does not apply to the same extent and room for funding new drugs may become limited. This shift raises significant concerns regarding the sustainability of drug plans going forward.

“PUBLIC PAYERS WERE INITIALLY VERY EXCITED ABOUT THE TREMENDOUS OPPORTUNITIES FOR SAVINGS WITH THE INTRODUCTION OF BIOSIMILARS; HOWEVER, THEY ARE NOW AWARE OF THE LIMITATIONS.”

### Public Payers

Over the next decade, a number of high priced biologics will lose their patent protection. Public payers were initially very excited about the tremendous opportunities for savings with the introduction of biosimilars; however, they are aware of the limitations. Overall:

- The initial excitement from payers about biosimilars has been tempered significantly.
- Scientific uncertainties remain; there is a need for evidence to support decision-making.
- Most of the saving opportunities come from switching drugs, and stakeholders have raised significant concerns about switching. Public payers understand that there are potential barriers to uptake:
  - Will clinicians prescribe?
  - Will patients agree to take biosimilars?
- Limited controls: challenges with certain funding approaches (e.g. tendering).
- Framework approach: simplicity, efficiency. The whole pathway is based on evidence.



## Biosimilar Price Discount

In Canada, the biosimilar market is still young and there are not many biosimilars approved yet. Infliximab was the first to be approved under the new pathway. It is interesting to see the wide range of variation in price discount from originators (e.g. from 15% to 47%) (Table 5).

Table 5. Biosimilars Price Discount in Canada

Originator	Biosimilar	Therapeutic Area	Market Entry	% Discount from Originator
Humatrope* (somatropin)	Omnitrope	Growth hormone deficiency	April 2009	33%
Remicade (infliximab)	Inflectra	Rheumatoid disorders, IBD	Jan 2014	47%**
Neupogen (filgrastim)	Grastofil	Supportive therapy (oncology)	Dec 2015	25%
Lantus (insulin glargine)	Basaglar	Diabetes Mellitus	July 2015	15%
Enbrel (etanercept)	Brenzys	Rheumatoid disorders	Aug 2016	25%

\*Used for pricing comparison (Genotropin not on the market in Canada in 2009)  
 \*\* price started at 35% rebate and decreased after the pCPA negotiation



## CASE STUDY: INFLIXIMAB IN CANADA

In terms of listings, infliximab is the only biologic/biosimilar seen in the entire system of public reimbursement. It is the only example, but perhaps not the best example, as it has a number of indications (which were approved at different times), and is an infusion (making it somewhat unique).

### Infliximab Originator: Remicade

A snapshot of public plan expenditures (at list price) of the infliximab originator, Remicade:

- Ontario public drug plans spent \$101M on Remicade in 2015.
- BC (private & public) in 2014/15, \$105M, BC's top drug expenditure.

The landscape is complex:

- Remicade has 6 conditions with 9 sets of specific listing criteria in place for its various adult and pediatric indications.
- There is inconsistency in funding approach across the country.
- There are concerns around dose escalation.
- Out-patient infusion clinics, services and extensive patient support programs are in place.

### Infliximab Biosimilar: Inflectra

Inflectra (Hospira Healthcare Corporation), received a NOC January 15th, 2014 for only four indications. On June 6th, 2016, a NOC was obtained for the remaining 2 IBD indications. The first indications were for rheumatologic disorders, and took about a year to complete negotiations with the pan-Canadian Pharmaceutical Alliance (pCPA). The negotiation for the 2nd set of indications went faster, as the biosimilar manufacturer was aware of the need to ensure similar access to infusion clinics and patient services. Private payer agreements were also made with Janssen to maintain Remicade listings.

Quebec listed Inflectra in early 2015, and the pCPA completed negotiations for Inflectra in November 2015. Since then, 10 additional provinces and territories have listed Inflectra. For the most part, there is consistency across the country as to how the drug plans have moved forward about funding the rheumatology indications. The majority have chosen to list Inflectra as the first infliximab biosimilar considered for infliximab naïve patients (YK, PEI, BC, NS, NFLD, AB, MB, ON, and NB). In terms of switching, it is allowed, but there is currently no forced switching. In Quebec, a slightly different approach was taken; similar to how the generics are handled in this province, a maximum amount to be reimbursed was set (in this case \$650.00 per 100 mg vial for Inflectra). That means patients can still get Remicade, but must pay the difference. Finally, one province, Saskatchewan, listed Inflectra at parity to Remicade.

### Conclusions: More Biosimilars are Coming

Several biosimilars have recently been approved (Table 6), and with more biosimilars coming, payers are working to develop a policy.

Table 6. Biosimilar Approval Dates

	Grastofil	Basaglar	Brenzys
Reference	Neupogen	Lantus	Enbrel
NOC	Dec 2015	Sep 2015	Aug 2016
CDR	Mar 2016	Apr 2016	Oct 2016
pCPA	Active (as of Nov 2016)	Active (as of Nov 2016)	Active (as of Nov 2016)

Grastofil has just completed their negotiation process (December 2016). Only one listing has been seen in Ontario. The payers are working with the pCPA Office to develop a consistent approach and policy moving forward. There are principles that were developed last April; they are in the phase of being consulted by multiple stakeholders.

“SEVERAL BIOSIMILARS HAVE RECENTLY BEEN APPROVED AND WITH MORE BIOSIMILARS COMING, PAYERS ARE WORKING TO DEVELOP A POLICY.”

## PRIVATE PAYER PERSPECTIVE

LAUREEN RANCE, PHARM.D - DIRECTOR, PHARMACEUTICAL RELATIONS, MANULIFE  
KIM MACFARLANE - PRODUCT DIRECTOR, GROUP BENEFITS, MANULIFE

This presentation aimed at providing an overview of the private payer's perspective approach to the emerging biosimilar market.

### Who is Manulife?

- Represents 24,000 employers, with:
  - 80% being small employers (2-49 lives)
  - 15% medium employers (50-399 lives)
  - 5% large employers (more than 400 lives)
- Represents 3.5 million Canadians coming from:
  - 10% small employers
  - 10% medium employers
  - 80% large employers

Manulife provides administration and coverage benefits for a wide range of clients, but what is important to note is that the financial arrangement and who is responsible for the financial risk can vary by client or size of client.

**Insured:** Manulife sets a rate that is intended to cover the benefit costs for the next year. To build this rate there are 2 components: the clients claims experience and the experience of the pooled claims (higher cost claims over a certain dollar threshold). If insurers have done their job well, there is a bit left over. Otherwise, they lose money.

**Administrative Services Only:** Administrative services only apply when larger employers take all the risk and cover the costs of the claims themselves. Pooling may also apply to this group and again represents high cost claims where they do not take on the risk.

### Pharmacy Benefits Approach

Manulife's approach is to balance cost, with the patient experience, while supporting the desired health outcomes. Pharmacy Benefits is an area that has really taken off in the industry. A few years ago, the focus was to pay claims as quickly/efficiently as possible, and that's how business worked. This has really changed with the advent of new higher cost drugs and increased drug utilization. The focus has shifted and insurers are responding to concerns of clients while watching their costs escalate. Over the past 7 years, Manulife brought their own clinical resources, including a number of pharmacists (in 2010, there were no pharmacists on their team) to help better understand the shifting drug landscape and to develop strategies that are clinically effective, while helping clients manage costs.

Managing costs associated with increasing drug costs cannot be the only focus as payers are also managing disability benefits. Decisions made related to drug benefit management cannot compromise the disability side of the equation.

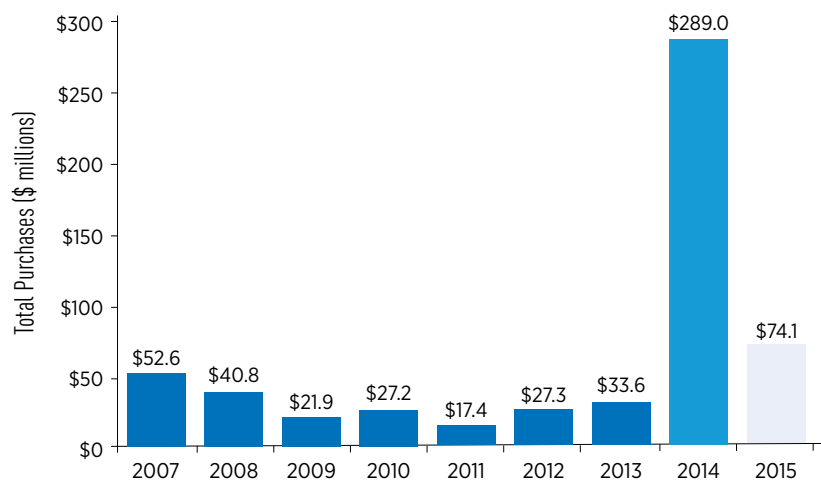
Likewise, employers have expressed loud and clear that they do not want to introduce change that will result in a lot of noise or disruption. They do not want decisions that Manulife makes to result in their plan members coming forward and complaining, and want to make sure that the plan members have a positive experience.

### Specialty Drug Spend

Specialty drug spend has more than doubled from 2007 to 2015 (from approximately 15% to 30% of all drug plan spend). During that time, many blockbuster drugs came off patent and several generic drugs were launched. The utilisation of specialty drugs is continuing to grow at an unprecedented rate; specialty drugs are anticipated to reach 42% of all drug plan spend by 2020.

There was a wake-up call in 2014 as there was a huge burst of costs, which was not understood or anticipated (Figure 7). A lot of other expensive drugs hit the market in 2014. Not surprising, the drugs targeting Hepatitis C were responsible for about half of the drug spending in 2014, but not all. Numbers from 2015 are not as high, but higher than prior to 2014. This trend is not anticipated to go down.

Figure 7: 2014: An unprecedented year for new product launches - Purchases of new active substances (and priority-NASs) launched, 2007 to 2015



### Conclusions: Biosimilar Opportunity and Strategy Considerations

As far as opportunities go, payers are welcoming the savings associated with the emerging biosimilars market. Private payers are developing a biosimilar strategy. Factors considered in the strategy include:

- Efficacy: Decisions need to be made that won't compromise the health of patients.
- Patient support program: Does the biosimilar provide for clinics and/or financial assistance - plan members are encouraged to participate in these services.
- Physician prescribing: How will physicians prescribe? Will they continue to prescribe the originator brand or will they start to prescribe a biosimilar?
- Switching therapies: While not high on the list of considerations. It makes sense economically; but there are too many uncertainties and patient disruptions associated with switching
- Provincial formularies / listing recommendations: Because Manulife integrates with the provinces, the decisions that are made by the public payer strongly influence their plans.

## ADVOCACY GROUP PERSPECTIVE

### CROHN'S & COLITIS CANADA

ERIC THOMSON, BA, MA - PUBLIC POLICY AND STAKEHOLDER RELATIONS MANAGER

This presentation aimed at highlighting Crohn's & Colitis Canada's position and campaign on biosimilars.

#### Introduction and Position on Biosimilars

Health Canada approved a biosimilar for Crohn's disease and ulcerative colitis for the first time in early 2016 (Inflectra®). However, Inflectra® is approved for adults, but does not have pediatric indications (where Remicade has been approved for pediatric).

Also, Health Canada does not recognize biosimilars as interchangeable or substitutable for their innovator biologic. It is important to note that ultimately, the provinces and territories decide whether a product is interchangeable.

Crohn's & Colitis Canada has developed a position on biologics and biosimilars:

- They support and welcome the introduction to market of safe and effective treatments for IBD. This includes biosimilars.
- Doctors and patients must be able to select the treatment option best suited to each patient's individual circumstances without undue interference from government or private payers. One size does not fit all.
- Patients being treated with an innovator biologic should not be forced to switch to a biosimilar by any government or private payer without the informed consent of the prescribing doctor and patient. Switching should be the choice of the patient.

This position will not change unless there is enough evidence which demonstrates that patient stability to a treatment could not be jeopardized by switching to a biosimilar.

#### No-Forced Switch Campaign

Crohn's & Colitis Canada launched a campaign called "No-Forced Switch". The campaign is accessible at: <http://action.crohnsandcolitis.ca/>.

The letter has a clear message:

- Crohn's & Colitis Canada calling on the provincial and territorial governments to protect patients by mandating "No Forced Switch."
- Once an IBD patient has found a treatment that works, the last thing they want is to be forced to switch to another medication (biosimilar).
  - The Ontario government has stated that patients on Remicade can continue to receive Remicade for the duration of the EAP approval period.

The campaign addresses the concerns of the patient community, patient focus group, and the larger community. Treatment stability is extremely treasured. This is for several reasons:

1. IBDs are likely to be diagnosed in young adulthood.
2. IBDs are chronic relapsing diseases with no known cure.
3. There are relatively few treatment options for these diseases.

Patients with IBD will likely live with the disease for decades. They need sufficient evidence that switching won't jeopardize their remission. This unknown is problematic to patients because there is a lack of medical evidence to support the claim that switching won't jeopardize their remission. This is disconcerting which in itself, may lead to stress, and there is evidence suggesting that stress may trigger or exacerbate an IBD flare.



PATIENTS NEED SUFFICIENT EVIDENCE THAT SWITCHING WON'T  
JEOPARDIZE THEIR REMISSION.



The primary goal of this advocacy campaign was to influence policy making across Canada. The second goal was to raise awareness in the patient community specifically to empower patients and to reach Canadians generally to help them understand this position. As a direct result of the campaign, the Minister of Health of Nova Scotia confirmed a no forced switch policy for IBD patients stable on innovator biologics.

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## LYMPHOMA CANADA

ELIZABETH LYE, B.SC. - SCIENTIFIC ADVISOR, LYMPHOMA CANADA

The objective of this session was to highlight the level of knowledge surrounding biosimilars among lymphoma patients in Canada.

### Introduction to Biosimilars

Biosimilars have been used in supportive care (G-CSF, EPOs) for a number of years; however, there is currently no approved biosimilars for lymphoma treatment in Canada. There are currently ~13 biosimilars in development for rituximab. A market authorization is expected for rituximab biosimilars in Europe in 2017, which is expected to enter Canadian market in 2020. With respect to patient awareness of biosimilars, it is limited in the Canadian lymphoma patient community.

### Position on Biosimilars

Lymphoma Canada's position is to offer equal access to safe and effective therapies for all Canadians living with lymphoma. While Lymphoma Canada supports the use of cost-effective therapies; however, safety and efficacy remain a priority. The decision to select a therapy option should be between the patient and their oncologist/ hematologist, through a shared decision-making process, without undue interference from public and/or private payers.

### Moving Forward

Several issues that are important to consider for patients with respect to biosimilars in the oncology treatment landscape:

- Goals and outcomes of lymphoma treatment must be considered from the patients' perspective. When it comes to goals and outcomes for patients with cancer, they want to be given a treatment that will give them the best chance at surviving.
- Lymphoma is not one homogenous disease (> 60 histologic subtypes of lymphoma); it is a very complex group of diseases.
- There are numerous treatments working to varying degrees in different subtypes. Rituximab is often used in multi-drug treatment regimens. Treatment-naïve vs. relapsed/refractory are available.
- Patients want to be reassured that they are getting the most effective therapy available.
- Patients need to be educated on the differences between a biosimilar and biologic in order to make informed choices.

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## MYELOMA CANADA

MARTINE ELIAS, B.SC., M.SC. - DIRECTOR OF ACCESS, ADVOCACY, AND COMMUNITY RELATIONS

This presentation aimed to highlight the level of knowledge surrounding biosimilars among myeloma patients in Canada.

### Introduction to Biosimilars

Myeloma Canada is an organization that looks after myeloma patients in terms of advocacy, education, and awareness. Myeloma is a cancer of the plasma cells. These cells are very important for the immune system. A lot of questions with regards to immunogenicity come to mind with regards to myeloma patients.

At the moment, there are no biosimilars available for the treatment of myeloma. However, myeloma patients do receive biologics to manage side effects (erythropoetin and filgrastim). There are new immuno-oncology drugs on the horizon will eventually bring biosimilars.

### Position on Biosimilars

Myeloma Canada does not have a published position on biosimilars yet, primarily because they are a few years away. However, they did look at how they would approach the question of biosimilars. The principles would be: non-interchangeability, clinically proven, choice (sequencing of drugs), no switching.

### Moving Forward

It will be important to work in collaboration with other cancer advocacy groups on awareness and shaping reimbursement policies. Developing a common position on the value of immuno-oncology drugs and biosimilars will be important for Myeloma Canada.

Myeloma Canada needs to educate and mobilize their patient membership. Explaining what a biosimilar is, is not an easy task, for instance discussing interchangeability, differences in the molecules, manufacturing processes.

It is crucial to recognise the pressure on health care sustainability, work with all parties to find viable solutions to ensure patients have access to the treatments they need. Decisions should not be made solely based on costs and need to be grounded on factors that are really important to patients.

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## ADVOCARE CONSUMER NETWORK

DURHANE WONG-RIEGER, PHD - CHAIR OF CONSUMER ADVOCARE NETWORK

The objective of this presentation was to highlight the knowledge level that patients have with respect to biosimilars.

### Survey

A survey was conducted in 2016 with the following characteristics:

- Canada-wide web-based survey
  - Conducted by Advocare and Canadian Organization for Rare Disorders
  - Directed to existing patient cohort of 2,000+
  - Secondary distribution to patient organizations and umbrella associations
  - Promoted through Facebook and Twitter
- Patient characteristics (Preliminary May-June 2016)
  - Respondents = 320; Complete survey = 200
  - Conditions = inflammatory, blood, immune-related, diabetes, cancers, multi-systemic, lysosomal storage, heart, pulmonary
  - Use biologics: 54% current; past or future; 24% not likely; 22% not aware
  - Familiar with definition: 44% unfamiliar; 36% somewhat; 20% very
  - Sources for information on biosimilars: 62% Web; 38% forum; 32% media; 25% clinician (note: respondents could pick more than one)

### Familiarity of the Definition of Biosimilars and Patient Perceptions of Biosimilars

Almost half of patients consulted were not familiar with biosimilars.

From those who are currently using biosimilars, the following was reported:

- To the question: "To what extent do you agree a biosimilar as compared to the original could expect a different response?"
  - Not surprisingly, about 2/3 responded they could expect a different response.
- A large proportion (84%) thought they could have other adverse effects.
- To the question: "Should I accept if much cheaper", the response showed that patients were ambivalent as 40% agreed and 42% disagreed. However, it was clear from the comments that patients do not want this to happen if it is the "only" reason.
- Just over 60% responded that they are willing to switch, with the caveat being they needed more information about the impact of switching.

Furthermore, the majority of patients agreed that:

- Government should ensure no interchangeability (88%).
- Patients should not be switched (78%).
- Patient should have a right to informed choice (96%).

### Oncology Patient Leaders' Attitudes about Biosimilars

Specific to cancer patients:

- Cancer patients have only one chance to get the right drug; they cannot tell right away whether treatment is working or if there are long-term side effects (that could appear years later). Patients would prefer treatment with 15 years of demonstrated safety and efficacy rather than two.
- Biologics are highly specific to the individual patient; cannot extrapolate from one tumour type to another or from one stage to another (ie. new to metastatic breast cancer).
- Oncology clinics lack long-term follow-up to assure pharmacovigilance needed for safe use of biosimilars.
- Biosimilars should support savings to the healthcare system but prescribing should be based on what is "best for the patient" versus what is "best for the system".
- Better information is needed on what "similarity" means; lack of confidence may affect adherence.

The most important message received from oncology patients was: "Do not extrapolate. Do not believe that a patient in stage four is in the same state as a patient in stage one. Do not tell me that you have done a study with this population, which can be extended." It is quite evident that patients have concerns about long-term outcomes. These patients do not have second chances. Overall, it is important to be responsible and reasonable about switching.

### Moving Forward:

The following recommendations are made from the Advocare Consumer Network:

- Develop accurate, balanced and evidence-based information about biosimilars and ensure this is made available to all patients.
- Establish means to address patients' concerns in open and honest ways.
- Provide tools to monitor use of biologics so that it is possible to track outcomes for specific biologics/biosimilars. Develop and implement platforms to collect and analyze real-world evidence to support and update appropriate use guidelines.
- Engage patients as partners in every step of the process, especially patient organizations.

It was great to have such a knowledgeable group of clinicians participate in this Congress.

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 WHILE SOME LEVELS OF EDUCATION CAN BE PROVIDED BY SPECIALISTS, NURSES, ETC., IT WILL ULTIMATELY BE UP TO THE ADVOCACY GROUPS TO EDUCATE PATIENTS AND HELP SHAPE POLICY. 

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# PHARMACIST PERSPECTIVE

SCOTT EDWARDS, B.SC., PHARM.D. - CLINICAL ASSISTANT PROFESSOR ONCOLOGY, DR. H. BLISS MURPHY CANCER CENTRE

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The objective of this presentation was to highlight the key issues that pharmacists may expect to see at work.

## Key Issues

These are practical issues identified for biosimilars: 1. Naming, 2. Interchangeability, 3. Authorization of indications.

### Naming

Canadian and international regulators have been unable to provide a consistent method across countries for naming biosimilars that would lead to better traceability. Different naming options are available: 1) Non-proprietary Only, 2) Non-proprietary Plus Suffix, 3) Non-proprietary Plus Prefix, or 4) Unique Brand Name.

There is not a clear guidance yet, however Health Canada is currently “evaluating the most appropriate naming convention for biosimilars and biologic drugs”.

The challenges related to naming biosimilars can be summarized as:

- There is a potential for errors when using four-letter suffix “devoid of meaning”, although there are some benefits, e.g., easier for pharmacovigilance and each product a unique name. This approach would require the originator to change their name too, which may bring an error to the pharmacist who would assume that the products are interchangeable.
- It will have an impact of naming on pharmacovigilance. Using the four-letter suffix will help keep track of post-marketing, but there is not a program in place to identify adverse events related specifically to biosimilars. Without using a four-letter suffix, it will be difficult in terms of tracing the adverse events related to these specific biosimilars.
- It will be a challenge to enter these names into electronic systems (ordering systems, pharmacy systems, dispensing, e-prescribing, order sets, and pathways) so that providers aren’t mixing up the names of products unintentionally.
- Results from a cross-sectional survey of 781 pharmacists show that:<sup>5</sup>
  - The preferred biosimilar naming convention included the non-proprietary name with a designated suffix.
  - The type of naming convention affected their confidence in substituting biosimilars for the reference biologic.

### Interchangeability

Health Canada’s authorization of a biosimilar is not a declaration of equivalence to the reference biologic drug. There are varying definitions of interchangeability. In Canada, the term often refers to the ability for a patient to be changed from one drug to another equivalent drug by a pharmacist, without the intervention of the doctor who wrote the prescription. Additionally, the authority to declare two products interchangeable rests with each province and territory according to its own rules and regulations

At the provincial level, the challenges related to interchangeability surround:

- The importance for provincial legislation to clarify and to educate pharmacist authority to substitute (e.g. Which drugs are interchangeable? Which drugs are biosimilars). In the US, there are interchangeable biosimilars and non-interchangeable biosimilars.
- The increased workload placed on pharmacists because of post-dispensing notifications and retaining of data (even in hospital settings).
- An interchangeable biosimilar versus a non-interchangeable biosimilar.

There are concerns about provincial pharmacy practice laws in terms of providing a pharmacist with sufficient authority to substitute a biologic.

### Authorization of Indications

A biosimilar sponsor may request authorization for all indications held by the biologic drug authorized in Canada to which a reference is made. Health Canada may authorize a biosimilar for use in more than one indication because of the rigorous demonstration of similarity between the biosimilar and the reference biologic drug.

From a pharmacist’ perspective, the challenges with regards to authorization of indications can be summarized as: From a pharmacists’ perspective, the challenges with authorization of indications arise: between curative and non curative settings (ie. what are appropriate endpoints? Is ORR and PFS enough?), between different disease categories (ie. using a biosimilar in gastroenterology versus oncology), as well as with clinician acceptance (will physicians prescribe biosimilars?). Pharmacists worry about these drugs having a range of indications and urge Health Canada to ensure that they understand that they’ll have different properties and mechanisms of action.

## SUPPORTIVE CARE: GASTROENTEROLOGY PERSPECTIVE

USHA CHAUHAN, NP - MCMASTER UNIVERSITY; CAN-IBD/CSGNA REPRESENTATIVE

This presentation aimed at educating stakeholders on the lack of nursing support in Canada and to bring attention to the patient support systems that could change.

### Introduction

Nurse practitioners and nurses working in the gastroenterology field are very familiar with biologics as well as their patient support systems (PSPs) available. However, less is known about biosimilars among supportive care staff.

At the recent IBD meeting in November, the topic of biosimilars was covered. This has raised a number of questions for the nursing community.

“ LESS IS KNOWN ABOUT BIOSIMILARS  
AMONG SUPPORTIVE CARE STAFF. ”

### Considerations

Patients diagnosed with IBD are diagnosed at an early age. This diagnosis of having a chronic illness where a patient must take injectable or intravenous medications for the rest of their life, may be difficult to accept.

There are currently three Canadian biological therapy patient support programs:

- BioAdvance
- AbbVieCare
- YourVantage

PSPs help with the process by organizing the infusion closer to patients' homes, providing injection support, and accessing the drug promptly. Also, the PSPs help with monitoring the drug, by ensuring that antibody screening and biomarker testing are available and these costs are covered.

With the introduction of biosimilars, there could also be changes in support systems. Questions that need to be answered include: What will happen? Will support systems be the same? Will there be prompt access to the drug or will there be a wait period?

### Nursing Support Extrapolation

Extrapolations from studies conducted outside Canada were made:

- The practice model in the UK and Europe infusions occur in the hospital setting.
  - The UK has consistent nursing support throughout hospitals.
  - Overall, there is more IBD nursing support in the UK and Europe (i.e. more than 300 vs. approximately 100 in Canada).
- In contrast, Canada has less clinical nursing support.
  - Most of the nurses are employed in academic centre.
  - Nurses are employed through PSPs.
  - Each center/ doctor's office has a dedicated patient support coordinator working closely with a health care team both in academic and community practice.

### Moving Forward

The CANIBD nurse group within CSGNA was recently formed in the last three years. More education is needed for both general GI nurses and IBD nurses in terms of shift in support systems.

With regards to IBD patients, they need to be educated in terms of:

- Who to call with questions or side effects and which side effects to observe for.
- Need more vigilance regarding which biosimilar received each time.
- Need to self advocate.

## SUPPORTIVE CARE: ONCOLOGY & HEMATOLOGY PERSPECTIVE

DIANA INCEKOL, RN, MSCN, CON(C) - ADVANCED PRACTICE NURSE EDUCATOR AT UHN, CANO-ACIO REPRESENTATIVE

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This presentation aimed at sharing CANO's knowledge/experience about biosimilars with other stakeholders, so that plans can be made to educate moving forward.

Background about CANO:

- CANO was established in 1985. There are approximately 1,000 members across Canada, not inclusive of the pediatric nurses since they have their own organization. Additionally, there are approximately 2,000 other nurses that are not members of CANO.
- CANO's mission: To promote and develop excellence in oncology nursing through practice, education, research and leadership.
- CANO's vision: "A driving force nationally and an influencing force internationally in advancing excellence in cancer nursing across the cancer control spectrum".

### Introduction

Biosimilars are not yet approved for any hematological and solid malignancies in Canada, outside of supportive care indications. Several biologics are coming off patent soon, and while not many biosimilars are approved yet, many are expected enter the market in near future. Several versions of rituximab will be available by 2020. With the introduction of novel cancer therapies, oncology nurses are constantly challenged to keep their knowledge and skills up to date. In 2010, CANO developed a national standards and competencies for cancer chemotherapy nursing practice to address the increasing complexity nurses faced in the areas of chemotherapy and biologics. However, there is a significant knowledge gap among oncology nurses and CANO leadership about biosimilars.

### CANO's Focus

- Canadian oncology nurses need to:
  - Be educated on the impact that biosimilars will have as a whole, as well as individual implications within each centre.
  - Know if a biosimilar is being used and what is the organization's interchangeability policy.
  - Understand of potential differences in AEs.
  - Provide support and teaching for patients and caregivers.
- Greater supports are needed for those who work in non-cancer centres and home-care setting.

### Moving Forward

There is a need for CANO to start thinking about developing a position on biosimilars (a position has been developed in the past on chemotherapy). CANO needs to collaborate with other partners who have previous experiences with biosimilars to create educational strategies to support oncology nurses across Canada.

“ THERE IS A NEED FOR CANO TO START THINKING ABOUT  
DEVELOPING A POSITION ON BIOSIMILARS ”

## POTENTIAL LEGAL LIABILITY FROM NON-MEDICAL SWITCHING BETWEEN BIOLOGIC DRUGS

EILEEN MCMAHON - CHAIR OF DRUG REGULATORY AND INTELLECTUAL PROPERTY PRACTICES, CHAIR AT TORYS LLP

This summary paraphrases the legal presentation at the CARE Congress. The presenter thanks Albert Chan and Yu Seon Gadsen-Chung of Torys LLP for their help. This presentation reflects the views of its author and not necessarily the views of Torys LLP, and is a general discussion of certain legal and related developments. The case studies presented in this presentation are intended to generate discussion. This presentation should not be relied upon as legal advice.

This session aimed to look at: 1) how might persons involved in a non-medical switch face legal liability if there is a non-medical switch, 2) what are the areas of uncertainty that require further consideration by persons involved in a non-medical switch, and 3) why do physicians need to be involved in developing policies on how biosimilars are used and reimbursed in Canada.

### What is Non-Medical Switching Between Biologic Drugs?

A non-medical switch between biologic drugs is illustrated by the following example:

- A patient is being treated with an innovator biologic, is stable, and responding to treatment
- The patient is then switched to a biosimilar, for example:
  - Because the common name for the biologic is written on a script (e.g., Infliximab) and the pharmacist dispenses the biosimilar; or
  - Because a public or private payer has instituted a policy requiring a switch; or
  - Because the patient is paying for his/her own treatment, and has requested a switch to a cheaper alternative; or
  - Because the pharmacist has the authority to make a “therapeutic switch”.
- In each case, there is no medical rationale for switching between the biologic drugs.

### Overview of Liability

There are various publications noting that, generally speaking, Canadians are becoming more litigious.<sup>6</sup>

What significance does this have in the context of a non-medical switch? Consider the scenario where there has been a non-medical switch and a patient’s condition deteriorates, or a patient who used to be compliant becomes non-compliant. Questions for discussion surrounding liability include:

- How might persons involved in a non-medical switch face legal liability? Will non-medical switching lead to litigation? Will widespread non-medical switching lead to class action litigation?
- What are the areas of uncertainty that require further consideration by persons involved in a non-medical switch?
- Why do physicians need to be involved in developing policies on how biosimilars are used and reimbursed in Canada?

The following hypothetical case studies explore these concerns. These case studies are provided to provoke discussion, but do not, to Torys knowledge, reflect action taken to date by any public or private payer in Canada.

#### Legal Liability

Defining legal liability:

- In assessing “harm,” a judge would consider:
  - Whether a patient’s condition worsened as a result of the non-medical switch.
  - Whether it is clear what caused the worsening of the patient’s condition.
  - The role that various persons played in the non-medical switch.



### CASE STUDY #1 – PRESCRIBING SWITCH

In this case:

- A patient has been taking an innovator biologic for several years and the patient’s condition is stable.
- The provincial drug plan directs physicians to switch their patients from the innovator biologic to a biosimilar.
- The physician prescribes the biosimilar to the patient.
- The pharmacist dispenses the biosimilar.
- The patient’s condition worsens (becomes unstable, is less or non-responsive to the biosimilar or the patient becomes non-compliant).



If the patient experiences harm as a result of the non-medical switch and initiates litigation, who might be named as parties to the litigation? Due to the nature of litigation, it is typical for all parties to be brought into the litigation. For example, the legal representative of the person harmed may look to Health Canada and ask, what role has Health Canada played in approving the biosimilar? Did Health Canada directly or indirectly encourage the non-medical switch? Did Health Canada play a sufficiently active role to discourage the non-medical switch?

The legal representative may also look to the payers themselves. What did the public or private payers do to address the non-medical switching? Did they encourage (or even require) the non-medical switching? What role did physicians play in speaking with the patient, such that the patient understands and consented to the circumstances of the non-medical switch? Did the patient fully consent and understand the implications? Further, the legal representative may look to the pharmacist to see if he/she can be brought into the litigation, in addition to the manufacturer.

What is the standard for an applicable Court to determine that there is liability and that someone should be responsible? The standard is negligence – and that is assessed by having regard to the standard of care that would have been reasonable, given the data that was available at the time of the decision making. This standard of care is likely to shift as more studies on non-medical switching are conducted.

Overall:

- In simple terms, this means that a person who has been harmed by a non-medical switch could bring a lawsuit against various parties.
- To assess legal liability, an applicable Court would consider the “harm” caused to the patient and who and what caused the “harm.” If a judgment is rendered against one or more parties, then damages are assessed those parties.



## CASE STUDY #2 – DOSE OPTIMIZATION

Another case might involve a situation where a product monograph contemplates a different dosing regimen:

- A patient has been taking an innovator biologic for several years and the patient’s condition is stable.
- The patient then shows reduced response to the innovator biologic.
- The physician prescribes a higher dose of the innovator biologic.
- The provincial drug plan considers this to demonstrate that the patient’s condition is not stable, and mandates a switch to a biosimilar (at either the prescribing or dispensing step).
- The patient’s condition worsens (becomes unstable, is less or non-responsive to the biosimilar or the patient becomes non-compliant).

The analysis of the situation is similar to that discussed under Case Study #1. Without providing answers, the point here is to start a discussion regarding potential liability, if someone is harmed due to a non-medical switch.



## CASE STUDY #3 – DISPENSING SWITCH

This 3<sup>rd</sup> case is a situation where:

- A patient has been taking an innovator biologic for several years and the patient’s condition is stable
- The provincial drug plan institutes a policy directing pharmacists to interchange the innovator biologic with a biosimilar when dispensing.
- The pharmacist dispenses the biosimilar to the patient.
- The patient’s condition worsens (becomes unstable, is less or non-responsive to the biosimilar or the patient becomes non-compliant).

In this case, the pharmacist implements the non-medical switch. This could happen where the innovator biologic product and the biosimilar have the same common name, and the pharmacist decides to dispense the biosimilar. What are the implications in this situation in terms of potential liability?

The following could potentially be named in a lawsuit:

- The physician who wrote the script.
- The pharmacist who dispensed the biosimilar.
- The hospital or pharmacy at which the physician or pharmacist works.
- The public payer or the private payer who implemented a policy requiring or encouraging the non-medical switch.
- The manufacturer of the innovative biologic, or the manufacturer of the biosimilar.

## Health Canada Approval

Health Canada makes it clear that it reviews in great details the data behind innovator biologics and biosimilars.<sup>7</sup> Overall:

- Health Canada's role is to approve drugs for sale in Canada and Health Canada approves biosimilars before they are sold.
- Can Health Canada's involvement insulate itself against liability?
  - Health Canada's position is clear: approval of a biosimilar does not mean that the biosimilar is pharmaceutically or therapeutically equivalent to the innovator biologic.
  - Health Canada recommends that any switching between innovator biologics and biosimilars be performed only if supported by specialized clinical studies.
  - Health Canada also notes that these specialized studies are not usually performed, and their relevance may decrease as both the innovator biologic and biosimilar undergo independent manufacturing changes.

Health Canada's position<sup>8</sup> on biosimilars is as follows:

- Health Canada **does not support automatic substitution** of a biosimilar for its reference innovator biologic.
- Health Canada recommends that switching a patient from an innovator biologic to a biosimilar is a decision to be made "by the treating physician in consultation with the patient," taking into account available clinical evidence and provincial policies.

Switching a patient from innovator biologics to biosimilars for reasons related to drug costs does not meet Health Canada's recommendation.

**One question to consider:** Having regard to Health Canada's expertise and the significant analysis it performs, how can payers (with less information and less expertise than Health Canada) reach a conclusion that a non-medical switch raises no safety or efficacy issues?

## Conclusions

In conclusion, all stakeholders may ask themselves what role do they play today and in the future regarding non-medical switching. Is it sufficient to sit back and let cost drive the decision? As Canadians and tax payers, of course cost is an important issue, but it is not the only issue. Wise people, whether they are physicians, pharmacists, drug manufacturers, etc., are urged to provide input to form a thoughtful view of the position to take on non-medical switching.

Concluding remarks:

- Payers in Canada (public and private) are investigating mandating use of biosimilar over innovator biologics, in response to budget pressures.
- These moves by payers form part of a greater trend to take greater control over prescribing and dispensing decisions.
- Health Canada recognizes that the choice of treatment should rest with the treating physician and the patient.
- Does the treating physician face legal liability for prescribing decisions, despite policies instituted by the payer?
- The case studies discussed in this presentation are to promote discussion around the implications of non-medical switching.
- Canadian physicians will want to be aware of the downstream consequences of payers taking greater involvement in prescribing decisions.
- Innovator biologics and biosimilars are important therapies for patient care, physicians should have confidence that the right therapy is used for each individual patient.

# KEY TAKEAWAYS

## FROM THE CARE CONGRESS ON BIOSIMILARS

The CARE Congress on biosimilars provided stakeholders with the opportunity to share their perspectives on biosimilars with a panel of leading specialists from across Canada. What follows are the key takeaways from each session presented at the Congress.



### BIOLOGICS ARE INHERENTLY COMPLEX MOLECULES.

It requires much diligence to produce safe and effective products.



### MORE TRIAL DATA IS NEEDED ON BIOSIMILARS.

The NOR-SWITCH trial provided real-world insights into whether it was safe to switch a stable patient to a biosimilar. It appears to be safe to switch when looking at the entire cohort, however, within Crohn's disease showed a 14.3% difference in disease worsening.

Health Canada takes the position that

**A BIO(SIMILAR) IS NOT** pharmaceutically or therapeutically equivalent to the originator biologic drug and should not be considered interchangeable.



With many major biologics set to lose patent protection in the next decade,

### PUBLIC/PRIVATE PAYERS SEE BIOSIMILARS AS AN OPPORTUNITY FOR SAVINGS.

However, they recognize there are challenges to overcome before biosimilars are adopted.



Advocacy groups want what is best for their patients.

### MORE EDUCATION

**NEEDS TO BE PROVIDED TO ALL STAKEHOLDERS,** and everyone needs to work in collaboration with other advocacy groups to help shape policies.

From a pharmacist's standpoint, there are

### 3 KEY CHALLENGES THAT COULD ARISE:

- 1 Naming
- 2 Interchangeability
- 3 Authorization of indications



Canadian physicians, pharmacists, and other relevant parties,

### WILL NEED TO BE AWARE OF THE DOWNSTREAM CONSEQUENCES

of payers taking greater involvement in prescribing decisions.



Nurses in gastroenterology and oncology are familiar with biologics, however

### LESS IS KNOWN ABOUT BIOSIMILARS.

There are concerns with the potential shift in patient support systems.

After hearing from each of the stakeholders, it is clear that knowledge gaps exist and it was apparent that all stakeholders need more education. Given that biosimilars are now available in the market with more to come, it is important for health care professionals, payers, and government, to work together to ensure high quality of care and patient satisfaction/safety is being delivered to patients.

Moving forward, this collaboration must continue to ensure the necessary measures are put into place, to achieve optimal patient outcomes. Over the course of 2017 and onwards, the CARE Faculty will meet and develop educational initiatives in order to do so.



# ABOUT THE CARE FACULTY

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The CARE (Community. Academic. Research. Education) Faculty is a pan-Canadian group of leaders in their field who gather, discuss and address gaps in knowledge, to develop education initiatives that frame news from a Canadian perspective.

The vision of the CARE Faculty is to share opinions and update Canadian specialists with news and developments from key conferences framed in a Canadian perspective.

The mission of the CARE Faculty is to enhance medical education, with the explicit goal of improving patient outcomes.

Learn more at [www.CAREeducation.ca](http://www.CAREeducation.ca)



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