

Biosimilars: State of Clinical and Regulatory Science

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ABSTRACT - Purpose. On May 12, 2017, various issues and challenges associated with biologics were discussed during a session of the annual joint conference of Canadian Society for Pharmaceutical Sciences and Canadian Chapter of Controlled Release Society at Hyatt Regency Hotel, Montréal, QC, Canada. An update on the Canadian regulatory guidelines for biosimilars was given, followed by viewpoints expressed by regulatory, academic and industry scientists. Topics of discussion included: reference biologic drug, clinical considerations, immunogenicity, extrapolation and clarification of terminology, product monograph, international collaboration, switching and interchangeability, naming conventions, clinical and non-clinical evaluation, authorization of indications, statistical equivalence, the nor-switch study and biologics marketplace.

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INTRODUCTION

On May 12, 2017, various issues and challenges associated with biologics were discussed during a session of the annual joint conference of Canadian Society for Pharmaceutical Sciences and Canadian Chapter of Controlled Release Society at Hyatt Regency Hotel, Montréal, QC, Canada. This was a follow up to a workshop in 2015 (1). The session was chaired by Agnes V. Klein of Health Canada, who also presented an update on the regulatory guidelines. The discussion continued by Jian Wang of Health Canada who dealt with the clinical considerations for authorization of biosimilars. Brian G. Feagan of Western University reflected upon a physician’s evaluation of biosimilars, followed by Mark Omoto of QuintilesIMS who dealt with the biologics marketplace.

PRESENTATIONS

GUIDELINE FOR BIOSIMILARS: RECENT UPDATES, FUTURE CONSIDERATIONS

Agnes Klein, Senior Medical Advisor, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario, Canada

Dr. Klein opened the session with the objective demystifying the regulatory framework for biosimilars, aiming to provide the audience with an appreciation of how the framework supports regulatory decision making for these products. It was noted that the Canadian public have become increasingly involved in seeking to understand regulatory decisions and expect Health Canada to follow a robust and transparent process.

In understanding the regulatory assessment of biosimilars, it is important to recognize first that biosimilars are not the same as generic products. In reviewing the Health Canada *Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs* (2), Dr. Klein illustrated the significant differences between the approaches for biosimilars and generics in the Canadian framework.

The foundation of the approach to biosimilar assessment is based on an extensive side by side structural and functional characterization of the biosimilar in comparison to the reference biologic drug, to demonstrate the similarity of the biosimilar

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to the reference biologic drug. Throughout, there is a need to uncover systematically and evaluate the impact of any residual uncertainties regarding the similarity of the biosimilar to the reference biologic drug at each step before proceeding to later stages of clinical assessment (see Figure 1).

The purpose of the clinical program is to establish that any subtle structural or functional differences between the biosimilar and the reference biologic drug are acceptable and do not result in clinically meaningful differences in either safety or effectiveness between the two drugs. A case by case approach tailored to the individual drug is applied, considering factors such as the inherent properties and scientific understanding of the molecule under assessment as well as the reference biologic drug.

In Canada, regulations governing new drugs in Part C, Division 8 of the *Food and Drug Regulations*, provide sufficient flexibility to accommodate the concept of assessing similarity within the regulatory framework when reviewing biosimilars, and thus it has not been necessary to develop new regulations specific to biosimilars. A key concept is that the regulatory assessment seeks a demonstration of *similarity* between the biosimilar and the reference biologic drug, and does not determine that they are *identical*. The demonstration of structural and functional similarity can provide the basis for accepting a reduced non-clinical and clinical data package to support authorization of a biosimilar. Thus, biosimilars are not thought of as “generic biologics”, and authorization of a biosimilar by Health Canada is not a declaration that the biosimilar has been demonstrated to be bioequivalent, or pharmaceutically or clinically equivalent to the reference biologic drug.

Health Canada issued a guidance document in 2010 to communicate the regulatory framework and drug submission requirements for biosimilars to stakeholders. The guidance document was subsequently revised in late 2016 to reflect the accrued experience of Health Canada in reviewing biosimilars over the intervening six years, and

included consideration of the learning from international collaboration, and comments and input from a broad range of stakeholders collected through public consultation.

The key revisions in the 2016 updated guidance document were as follows.

Reference Biologic Drug

Unlike generics which are often developed with regionally customized plans, biosimilars are typically developed for international registration purposes and aim to use a single development program that serves the requirements of all jurisdictions. Therefore, Health Canada accepts the use of non-Canadian sourced versions of the reference biologic drug as a proxy for the Canadian drug in comparative studies.

Where more than one source of reference biologic drug is used in clinical studies, for example where both the US authorized version of the reference biologic drug and the EU authorized version of the reference biologic drug are incorporated in development, as a scientific matter, the type of bridging data needed will always include structural and functional data from analytical studies that compares directly all of the products (e.g. the proposed biosimilar product, the US-authorized product and the EU-authorized product) and may also include clinical pharmacokinetic and, if appropriate, pharmacodynamic data for all the products.

Clinical Studies

Clinical studies are required for proposed biosimilars in order to address any areas of residual uncertainty remaining regarding similarity after structural and functional analyses, and to demonstrate that there are no clinically meaningful differences between the biosimilar and the reference biologic drug. Pharmacokinetic studies may be conducted in healthy subjects when appropriate, as they are usually considered to be a homogeneous and sensitive population. In the event that a well-established pharmacodynamic marker relevant to



Figure 1

the mechanism of action has been characterized, a clinical efficacy study may not be required. During the development program for a biosimilar, a step by step sequential approach is used, which seeks to provide the guidance to allow the inclusion of factors when considering the designing of adequately sensitive studies to rule out clinically meaningful differences between the biosimilar and the reference biologic drug, as will be discussed by Dr. Wang.

Immunogenicity

The 2016 revised guidance includes a new and detailed subsection on immunogenicity and considerations providing additional clarity on the requirements of comparative immunogenicity studies to rule out clinically meaningful differences in immunogenicity between the biosimilar and reference biologic drug. The guidance focuses on addressing areas of greatest concern, such as antibodies that have the potential to impact safety and/or efficacy, for example through altering pharmacokinetics, inducing anaphylaxis, or neutralizing the drug or the endogenous protein counterpart.

Extrapolation and Clarification of Terminology

At the consultation stage, the 2015 draft guidance clearly resulted in confusion of stakeholders on the concept of “extrapolation” and references to extrapolation of clinical data obtained in one indication to support authorization of other indications held by the reference biologic drug. The challenge in clearly communicating the concept of extrapolation in the context of biosimilars has been experienced by Regulators internationally, and extrapolation of indications is the topic of a current concept paper published by the International Pharmaceutical Regulators Forum (IPRF) Biosimilars Working Group (3). In an updated section, “Authorization of Indications”, the final revised guidance clarifies Health Canada’s position to granting indications based on a “totality of evidence” approach. This totality of evidence approach takes into consideration all of the data from comparative structural, functional, and non-clinical studies conducted to demonstrate similarity as well as data from comparative clinical studies conducted to demonstrate that there are no clinically meaningful differences between the biosimilar and the reference biologic drug, for any

of the indications granted to the biosimilar. While the terminology used to communicate the basis for authorization of indications has been revised for clarity, the supporting data requirements remain unchanged.

In response to input from stakeholders and to reduce potential confusion and increase international alignment, the former Canadian terminology of “subsequent entry biologic” has been brought in line with the international terminology of “biosimilar” throughout the guidance document.

Product Monograph

Experience gained in generating the product monographs for previously authorized biosimilars is now reflected in a product monograph template specifically for biosimilars, which will provide clarity and consistency moving forward. Key elements of the template include a statement denoting that indications have been granted on the basis of similarity between the biosimilar and the reference biologic drug. The comparative data generated by the biosimilar sponsor comparing the biosimilar and reference biologic drug is summarized in a clear and easily interpreted tabular format, rather than text format. The template also requires that relevant safety and efficacy information from the product monograph of the Canadian reference biologic drug be incorporated, including warnings and precautions, adverse drug reactions/adverse drug effects and key post-marketing safety information for all indications that are authorized for the biosimilar. This approach to labelling an authorized biosimilar is consistent with the demonstration of a satisfactory degree of similarity to the reference biologic drug, and the expectation that the biosimilar will not perform differently from the reference biologic drug in an authorized indication.

International Collaboration

Health Canada works closely with the World Health Organization (WHO) as well as other regulators to enable information sharing and learning, and to promote regulatory alignment where possible. Specific activities include regular “cluster” teleconferences with the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and active

participation in the IPRF biosimilars working group and WHO biosimilar guideline drafting groups. Relevant learnings from all of these interactions are reflected in the 2016 revised guidance.

Dr. Klein then focused the remainder of her presentation on current issues of debate in the realm of biosimilars.

Switching and Interchangeability

Switching and interchangeability are current topics of both interest and confusion amongst stakeholders. Clear terminology and definitions of switching and interchangeability are critical. Switching is generally taken to refer to a one-time change in a patient's medication, for example moving from a reference biologic drug to a corresponding biosimilar. Health Canada considers switching to be distinct from interchangeability. In Canada, interchangeability typically refers to the ability of a patient to be changed from one drug to another equivalent drug by a pharmacist, without the intervention of the physician who wrote the prescription. Approaches to interchangeability vary somewhat between jurisdictions (see Table 1).

Health Canada is frequently consulted to state positions on switching and interchangeability. Health Canada considers a well-controlled switch from the reference biologic drug to a biosimilar in an approved indication to be acceptable. Health Canada recommends that a decision to switch a patient being treated with a reference biologic drug to a biosimilar, or between any biologics, be made by the treating physician in consultation with the patient, and taking into account any policies of the relevant jurisdiction.

In Canada, authorization of a biosimilar by Health Canada is not a declaration of equivalence to the reference biologic drug, and the authority to declare a product interchangeable rests with each province and territory. Somewhat similarly, in the European Union, authorization of a biosimilar by EMA (5) does not include any recommendation on the interchangeability of the product, and the policies on substitution vary among different member states.

In contrast, the legislation pertaining to authorization of biosimilars in the US includes a

specific definition and associated requirements for a biosimilar product to be designated as an interchangeable biosimilar. As a result, the FDA published a draft guidance document entitled *Considerations for demonstrating interchangeability with a reference product* in January 2017. To date, no interchangeable products have been licensed by the FDA. The FDA draft guidance sets out a rigorous standard of data to be provided in applying for authorization as an interchangeable product, and at this stage, the extent to which biosimilar manufacturers will conduct the types of study outlined in the FDA draft guidance remains to be seen (6).

Naming Conventions

A number of stakeholders, including industry, physicians and patients have called for a naming convention that distinguishes between biologic drugs sharing the same common name, to facilitate accurate prescribing and pharmacovigilance. To date, Health Canada has supported WHO efforts to develop a global naming convention. WHO has developed a proposal for a "biological qualifier" (BQ), a 4-letter suffix to the non-proprietary name, that would be applicable to all biological active substances. However, there have been mixed reactions to this proposal nationally and internationally, and timelines for implementation are currently uncertain. The US FDA is implementing an alternative suffix-based naming convention (7). There is currently no international consensus on a naming scheme (Table 2).

At this time, Health Canada is evaluating the most appropriate naming convention for biologic drugs including biosimilars, taking into account Canadian prescribing, dispensing and pharmacovigilance needs, as well as considering an international approach. As the value of any distinguishable naming convention, whether suffix-based, or brand name-based, is dependent on its uptake by end-users, Health Canada to consult interested stakeholders including pharmacists and physicians to understand the compatibility of different schemes with the electronic systems used for the prescribing, dispensing and tracking of biologic drugs. In the meantime, biologics in Canada are identified by brand name, common or non-proprietary name, and Drug Identification Number (DIN).

Table 1: Summary of approaches to interchangeability of biosimilars by select health authorities

Health Canada	Europe EMA	US FDA
<ul style="list-style-type: none"> Health Canada's authorization of a biosimilar is not a declaration of equivalence to the reference biologic drug The authority to declare two products interchangeable rests with each province and territory 	<ul style="list-style-type: none"> Authorization by the EMA does not include a recommendation on interchangeability Substitution policies vary between member states 	<ul style="list-style-type: none"> Interchangeability designation and standards are mandated by law Draft guidance published by FDA in January, 2017 No interchangeable biosimilar products licenced to date

Table 2: Comparison of approaches to naming of biosimilars by select health authorities

	Health Canada	Europe EMA	US FDA	WHO BQ proposal
Approach	<ul style="list-style-type: none"> Unique brand name Shared common name 	<ul style="list-style-type: none"> Unique brand name Shared common name 	<ul style="list-style-type: none"> Unique brand name Shared common name Unique suffix 	<ul style="list-style-type: none"> Unique brand name Shared common name Unique suffix
Biosimilars distinguished by	<ul style="list-style-type: none"> Brand name DIN 	<ul style="list-style-type: none"> Brand name 	<ul style="list-style-type: none"> Brand name Suffix 	<ul style="list-style-type: none"> Brand name Suffix
Suffix	Under consideration	No	4 letters proposed by manufacturer	4 random consonants

Outreach and Future Directions

Health Canada is keenly aware of a misperception amongst some stakeholders that biosimilars have less rigid pre- and post- market data requirements, and as a new category of drug products, there is a need to actively educate stakeholders on the regulatory review process to build confidence in the safety and efficacy of biosimilars. Avenues for providing appropriate stakeholder education and transparency are being actively pursued, including educational workshops, and ongoing publication of

information on the regulatory review of biosimilars. Publicly accessible Health Canada information sources include the Drug Product Database, Product Monographs, Summary Basis of Decisions documents, listings of submissions under review, regulatory decisions summaries and summary safety reviews. Dr. Klein concluded by stating Health Canada's commitment to continue to undertake regular review of the biosimilars guidance document and to educate stakeholders.

CLINICAL CONSIDERATIONS FOR AUTHORIZATION OF BIOSIMILARS

Jian Wang, Chief, Clinical Evaluation Division – Haematology/Oncology, Center for the Evaluations of Radiopharmaceuticals and Biotherapeutics, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario, Canada

Dr. Wang shared the position of Health Canada on clinical considerations in the approval of biosimilars and discussed potential global convergence among regulatory agencies. After a brief overview of the Canadian guidance document, Dr. Wang proceeded onto more detailed discussion of preclinical and clinical program requirements to

support a demonstration of biosimilarity (8). It was noted that there is no one model development program suitable to fit all biologic molecules. Development programs can be tailored and thus it is recommended that biosimilar sponsors discuss their development plans with the regulatory agencies at an early stage. Health Canada has established a scientific consultation program for biosimilars to facilitate early discussions on the quality comparability package, although to date there have been inquiries from sponsors but no uptake. Unlike generic drugs, biosimilars take a global approach to their development program.

Quality Evaluation

The first critical steps in biosimilar development are to define and then compare the critical quality attributes of the biosimilar and those of the reference biologic drug. A major principle is that the amino acid sequence of a biosimilar is expected to be the same as the reference biologic drug. Due to differences in the cell lines used as well as in the manufacturing, small residual differences between the biosimilar and the reference biologic drug may

exist that require sophisticated modern analytical technology to compare and characterize the quality attributes (Table 3).

Non-clinical Evaluation

Comparative non-clinical studies are conducted following the principles recommended by ICH S6 (R1) including *in vitro* and *in vivo* studies. Currently it is believed that *in vitro* studies are more sensitive to detect potential differences between the biosimilar and the reference biologic drug. Where similarity is well established by structural and functional studies, and where extensive *in vitro* mechanistic studies are indicative of similarity, *in vivo* non-clinical studies may not be necessary. However, if clinical trials are to be conducted in Canada, according to Division 5 (Clinical trial regulations), some animal studies may be requested before the first-in-human study. The necessity of *in vivo* animal studies will depend on the type of biologic, and at a minimum, satisfactory structural, functional and non-clinical *in vitro* evidence of similarity would still be required before commencing the first-in-human studies.

Table 3: Summary of typical methods used to assess quality attributes of biosimilars

Quality Attribute	Methodology
Amino acid sequence and modifications	Mass spectrometry (MS), peptide mapping, chromatographic separation
Folding	S-S bonding, calorimetry, HDX and ion mobility MS, NMR, dyes, circular dichroism, Fourier transform spectroscopy, fluorescence
Subunit interactions	chromatography, ion mobility MS
Heterogeneity of size, charge, hydrophobicity	Chromatography resins; gel & capillary electrophoresis, light scatter, IM-MS
Glycosylation	Anion exchange, enzymatic digestion, peptide mapping, CE, MS
Bioactivity	cellular and animal bioassays; ligand & receptor binding (ELISA, surface plasmon resonance), signal transduction
Aggregation	Analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy
Impurities	proteomics, immunoassays, metal & solvents analysis
Adventitious Agents	sterility, qPCR, bioassays, clearance

Unlike generic small molecule drugs, comparative pivotal pharmacokinetic (PK) studies alone are not sufficient to support authorization, as PK studies do not address the question of how the biosimilar will perform clinically. Comparative PD studies, which may be combined with PK studies, are required to rule out differences in parameters such as bioactivity or immunogenicity. Comparative PK/PD studies are thought to be more sensitive to rule out clinically meaningful differences between the biosimilar and the reference biologic drug than comparative clinical efficacy studies. However, not all biologics have well established, relevant PD endpoints. In most cases, clinical efficacy studies are needed to rule out clinically meaningful differences between the biosimilar and the reference biologic drug.

Clinical Evaluation

Typically, one comparative PK study should be conducted in a setting that is reflective of the clinical situation and/or is sensitive to rule out differences between the biosimilar and the reference biologic drug. The most sensitive PK study design to rule out potential differences is the single dose cross-over design, if the biosimilar half-life is short, and in principle, this is very similar to the approach employed for small molecules. However, many biologics have a long half-life, limiting the utility of a single-dose cross-over design and so parallel and/or multiple dose design studies may need to be considered as an alternative. For products with intermediate half-lives, the sponsors may choose at their own risk to conduct a cross-over study instead of a parallel study. However, the longer length of the washout period required for products with longer half-lives could increase the overall variability and potentially increase the risk of failure of the PK trial. Despite these potential challenges of study design, it is the opinion of Health Canada that a cross-over study remains a better design for a PK/PD comparison study than a parallel group design.

In general, the PK studies can be conducted in healthy volunteers rather than in patients suffering from the disease of interest as they are usually considered to be a homogeneous and sensitive population. This statement reflects a change in Health Canada's position from the original guidance document, which recommended

conducting the studies in the relevant patient population. However, there are situations in which a PK/PD study cannot be conducted in healthy volunteers due to ethical considerations or an anticipated clinical effect. For example, it would be inappropriate to study an anti-CD20 antibody in healthy volunteers due to the anticipated depletion of B cells and associated health risks. Thus, a justification for the choice of the population studied should be provided.

For generic small molecules reviewed under the regulations for Abbreviated New Drug Submissions, bioequivalence standards are well established. Although these standards were developed for generic drugs, the principles should also be considered for biologics. However, attention needs to be paid to the different regulatory requirements in different jurisdictions. Some jurisdictions require that standards be met for AUC_t, AUC_i and C_{max}, but Health Canada standards do not include AUC_i; AUC_t and C_{max} are sufficient. Health Canada requires the 90% confidence interval of the relative mean AUC_t and the relative mean C_{max} to fall within the range of 80% to 125%. The absence of international standards or ICH guidance on bioequivalence standards for biosimilars means that a biosimilar may fail to meet bioequivalence standards in one jurisdiction, but pass in another.

For a biosimilar, a PK study alone is not sufficient. If a PD study is conducted, it is generally part of the PK study. It is also recommended that the PD profile be monitored during any comparative clinical trials in order to gain confidence in the comparability of the biosimilar and to reduce residual uncertainty.

When conducting PD studies, the following factors should be considered:

- Availability of a sensitive PD biomarker/surrogate marker
- Availability of reliable assay(s) for the PD surrogate
- Determination of whether the PD marker is a valid clinical surrogate; any quantitative relationship between the surrogate and a clinical endpoint
- Relevance of the PD surrogate to the mechanism of action
- Correlation between the PK and PD values

The PD endpoint used should be clinically sensitive and relevant. To ensure assay sensitivity, the dosage studied should fall on the steepest part of the dose-response curve. For comparative studies conducted in a healthy population, the therapeutic dose may induce a ceiling effect. For example, if a therapeutic dose of G-CSF is given to a healthy subject, a maximal response of the bone marrow could be expected, and this resulting plateau response would mask any potential differences between the reference biologic drug and the biosimilar. Therefore, in this case, a lower dose or even a sub-therapeutic dose may be justified providing there is dose linearity.

In situations when there is no PD marker or PD surrogate such as with a monoclonal antibody, at least one comparative clinical efficacy trial is required. Since the reference biologic drug has already established efficacy and safety for each authorized indication, biosimilar sponsors do not need to establish de novo a benefit/risk ratio for the biosimilar; instead the purpose of the clinical program is to show that any residual uncertainty arising from the quality assessment is not associated with clinically meaningful differences in efficacy, safety and/or immunogenicity. The clinical trial comparing the biosimilar and the reference biologic drug should be carried out in a population that is sensitive to detect clinically meaningful differences between the biosimilar and the reference biologic drug so that comparative clinical studies would not need to be conducted in all indications.

Determining which population is the most sensitive in which to conduct clinical trials may be a matter of debate, and therefore it is important for biosimilar sponsors to seek advice from various regulatory agencies as there may be differences of opinion on the most appropriate population.

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 reference biologic drug. In general, the guidance is that:

- A homogeneous population would give a better chance to detect potential differences between a biosimilar and its reference biologic drug;
- Observed clinical effects are the direct action of the biosimilar or the reference biologic drug without interference of other concomitant

medication (i.e. settings involving monotherapy preferred over settings involving combination therapy);

- Clinical settings with large treatment effect sizes are preferred in order to rule out any small differences between the biosimilar and the reference biologic drug;
- The mechanism of action involved in the study setting should be well-understood and representative of the indications for which the biosimilar sponsor is seeking authorization

Typically, a large body of historical data is available in the disease under study, for validation of the most appropriate study outcomes.

For biosimilar evaluation, an equivalence trial design should be employed with pre-specified lower and upper boundaries and a primary objective of showing that the response to two or more treatments differs by an amount which is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.

It is important to note that in addition to choosing an appropriately sensitive study population, a sensitive study endpoint is also required. However, this endpoint need not be identical to the endpoint that was used by the innovator in their original study. For example, Objective Response Rate (ORR) or Progression Free Survival (PFS) may serve as a primary endpoint instead of Overall Survival (OS) in oncology trials for biosimilars due to the length of time needed to observe an effect on OS. Also, given the time between the innovator trials and biosimilar trials, new surrogate/s or more sensitive clinical endpoints may have been identified in clinical practice in the interim.

In addition to different study endpoints, consideration may be given to choosing a different clinical assessment timepoint from the original studies conducted to support licensure of the reference biologic drug. For example, if the innovator clinical assessment timepoint of 16 weeks falls within the plateau of response, it may be more appropriate to use an earlier assessment timepoint in comparative clinical studies for the biosimilar, where any differences may be more likely to be detected.

Different agencies may have different

approaches and expectations on clinical and statistical standards (see example in Table 4). Therefore, it is important to discuss the trial design with the different agencies or to design the trial to satisfy the different authorities.

Table 4: Example of potential differences in approach between regulatory agencies regarding clinical and statistical standards for design of biosimilar clinical trials

	Agency 1	Agency 2
Equivalence Margin	±18	±15
Equivalence Margin	asymmetric	symmetric
Confidence Interval (CI)	90%	95%
Statistical Power	90%	80%
Sensitive Population (e.g. oncology)	monotherapy	combination therapy
Statistical Analysis on endpoint (e.g. oncology)	Risk Ratio	Risk Difference
Sensitive Endpoint (e.g. RA)	DAS28	ACR20

Immunogenicity

Most biologics induce some level of anti-drug antibody (ADA) production, and these ADA may have undesirable clinical effects on pharmacokinetics, efficacy and/or safety, including immunogenicity. An assessment of ADAs is a key area of focus during review of biosimilar submissions. There are multiple factors influencing ADA production including:

- sequence variation
- glycosylation
- formulation change
- manufacturing process change
- contaminants and impurities
- route of administration
- dose
- length of treatment
- patient characteristics
- unknown factors

Immunogenicity should be compared between the biosimilar and the reference biologic drug in at least one clinical study enrolling a sufficient number of patients for a sufficient period of time to assess the possibility of clinically meaningful differences in ADA production.

The methodology for immunogenicity assessment should start with the very sensitive screening assays. Next, confirmatory studies are conducted with more specific assays, in order to eliminate false positives due to non-specific binding. These are followed by functional assays to determine if the ADA are binding or neutralizing antibodies. Neutralizing antibodies are of greatest concern and require PK and clinical assessments to determine if there is an effect on PK/PD or clinical outcomes. Surprisingly, some neutralizing antibodies have no clinical effect. Ultimately, the biosimilar should not be more immunogenic than its reference biologic drug in terms of ADA incidence or ADA concentration.

Authorization of Indications

Since a biosimilar is very similar in structure and function to a reference biologic drug with well-established safety and efficacy, clinical studies do not need to be repeated for each indication. However, biosimilars are not automatically granted all the indications of the reference biologic drug. The scientific decision to authorize the requested indications is dependent on the demonstration of similarity between the biosimilar and the reference biologic drug based on data from comparative structural, functional, non-clinical and clinical studies and a detailed scientific rationale for each indication to be claimed.

A biosimilar sponsor is eligible to apply for the indication(s) and condition(s) of use that are held by the reference biologic drug authorized in Canada. However, the biosimilar manufacturer may choose not to seek all indications held by the reference biologic drug. Health Canada may decide not to authorize a certain indication for the biosimilar as a result of scientific or benefit/risk-based considerations. Any scientific or benefit/risk-based concerns are transparently identified within the *Summary Basis of Decision*, published on the Health Canada website following a final decision. In addition, some indications may be impacted by patent (intellectual property or IP) considerations and therefore cannot be authorized.

There are many factors considered by Health Canada in the granting of therapeutic indications including physicochemical characterization, biological activity/mechanism of action, non-clinical studies, PK/PD profile, clinical trial, route of administration, dosage range, monotherapy and combination therapy. The granting of indications is a scientific decision, based on the totality of evidence obtained from all comparative analyses.

Switching and Interchangeability

The US Food and Drug Administration (FDA) has released a draft guidance outlining the data and information needed to support an interchangeability designation under the provisions of the US Public Health Services Act.

FDA expects sponsors to submit data and information demonstrating interchangeability in all of the licensed indications held by the reference product. The FDA will generally consider the totality of the evidence, including analytical similarity and risk of immunogenicity of the reference product. The specific data requirements for each biosimilar will depend on the structural complexity of the molecule. Products with low structural complexity may have low residual uncertainty regarding interchangeability due to high analytical similarity with a reference product, and thus may require less data.

For products used more than once, the FDA expects data from switching studies in one or more appropriate conditions of use. Post-marketing data alone will generally not suffice to support an interchangeability designation. However, such data may be useful in lowering residual uncertainty about interchangeability. FDA will permit sponsors to extrapolate data and information supporting a demonstration of interchangeability in one condition of use to the remaining conditions of use for which the reference product is licensed. The FDA has also stated a requirement in the draft guidance that US sourced product be used for all clinical studies used to support an interchangeability designation.

In contrast, EMA has no official position on interchangeability, as mentioned before by Dr. Klein. Interchangeability is the decision of each member country of EMA. Recently, however, members of the CHMP Biosimilar Medicinal Products working party published a paper discussing opinions on the matter of

interchangeability. These authors consider interchangeability to be the “the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber”.

Health Canada considers well-controlled switches from the reference biologic drug to a biosimilar in an approved indication to be acceptable. Health Canada recommends that a decision to switch a patient being treated with a reference biologic drug to a biosimilar or between any biologics be made by the treating physician in consultation with the patient and taking into account any policies of the relevant jurisdiction.

In response to a question from an audience member, Dr. Wang explained that this is a position statement by Health Canada; it is not under federal jurisdiction to determine when switching is to occur, much like it is not federal purview to decide on interchangeability.

When Health Canada, the FDA or EMA refer to interchangeability with respect to biosimilars, it is important to understand that these agencies are referring to the ability to interchange from a reference product to a given biosimilar. This differs from the traditional concept of interchangeability used for small molecules whereby in practice, interchanging back and forth amongst the reference product and other generics of the same class is acceptable.

From a clinical perspective, currently, some biosimilar sponsors have designed clinical trials intended to support decisions on interchangeability or switching. An example of a multiple switch study design is presented in Figure 2.

As new biosimilars are developed, data may become available to satisfy FDA interchangeability requirements, such as multiple switches, switching biosimilar and reference biologic drug arms, comparisons to arms of continuous treatment with reference biologic drug or biosimilar, use of appropriate statistical power and controls. Health Canada could consider meaningful results from well conducted studies of this sort, for inclusion into the Product Monograph, when there are well defined, pre-specified endpoints, appropriate sample size and statistical power for the analysis, of these studies.

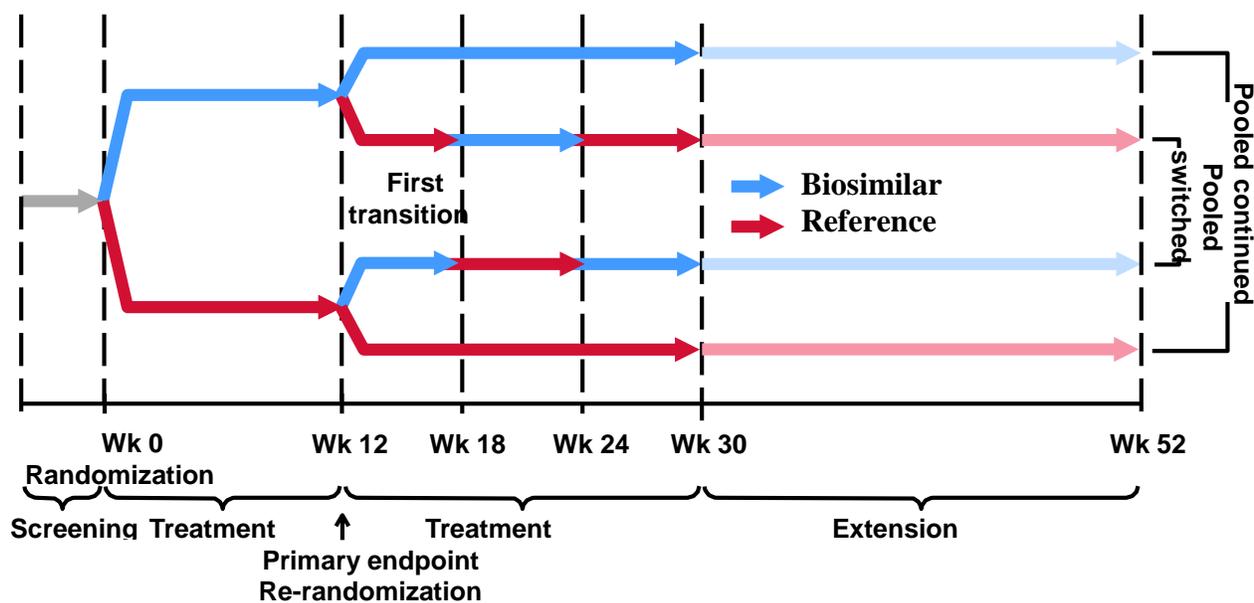


Figure 2: Example of a potential study design incorporating multiple switches between a biosimilar and reference product

In conclusion, authorization of a biosimilar by Health Canada means that the biosimilar has met all quality, safety and efficacy requirements. Authorized biosimilars are functionally and structurally similar to the reference biologic drug, with no clinically meaningful differences in safety and efficacy between the two drugs in the authorized indications granted to the biosimilar.

A PHYSICIAN'S EVALUATION OF BIOSIMILARS

Brian Feagan, Professor of Epidemiology and Biostatistics, Western University, London Ontario

Dr. Brian Feagan started by stating that while regulators and clinicians might not always agree about the role of biosimilars in treating chronic inflammatory diseases, they are aligned to the principle that biosimilars are not identical to the reference product and that biosimilars are not generic drugs.

The human immune system has evolved to do one thing very well, to recognize “self” from “non-self”. The environment in which a foreign protein presents itself to the body is very important in determining whether sensitization or tolerization occurs. This concept leads us to one of the key

questions relating to the issues of interchangeability or non-medical switching of biosimilars, which were discussed earlier in both Dr. Klein's and Dr. Wang's presentations. In fact, interchangeable use of a biosimilar with intermittent exposure may be the ultimate stress test for sensitization due to “priming” of the immune system - intermittent exposure to similar but not identical antigens. Thus, it is somewhat amazing to clinicians that the European Medicines Agency is so confident regarding the risk of sensitization attendant to non-medical switching, given that nothing is known about the immunogenicity of repeated switching between biosimilars.

It is well known that protein structure consists of primary, secondary, tertiary and quaternary structures, but it is the quaternary structure and the glycosylation patterns that determine the response of the immune system. Post translation glycosylation by human/mammalian cells is not a precise process, and is not easy to control. Consequently, glycosylation can be highly variable dependent upon culture conditions. Multiple branch points are present on carbohydrate side chains, each introducing a degree of freedom in the final quaternary structure, ultimately providing the opportunity for an infinite number of structural configurations.

When T cells evaluate the 3D structure of protein molecules, they are influenced by the glycosylation pattern, and sensitize or tolerize based on the nature of the structure they encounter. Due to the huge heterogeneity in glycosylated structures, it is almost impossible to predict the potential impact on immunogenicity without obtaining empiric data.

Dr. Feagan recounted that at a recent conference, he was reassured by a meeting attendee that the molecular species in any given mixture of a biological preparation can be reliably evaluated. However, given his understanding that the method employed uses enzymes to digest the carbohydrates prior to separation on HPLC, it may be true that percentage changes in sugar moieties may be detected, however this technology does not characterize the 3D structure of the protein, nor predict the immunogenicity profile of the product.

Dr. Feagan indicated that the two issues that clinicians care about most are interchangeability and non-medical switching, and their relationship to immunogenicity, and that these topics would be his primary focus. However, Dr. Feagan first mentioned that from his viewpoint, although regulatory authorities have concluded rightly that biosimilars are not generic drugs, there appear to be two aspects of the generic drug approval process that have carried over into the evaluation of biosimilars:

Extrapolation of Indications

While Regulators use the term “assay sensitivity” (a terminology more at home in the world of generic drug bioequivalence studies) in assessing the clinical trials in support of biosimilarity and indication extrapolation, clinicians might state this more simply as identifying the clinical setting in which, should a difference exist between the two products, the difference will be detectable with high sensitivity and specificity. Dr. Feagan noted the concern within the community of gastroenterologists regarding the experience to date with indication extrapolation, where studies conducted in rheumatoid arthritis (RA) have served as the basis for granting indications in inflammatory bowel diseases. The ACR20 score used in RA studies is perceived by clinicians as a rather insensitive endpoint, and indeed RA itself may be considered a rather homogeneous disease, which may potentially minimize the ability to detect differences between the reference and biosimilar

product. For example, the pharmacokinetic challenges experienced with monoclonal antibodies used in ulcerative colitis (UC), where clearance of the drug occurs in large part through the gut, gives rise to a wide inter-patient variance in PK/PD relationship, not observed in RA. Dr. Feagan indicated that, in his opinion, UC is a more “assay sensitive” indication in which to properly assess residual uncertainty, and that the decision to conduct clinical studies in RA may have been dictated by reasons of prevalence.

Statistical Equivalence

A second concept which has been carried over from the generic drug framework is the use of equivalency designs to demonstrate biosimilarity. Dr. Feagan stated that as a clinician, the key interest is simply to know that the biosimilar is not inferior to the reference product, and herein lies a problem. Figure 3 (8) shows an example of the key parameters of sample size calculations for different statistical claims in Crohn’s disease. First it is necessary to declare a minimum clinically *significant* difference (i.e. the smallest difference that clinicians or patients would think is important), which in Crohn’s disease is typically considered to be approximately 15%. In a superiority trial, this would result in a required a sample size of about 300 patients. However, if statistical claims of non-inferiority or equivalency are desired, then the sample size increases enormously. For these statistical tests, first a clinically *insignificant* difference must be declared, which is challenging conceptually and something of a clinical judgement. For a monoclonal antibody, it may be reasonable to consider half of the clinically significant difference, i.e. about 7.5% in the example. Based on this assumption, the sample size for a non-inferiority study is upwards of 1500 patients, and for an equivalence design, the sample size required would be even greater. However, so far none of the equivalency studies seen with biosimilars reflect this sample size requirement.

Dr. Feagan stated his assumption that this relaxation of required sample size and boundaries for non-inferiority by regulatory authorities is based on a reliance on the extensive pre-clinical analytic assessment of the biosimilar, which while understandable is not reassuring to clinicians. From a clinical perspective, with the FDA, EMA, and Health Canada having all approved the biosimilar

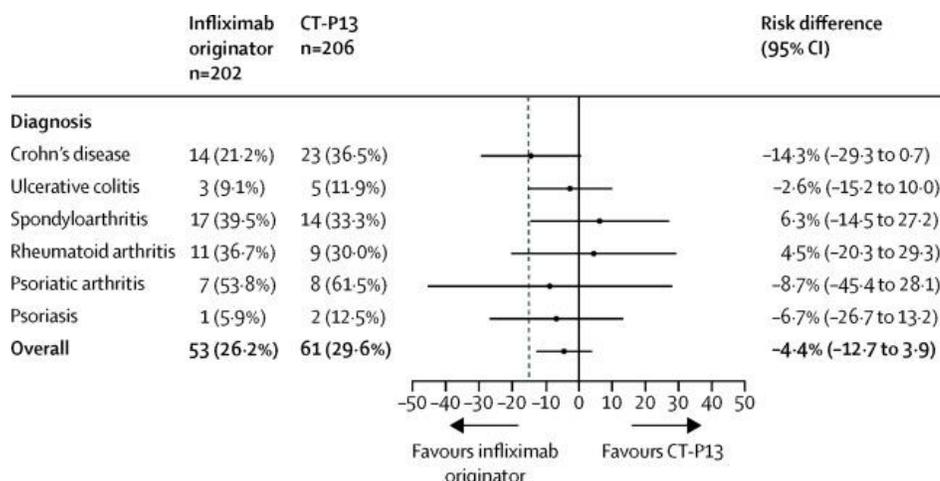


Figure 3: NOR-SWITCH study results (From reference 9 with permission)

treatment in inflammatory bowel disease (IBD) by extrapolation, new patients are now started on the biosimilar in all jurisdictions. However, it is important to note that Health Canada has not endorsed non-medical switching i.e. automatic substitution at the level of the pharmacist.

Interchangeability and Switching of Biosimilars

Various switching scenarios can be envisaged, including multiple switches and simple one way switch. With the FDA recently approving a second biosimilar infliximab, potential future scenarios will include switching between the reference product and 2-3 or potentially multiple biosimilars. Such scenarios could set the stage for immunogenicity if there are molecular differences between the mixtures of drugs, and this might be the precise reason for the recent FDA guidelines on interchangeability.

The concepts that govern sensitization versus tolerization were established by MacFarlane Burnet, Peter Medawar and collaborators in the 1940s and that led to the framework for modern transplantation. The basic premise here is that T cells recognize the three-dimensional shape of immunogens. Multiple factors govern sensitization to a foreign protein including the genetic make-up of the host. In fact, mice can be bred to be sensitized or tolerized to specific antigens.

Other factors influencing immunogenicity include the route of administration (subcutaneous administration is typically more sensitizing than intravenous administration) molecular weight (with larger proteins tending to sensitize more frequently)

and the influence of concomitant treatments (for example methotrexate is frequently co-administered with biologics in RA patients but rarely in IBD patients, and may tend to dampen immune sensitization). Administration schedule also matters, with intermittent dosing with monoclonal antibodies having proven to be immunogenic, whereas continuous dosing tends to be tolerizing. Dr. Feagan reflected that gastroenterologists have learned the hard way with the intermittent use of infliximab without anti-metabolite therapy, where 40% of patients show sensitization within 1 year. Additionally, the highest doses evaluated in almost every trial have typically exhibited lower rates of anti-drug antibodies (ADA) than the lowest doses.

It is important to recognize that humanization of proteins has not solved the problem of immunogenicity. The proportion of patients developing ADA to a fully human monoclonal antibody increases over time. About 30% of patients sensitize, but most of this occurs in the first 8-12 weeks. The cell line of origin does not help determine whether a patient will sensitize or tolerize. What is critical, however, is that once a patient has become sensitized, they are unable to return to the same treatment in future.

If there is a risk of immunogenicity that is related to differences at the molecular level, then how should this be properly assessed? From a clinician's perspective, well designed switching studies are needed and this conclusion is shared by the FDA, who are giving a very clear message to industry to mandate the manufacturer to complete the proper switching studies. Dr. Feagan suggested

that a proper switching study should be required in Canada to address the concerns of clinicians regarding immunogenicity, and that this would be good for patient care by alleviating the conceptual problem that physicians have with jurisdictionally forced switching (that is non-medical switching, driven by Health Policy rather than the decision of the treating physician). When switching patients in remission, the only gain would be reduced cost, and most patients and their physicians operate in a “don’t fix if it ain’t broken” mode. That concept is really the essence of the concerns that clinicians and patients have against non-medical switching.

The NOR-SWITCH Study

The NOR-SWITCH study was an attempt by academic investigators and the Norwegian government to address the question of non-medical switching (8). Given the population of Norway, a country much smaller than Canada, it was logistically necessary to take patients across multiple disciplines who were in stable remission for 6 months on originator infliximab and then randomize them to a one-way switch to biosimilar infliximab (CT-P13) or to continue on the originator. NOR-SWITCH was not a multiple switch study, therefore, could not address the question of sensitization. The design was a one-way switch study with an observation period of 52 weeks that looked at clinical endpoints. It is not ideal as the patient population comprised 6 unique disease entities. The study attempted to apply a common outcome measure to those various clinical conditions. Patients with Crohn’s disease and ulcerative colitis comprised almost half of the enrolled population.

The study used a non-inferiority margin of 20%. The point estimate favoured the reference product, but the two-sided 95% confidence interval overlapped. While the trial is technically positive, showing the biosimilar is not inferior to the reference product, data from the subgroup analysis is hard to interpret especially without a pre-specified endpoint. The data showed that the Crohn’s disease point estimate touches the line of identity with a point estimate of minus 14.3% (95% CI -29.3, 0.7) in favour of the reference product. Therefore, one cannot put too much weight on post-hoc interpretation of this finding due to all the usual caveats.

The NOR-SWITCH study concluded that a

one-way switch from reference product to biosimilar is effective and safe. However, the study methodology was weak, the precision of the estimates was crude and the trial did not address the potential risks of immunogenicity from multiple switches. Therefore, a critical question remains. Are interchangeability and non-medical switching provocative maneuvers for triggering immunogenicity?

Dr. Feagan closed his presentation by illustrating the question using the “snowflake” analogy. No two snowflakes are identical, and based on the side chain branching paradigm on glycosylation discussed at the start of the presentation, it can be imagined that no two molecules of infliximab are identical in a given vial of product. One interpretation of the question is that this experiment of differentially exposing patients to different types of molecules over different time points has essentially been done already and relates to the 10% immunogenicity rates observed with today’s monoclonal antibody therapy. Alternatively, a subtly different mixture or exposure to repeated switches involving exposure to different biosimilars might be more immunogenic than continuous exposure to the reference product despite its inherent molecular heterogeneity. The answer to this question is unknown, and empiric data from controlled studies are needed to provide an answer. This conclusion is reflected in a recent FDA guidance on this topic, and stated his belief that clinicians and regulatory authorities need to work together to further evaluate this issue, and stated that while he expects that multiple non-medical switches do not confer a substantial increased risk of immunogenicity, this needs to be proven before payers arbitrarily switch patients who are stable on current reference therapy.

BIOLOGICS MARKETPLACE: DISRUPTION AND MATURITY: IMPLICATIONS FOR THE NEXT EVOLUTION OF BIOLOGICS IN CANADA

Mark Omoto, General Manager, Corporate Affairs, QuintilesIMS, Toronto, Ontario, Canada

Mark Omoto presented a landscape view of the biologics market to shed light on why there are so many questions about biosimilars. He discussed current challenges in specific markets, and offered

his opinion on the future of the marketplace.

In Canada, the prescription biologic and small molecule market is about 25 billion dollars. In 2017, biologics account for about 27% of total prescription pharmaceutical in the Canadian market, yet they only represent about 1.7% of prescriptions written. In 2009, the top selling products were mainly small molecules. The marketplace has evolved so that in 2017 biologics now represent 7 of the top 10 selling products.

Biologic and specialty products have dramatically shaped the Canadian pharmaceutical market. On the clinical front, biologic products have changed the treatment paradigm in multiple therapeutic areas ranging from Oncology to Immunologic diseases, such as Rheumatoid Arthritis, Ulcerative Colitis and Psoriasis. These products have made a significant impact on patient's lives and outcomes.

In the product pipeline of pharmaceutical companies almost 30% is comprised of biologics. What is striking is that the products in development are for diseases mostly considered primary care conditions such as cardiovascular disease, CNS, and Alzheimer's. As these new and potentially more expensive therapies become available, it will raise budget impact and cost concerns at both the government and private payors level.

In terms of regulatory approvals of biosimilars, Europe and Japan are the furthest ahead while Canada and the US have a mid-range number of approvals. The impact worldwide is that three geographic regions, the US, EU, and Japan, represent 86% of total global biologic sales and they also account for about 93% of biosimilar sales. The way commercially things are evolving, other regions are mimicking the way things are going in Europe and the US. In Canada, in terms of biosimilar approvals there has been a time difference of about 3-5 years compared to Europe, and consequently Canadian and U.S. commercial experience with biosimilars has been very limited, while Europe has had multiple biosimilar products available for over 10 years. Recent Canadian approvals for biosimilars have the European commercial model to benchmark the potential impacts on product uptake and reimbursement.

Regulatory agencies like Health Canada, EMEA, and the FDA are considered ahead of the game in developing frameworks and guidance for biosimilar approval. As pharmaceutical companies

are rushing to commercialize their products, they are navigating the changing worldwide regulatory landscape to get approval. Every day earlier that a product gets approved has an impact in terms of timing of commercialization.

Once a product is approved, commercializing and trying to generate sales requires getting coverage through the private market or the provincial/public drug coverage. For provincial coverage, once a product goes through the CADTH review process a recommendation is made regarding the suggested rate of discount for the biosimilar relative to the name brand biologic. To date in Canada, these listings have included a recommended discount of 25% or more for the biosimilar.

In the reimbursement process, there is a lot of grey area. A listing price may not end up being the actual price that a government body will pay through these confidential agreements and so there is a lot of interest from payors for transparency of pricing. The commercial landscape for biologics is becoming increasingly complicated as we have reached a stage where name brand biologics are launching into the marketplace with multiple biosimilars and/or "Me-too" biologics resulting in a hyper competitive pricing and market access environment.

Based on a snapshot of products that are about to lose their patents and the commercial value they represent, there are significant potential revenue opportunities and biosimilars are moving into this market place very quickly to capitalize on these opportunities. The Patented Medicines Review Board, the agency that oversees the maximum allowable price for patented medicines in Canada, conducted their own analysis of a select group of biologics for the potential impact to the marketplace if their biosimilars were introduced into Canada. The conclusion of that analysis was the potential to realize savings in the range of 8-43%. The reason for this wide range is due to the potential differences in authorized indications for biosimilars versus the reference product.

For manufacturers, there are 3 things that are driving the biosimilar marketplace. First, there are big players in terms of pharmaceutical companies who have been involved in developing biologics that are looking at whether they can expand by getting into the biosimilar market place. Next, biosimilar uptake is driven to a large degree by

savings and cost impacts to our health care system by both public and private reimbursors. The other component driving the biosimilar marketplace is patient access. Anticipated cost savings from biosimilars needs to be balanced by the desire for innovation in part driven by patients seeking access to breakthrough therapies to achieve better health outcomes.

Biosimilar Uptake

Mr. Omoto presented the latest biosimilar penetration data for Europe for the selected products infliximab, insulin glargine and etanercept. In Europe, there is a wide range of uptake. For example, infliximab treatment share ranged from 19% in France to 93% in Norway relative to the market share of their name brand biologic. In some cases, uptake is further complicated when there are multiple biosimilars of a given molecule the marketplace.

In Canada, the best information on biosimilar uptake comes from for infliximab claims data. This data shows the shares or the emerging shares are 4.3% in Ontario, 1.6% in private plans and 0.6% on RAMQ for patients receiving biosimilar infliximab. Mr. Omoto remarked that you would expect to see more market share. What is unique in Canada currently is that across the country for the biosimilars of infliximab and many others, drug reimbursors are requiring that all new patients would automatically be started on the biosimilar.

The question has been raised as to why there are so many differences between the countries, jurisdictions, and between molecules in terms of biosimilar uptake. The differences can be driven by the differences in health care systems and mechanisms for drug acquisitions. Many of the smaller Norwegian-like countries are on tender systems resulting in prices getting driven down. There are also different types of price reimbursement systems with mixes between public and private systems in different jurisdictions. There are also implications due to differences in authorized indications by jurisdictions. In addition, name brand companies employ different strategies to retain and promote use of their product.

Future Trends

One of the factors that is going to influence changes in the marketplace is when multiple biosimilars of the same reference product become available. In

five years, the Canadian marketplace is going to be close to 35 billion dollars in total pharmaceutical sales. Based on QuintilesIMS forecasting, biologics and biosimilars would account for 8 billion dollars. It is expected that increased competition is going to drive down costs. However, given the short history of some of these biologics and the significant impact they have had on patients' lives, there is a natural hesitancy on the part of physicians and patients to discontinue a patient from an originator product that is working well in exchange for a biosimilar.

We will start to see an era of "Me-too" biologics and multiple molecules of the same biosimilar with the potential for private and public reimbursement policies moving towards the small molecule generic type model. There is the realization that drug coverage is not a bottomless pit so value is going to have to drive the appropriate price. At the same time, biologics offer amazing opportunities for innovation in terms of patient benefits and savings down the road. The challenge for the next chapter is how is our changing reimbursement landscape and all of the initiatives that are going on at the federal and provincial level going to impact the marketplace and continue to deliver value to patients and the health care system.

Editorial note:

For speaker biographies check
<http://dx.doi.org/10.18433/J3P36G>

For the US FDA's guidance to statistical approach to evaluation of analytical similarity visit
<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm576786.pdf>

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