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Health Canada/BIOTECANADA Summit on regulatory and clinical topics related to subsequent entry biologics (biosimilars), Ottawa, Canada, 14 May 2012

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ABSTRACT

In May 2012, Health Canada and other participants held a National Summit on Subsequent Entry Biologics (SEBs). Health Canada released a guidance document in March 2010 describing policy positions and data requirements for approval of SEBs. While Health Canada and health agencies in other regulatory jurisdictions are aligned on many scientific principles related to biosimilar drugs, Health Canada's specific requirements may not be widely understood by many Canadian stakeholders. The Summit provided an opportunity for education and dialog among physicians who prescribe biologics, provincial payers, and industry on the following topics: preclinical and clinical comparability studies; manufacturing and other product differences; extrapolation of indications; substitution and interchangeability of SEBs with reference biologic drugs in clinical practice; payers' current perspective; pharmacovigilance and naming. It is anticipated that the consensus reached at this meeting will further educate Canadian healthcare professionals, provincial payers, and insurers about the appropriate use of SEBs, and may be of general interest to others internationally.

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1. Introduction

As patents on biologic drugs expire, biopharmaceutical companies have been developing subsequent versions of originator biologic agents. The term “biosimilar” has been coined to reflect that these biologic drugs, which are produced in living systems, are not identical to their respective reference products. Major health agencies have held multilateral discussions on key scientific and regulatory issues [1,2], and most jurisdictions have issued guidance documents describing scientific principles and data requirements

for the approval of these biosimilar drugs. The European Medicines Agency (EMA) issued the first guidelines in 2005 and 2006 [3,4]. The World Health Organization (WHO) and Health Canada issued guidelines in 2009 and 2010, respectively [5,6]. The US Food and Drug Administration (FDA) released draft guidelines in 2012 which will be finalized after consideration of comments from stakeholders [7,8].

While the above-named agencies are aligned on many scientific principles related to biosimilar drugs (known as subsequent entry biologics in Canada, or SEBs), and despite an extensive pre-publication consultation process, Health Canada's specific requirements may not be widely understood by many Canadian stakeholders. Provincial bodies and prescribers are facing important questions such as interchangeability between SEBs and their respective reference biologic drugs (RBDs), and only one SEB has been approved in Canada to date (which occurred prior to the

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finalization of Health Canada's guidance [9,10]). Therefore, an in-depth discussion and clarification of the scientific principles applied by Health Canada in its guidance document would allow prescribers and payers to make informed decisions in practice and reimbursement as more SEBs enter the Canadian market.

In May 2012, Health Canada and BIOTECANADA (the Industrial Biotechnology Association of Canada) jointly organized a National Summit on SEBs. Panelists (who are authors of this report) consisted of directors and scientists from the review bureau of Health Canada, clinical specialists who are prescribers of biologic drugs, scientists who specialize in biologics manufacturing, pharmacokinetics (PK) and pharmacodynamics (PD), and also a reimbursement specialist. In addition, over 20 observers attended the Summit, including Health Canada reviewers and policy specialists, private insurers and provincial payers, industry, academic scientists, the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Government of Canada's Patented Medicine Prices Review Board.

2. Opening remarks

Dr. Kay (rheumatologist, UMass Memorial Medical Center, University of Massachusetts Medical School) chaired the Summit and opened with an overview of regulatory aspects of biosimilars in the European Union (EU) and the United States (US) to set the stage for discussion of the regulatory pathway for approval of SEBs in Canada.

Biosimilars, unlike small molecule drugs, are not generic medicines, as they are not identical to their respective RBDs. Preclinical and clinical studies must be carried out to demonstrate that biosimilars and their RBDs have comparable efficacy and safety. Dr. Kay posed several key questions about biosimilars: Will a biosimilar drug be as safe and effective as its RBD? Will dispensing pharmacists be able to substitute a biosimilar for the RBD and could this substitution adversely affect patients. Will the availability of biosimilars reduce the cost of biologic therapies?

Dr. Kay provided an overview of the statutes governing the licensure of biologic drugs in the US [reviewed in [11,12]]. The Patient Protection and Affordable Care Act of 2010 was signed into law on March 22, 2010. Section 7002 of this statute, called the Biologics Price Competition and Innovation Act (BPCIA) of 2009 created an abbreviated Biological Licensing Application for highly similar biologic products. Dr. Kay reviewed the pathway for approval of a biosimilar, consisting of non-clinical and clinical studies and post-marketing pharmacovigilance monitoring, that is specified in the Act.

Dr. Kay also reviewed EMA guidelines for the approval of biosimilars, including the non-clinical and clinical studies and post-marketing commitments that are required of biosimilar manufacturers [3,4]. In addition, he reviewed the EMA draft guideline for assessment and approval of biosimilar monoclonal antibodies (mAbs) [13].

Dr. Kay focused on the aspect of interchangeability as defined by the BPCIA. According to the BPCIA, a biological product can be deemed interchangeable with a reference product only if it is "biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient." Also, "the risk in terms of safety or diminished efficacy of alternating or switching between the biosimilar and the reference product [must not be] greater than the risk of using the reference product without such alternation or switch." He highlighted that a clinical trial to meet these criteria must be designed to demonstrate that patients switching repeatedly between the two biologic drugs would not experience greater safety risk than patients receiving the biosimilar or the RBD alone without

switching. Such a study presumably would involve multiple switches between the RBD and biosimilar. Dr. Kay considered that, because such a study might put subjects in the experimental group at risk for developing antibodies to either or both biologic drugs without providing benefit beyond that experienced by control subjects receiving the RBD, institutional review boards might view the study design as unethical because of an unacceptable risk-benefit ratio.

Interchangeability between biologic drugs is much more problematic than interchangeability between small molecule drugs. Dr. Kay highlighted that a patient who is switched between two biologic drugs might develop anti-drug antibodies (caused by small differences in post-translational modifications of the proteins and/or product/process-related impurities), which could compromise efficacy and safety. Such immunogenicity was observed when EPREX[®] underwent a change in formulation that resulted in the induction of antibodies to erythropoietin, possibly caused by leachates from the rubber stopper of the syringe. The development of antibodies to this non-redundant hormone resulted in over 200 cases of pure red cell aplasia [14,15].

Dr. Kay stated that the draft FDA guidance does not specify requirements for the clinical trial size, duration or non-inferiority versus equivalence design [7,8]. If there is sufficient scientific justification, the FDA may allow data from a clinical trial of the biosimilar in one disease to be used to support approval of the biosimilar for other indications for which the RBD is already licensed (e.g., if the biologic drug has the same mechanism of action in these disease states). Dr. Kay raised a potential problem with such data extrapolation. For example, ENBREL[®] is licensed for the treatment of rheumatoid arthritis at 50 mg per week but must be used at double that dose (50 mg twice weekly) to achieve efficacy in psoriasis. Thus, could a biosimilar etanercept be deemed effective for treating psoriasis based on a clinical trial in rheumatoid arthritis, given that the effective doses of ENBREL[®] are different in the two diseases?

Dr. Kay concluded by stating that the details of how the FDA will implement the abbreviated pathway for approval of biosimilars created by the BPCIA are still being worked out, and that no biosimilar has yet been approved in the US using this regulatory pathway.

3. Overview of Canadian guidance and international update

Dr. Nyarko (Office of Policy and International Collaboration, Health Canada) provided an overview of the Canadian guidance on SEBs and clarified a number of critical aspects. Dr. Nyarko stated that Health Canada uses a science-based, pragmatic approach to the evaluation of SEBs, and that this approach is aligned with international best-practice guidelines to which Health Canada has contributed.

Health Canada's definition of an SEB is a drug that would enter the market subsequent to a named reference drug to which it would be similar. Both conditions (i.e., "subsequent to" and "similar to" the RBD) must be met. The approval of an SEB will rely, in part, on information about the RBD for the demonstration of similarity. The SEB sponsor is responsible for providing the necessary evidence to support all aspects of an application for establishing biosimilarity and achieving marketing authorization. Health Canada will not assist an SEB sponsor by providing any information from the dossiers of an approved RBD. Many characteristics of the marketing authorization process and marketed use of generic pharmaceutical drugs do not apply to SEBs. Therefore, the authorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the RBD. Since the submission of an SEB involves a comparison to an RBD, the principles of intellectual

property, patents, and regulations for data protection apply to these submissions.

Once a Notice of Compliance (approval/marketing authorization) is issued, the SEB will be regulated as a stand-alone biologic drug similarly to an innovator biologic drug. Therefore, once the SEB is approved, any subsequent changes to the RBD will not automatically apply to the SEB. The SEB would require relevant clinical and non-clinical data to support any additional changes to the product monograph.

The evaluation of an SEB involves a side-by-side demonstration of similarity to the RBD. A full chemistry and manufacturing data package is required, plus an extensive side-by-side characterization of the SEB and RBD as per the principles of ICH Q6B [16]. The comparability principles outlined in ICH Q5E also apply [17]. The results of the comparability exercise should demonstrate a high degree of similarity between the SEB and RBD and will determine the extent of additional non-clinical and clinical investigations required. Therefore, an SEB should be developed (and evaluated) in a stepwise manner.

Dr. Nyarko stated that comparative non-clinical and clinical studies should be designed to detect any differences between the SEB and RBD. Health Canada recommends conducting non-clinical studies prior to the design and initiation of clinical studies. Clinical studies should be provided for each indication being sought, and must have statistical power to detect major differences in safety. In justified cases, a comparative PK/PD data package to bridge two or more indications may be sufficient.

As per Health Canada's guidance, safety data from a sufficient number of patients in a study of sufficient duration should be provided to compare the nature, severity, and frequency of adverse reactions between the SEB and RBD. The immunogenicity of the SEB should be tested using state-of-the-art methods in terms of its effects on both efficacy and safety. In cases where a high degree of similarity between the SEB and RBD cannot be established, Health Canada will not consider the SEB biosimilar to the RBD, and a full dossier including complete non-clinical and clinical data will be required for approval.

A final determination of similarity will be based on a combination of analytical testing, biological assays, and non-clinical and clinical data. The demonstration of comparability does not necessarily mean the quality attributes of the two products are identical, only that they are highly similar. A decision to issue a Notice of Compliance is based on a risk-benefit assessment after considering all of the safety, quality and efficacy data submitted by the sponsor. The same principle is applied during review of any medicinal product. In a manner consistent with Health Canada, FDA describes this approach as considering the totality of the evidence.

The indications granted to an SEB in Canada will be based on data provided by the SEB sponsor. If the sponsor does not provide sufficient data, the SEB will not automatically be approved for all indications held by the RBD. Furthermore, if the SEB sponsor applies for indications not approved for the RBD, full clinical trial data packages are required. Authorization of an SEB is not a declaration of interchangeability or substitutability between the SEB and RBD.

A Risk Management Plan (RMP) for an SEB should be presented to Health Canada prior to marketing authorization. Plans for monitoring immunogenicity, inherent safety concerns, and unknown safety signals that could result from the impurity profile and other characteristics of the SEB should be agreed upon. Adverse reactions are reported as required by the Food and Drug Regulations as is the case for any other medicinal product. Submission of Periodic Safety Update Reports (PSURs) will be required as per ICH E2E guidelines.

With respect to harmonization of regulations among regulatory jurisdictions, Dr. Nyarko commented that Health Canada, EMA and

draft FDA guidelines follow many of the same scientific principles [3,4,6–8]. WHO guidance was released around the same time as the Health Canada guidance, and WHO continues to conduct implementation activities and workshops so that other regulators can adapt the WHO guidance as appropriate [5]. He provided an update on a Biosimilars Workshop held at a recent international APEC Harmonization Centre Conference in Seoul, Korea, which was attended by several International Regulators as well as industry [18]. Discussions confirmed that the scientific principles for evaluation of biosimilars are consistent among most regulatory authorities, and that the Canadian guidance on the use of reference products not approved in the country of filing is being adopted internationally.

Acknowledging the lack of major safety concerns to date for biosimilar products approved in the EU, Dr. Nyarko clarified that some products on the global market do not meet the Canadian, European or US criteria for SEBs, and highlighted the need for caution around definitions of the term biosimilar. A biosimilar or SEB as defined by Health Canada is based on the comparability exercise at the product quality level. In contrast, some subsequent entry products available on the global market have not demonstrated a high degree of comparability yet are still referred to as biosimilar.

4. How similar is similar? Manufacturing considerations

Dr. Lubiniecki (Janssen Pharmaceutical Companies of Johnson & Johnson) discussed the fact that, compared to small molecule drugs, biologic drugs are much larger in size and have more complex molecular structures. As a result, millions of different chemical forms of active ingredient can be present in a biologic drug product. For example, the 527-amino acid tissue plasminogen activator (tPA) protein, with its 17 disulphide bridges and 3 glycosylation sites, may contain more than 1 billion chemically distinct active ingredient molecules in the final drug product. Analytical tools are limited in their ability to accurately monitor all possible variations of biologic products; therefore, a high degree of process control is required to ensure product quality and consistency. In contrast to biologic products, typically 95 percent of the active ingredient molecules in a small molecule product are chemically identical. Also, the interactions between small molecules and their binding targets cover a much smaller surface area than those of biologic products and their receptors, highlighting the importance of proper three-dimensional structure and surface characteristics of biologic drugs. Therefore, SEBs are not analogous to small molecule generics.

Dr. Lubiniecki discussed the limitation of the available guidelines for defining the comparability of SEBs. ICH Q6B mainly defines product specifications, whereas ICH Q5E is the comparability guideline for demonstrating that product attributes remain highly similar following changes in raw materials, manufacturing unit operations, critical process parameters or manufacturing sites [16,17]. Dr. Lubiniecki noted that the comparability practice as described within ICH Q5E applies to a single product before and after process changes within a single manufacturer. ICH Q5E would not sufficiently cover differences in the manufacturing process of the SEB compared to that of the RBD including expression system (host cell type, species, clonal isolate), recombinant DNA plasmid, fermentation system (media, vessel, environmental conditions), control strategy, and purification process (unit operations, chromatography, resins, buffers). The process-related and product-related impurities of the SEB will not be identical to those of the RBD, and the SEB and RBD may or may not be biosimilar. Other potential differences in the SEB include formulation, container-

closures system, drug product manufacturing, storage, and manufacturer.

Dr. Lubiniecki addressed the notion of an acceptable level of difference between an SEB and RBD, asking whether the absence of detectable differences due to lack of adequate detection methods could be misinterpreted as evidence of biosimilarity. Furthermore, the methods used to define adequate biosimilarity may be product-specific. Defining acceptable levels of biosimilarity will depend on knowledge of structure–function relationships and mechanisms of action for different indications, as well as mechanisms of toxicity. Dr. Lubiniecki described examples of erythropoietin products marketed in Asia, India, and Argentina subsequent to innovator erythropoietin that may not meet the standards for biosimilarity as defined by some regulatory jurisdictions. These products exhibited differences in charge, in vivo potency, sialic acid content, batch-to-batch properties, impurities, cell line, and unfolded protein content [19–22].

Dr. Lubiniecki discussed examples of so-called biosimilars of tPA (India) and trastuzumab (China) that have differences in carbohydrate forms and primary sequence as well as other differences when compared to their RBDs [23,24]. Previous work on tissue plasminogen activator has shown that these differences affect potency in animals. Due to the number of possible mechanisms of action for mAbs in particular (e.g., antigen binding and Fc-mediated accessory functions), it is not possible to predict the clinical impact of observed differences; therefore, some clinical impact might be expected.

Dr. Lubiniecki concluded that no matter how similar to an RBD an SEB appears to be, there is residual, un-discharged risk that the SEB will have a different profile of safety and efficacy. Therefore, appropriate non-clinical and clinical studies are required to mitigate the residual risk. In addition, if the SEB sponsor has deliberately introduced changes to the protein sequence, to the formulation, or to the container closure system then there are further risks of clinical differences. In these instances, the appropriate regulatory pathway may be that of a New Drug Submission.

Dr. Ridgway (Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, Health Canada) stated that the regulatory approach of Health Canada to biosimilars is based on concepts of comparability and the importance of product characterization. The motivation within Health Canada to develop guidance for the evaluation of SEBs was neither political nor financial. Rather, acknowledgment of the need for a science-based, practical approach to review pending submissions for SEB products prompted development of the guidance.

Dr. Ridgway stated that for some biologics, there are multiple innovator versions that are safe, effective, and non-identical; therefore, he reasoned that some differences between products are not critical. Innovators also make manufacturing changes with minimal or no supporting clinical data. As a result, Health Canada has used the comparability exercise undertaken by innovators after a manufacturing change as a model for biosimilar comparability, and adapted international guidance (especially from ICH including Q5E and Q6B) for this purpose [16,17]. The studies required to determine whether a product undergoing a manufacturing change is equivalent to the product prior to the change will depend on the stage at which the changes are introduced, the impact or potential impact on the product, analytical limitations, and the link between the quality criteria and possible implications on safety and efficacy. To address these issues, the ICH developed the Q5E guideline. While Q5E applies only to changes within one manufacturer, Dr. Ridgway commented that much of the guidance is relevant to SEBs. One of the general principles of the guideline is that “the demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are

identical but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon the safety or efficacy of the drug product”; therefore, the previously derived clinical data are still relevant. If comparability is not established, more extensive clinical trials are usually requested.

To date, five different types of products have been approved in Europe as biosimilars. Dr. Ridgway commented that he is not aware of any major adverse events or withdrawals associated with these products, to date. The European review system also identified products that did not meet standards for biosimilarity, such as an interferon-alpha product by Alpehon (due to impurities, adverse events, and clinical relapse) and insulin products by Marvel (not clinically comparable) [25,26]. These examples demonstrate the value of going beyond the chemistry and manufacturing data to assess safety and efficacy in patients.

Dr. Ridgway commented that the weight of the evidence to determine whether a product will be considered biosimilar will be provided by the product quality studies. It is going to be a great advantage if the sponsor uses a similar manufacturing process to that of the RBD. Significant differences and gaps in the product quality determinations cannot be filled in by a demonstration of clinical similarity.

All bioactivities and associated critical quality attributes of the molecule should be assessed. Different parts of some molecules have different activities and contribute in different ways to clinical efficacy, and some of these may be more or less important in different clinical indications. It is not acceptable to focus only on the part of the molecule that is important for the clinical indication that one is interested in. The whole molecule must be evaluated and shown to be similar.

To avoid the need for an internal comparability bridging study, the SEB material used in clinical trials should be from the commercial process and the same material used in the quality and non-clinical studies. Process changes late in development should also be avoided.

For comparability studies, Health Canada recommends that sponsors obtain different lots of the RBD (e.g., with different expiry dates), with documentation of purchase locations which may reflect where the product has been manufactured. The assessment of inter-batch variability of the RBD may help support an assessment of similarity for the SEB. This approach does not imply that every test should be performed on every batch; a matrix approach could be rationalized.

Comparability tests should be selected and optimized to maximize the potential for detecting relevant differences in quality attributes. Also, more than one analytical procedure should be used to evaluate the same attribute in order to maximize the possibility that any differences will be detected. Stability data, including data from accelerated or stress conditions, can provide insight into potential product differences in the degradation pathways of the drug product and, hence, potential differences in product-related substances and product-related impurities.

Dr. Ridgway discussed a study in which multiple lots of biologic products (RITUXAN® and ENBREL®) were characterized by a company developing biosimilars (Sandoz Biopharmaceuticals) [27]. The products were purchased over an extended period to try to obtain product from different manufacturing batches. The approach appeared to capture the products before and after manufacturing changes, and differences were detected using several analytical methods. Such changes to a product over time are known as “manufacturing drift.” Manufacturing drift may affect the similarity of an SEB to an RBD over time, and, although the products may be similar at the time of approval of the SEB, they may not be similar after introduction of subtle changes to either product. The

clinical implications of manufacturing drift are difficult to predict. Therefore, “once granted a Notice of Compliance, an SEB is considered to be a new (‘stand-alone’) product with all of the associated regulatory requirements” [6] and, from a regulatory standpoint, is not considered interchangeable/substitutable with the RBD. Furthermore, a demonstration of similarity or therapeutic interchangeability supported by specifically designed clinical studies would only be valid at the time the data were generated due to possible manufacturing drift of either product over time. The position of Health Canada is that, while it is appropriate for a physician to substitute or prescribe an SEB for a patient for an approved clinical indication, the SEB should not be substituted automatically. SEBs in Canada will not be labeled interchangeable with RBDs.

SEBs, once approved, would be regarded as stand-alone products and may later gain approval for additional strengths, dosage forms, and clinical indications if substantiated by a full supportive dossier. Such products with different strengths, presentations, and indications would also not necessarily be interchangeable with the RBD.

5. Clinical perspectives: clinical study design, sensitive patient populations, extrapolation of indications, immunogenicity

Dr. Feagan (gastroenterologist, Robarts Research Institute, University of Western Ontario) described the prevalence of inflammatory bowel diseases in Canada, and commented that monoclonal antibodies have improved treatment options for patients, especially in Canada, which is one of the largest users of monoclonal antibodies in gastroenterology on a per capita basis.

The PK of monoclonal antibodies is complex, and can be affected by co-administration of antimetabolites such as methotrexate and azathioprine which can affect clearance as well as immune responses to drug (when patients develop anti-drug antibodies). Anti-drug antibodies can also affect PD and clinical efficacy. Therefore, Dr. Feagan commented that differences between molecules (e.g., SEB versus RBD) can have consequences in terms of PK, PD, and immunogenicity.

Dr. Feagan presented clinical findings that development of higher titers of anti-drug antibodies to infliximab or adalimumab correlates with shorter duration of response and higher incidence of infusion reactions [28,29]. Also, co-administration of antimetabolites with infliximab reduces the risk of developing neutralizing antibodies and increases trough levels of drug [30]. In the near future, gastroenterologists will have access to assays that can detect therapeutic antibodies in clinical samples. Dr. Feagan suggested that specific assays could be developed for each biosimilar, thereby allowing clinicians to evaluate treatment decisions based on the serum levels of the therapeutic antibody as well as anti-drug antibodies, as previously described [31].

Dr. Feagan used the examples of abatacept and etanercept, which have similar efficacy in rheumatoid arthritis but not in Crohn’s disease, to reason that extrapolation of indications should not be permitted [32]. He added that the mechanisms of action of the TNF α antagonists are not completely understood, and that subtle molecular differences in a biologic drug may alter binding to targets in the body and lead to different clinical effects. For example, etanercept, adalimumab, and infliximab avidly bind soluble TNF α and induce reverse signaling through membrane-bound TNF α . However, the signaling effects induced by the three molecules are quantitatively and qualitatively different [33]. Which of the downstream effects contribute to efficacy in various disease states is not known; therefore, Dr. Feagan questioned the validity of pharmacodynamic markers for anti-TNF α agents.

Dr. Feagan concluded with a discussion of the size of clinical trials required to evaluate the equivalence or non-inferiority of an SEB versus an RBD. He suggested that a margin of effect of 15% in a superiority trial would require 300 patients, and a margin of 7.5% in a non-inferiority trial would require 1500 patients. He expressed concern about whether large biosimilar trials could be conducted alongside trials for new innovator compounds in limited patient populations.

Dr. Wang (Clinical Evaluation Division – Hematology/Oncology, Health Canada) discussed the regulatory perspective on defining a sensitive population for clinical studies, and on extrapolation of indications. To determine whether an SEB achieves an acceptable level of similarity, Health Canada must evaluate whether any differences in quality between the SEB and RBD could affect safety and efficacy. Dr. Wang described that the quality data package for an SEB includes comparability data between the RBD and SEB in addition to the usual requirements for an innovator product. However, because the clinical data package for an SEB is not as extensive, a patient population that is most sensitive should be selected and the patient number must be large enough to detect meaningful differences in safety, efficacy, and immunogenicity. Dr. Wang emphasized that Health Canada should be consulted regarding the design of clinical trials as well as the selection of a sensitive population prior to the trial getting underway. He explained that in a sensitive population, differences between an SEB and RBD can be more easily detected. Both healthy subjects and patients could be considered sensitive populations for different stages of clinical assessment depending on the questions at hand. Dr. Wang cautioned that healthy subjects may not be considered a sensitive population when a clinically relevant dose may induce a ceiling effect in the clinical response (i.e., because subjects have intact physiological function), or when a targeted effect of a monoclonal antibody is being studied. A study in a healthy population may be used to demonstrate dose–response relationships. For such a study, a dose in the steep part of the curve should be chosen to avoid masking effects.

Only in well-justified cases, a properly conducted clinical study in a sensitive population may allow for extrapolation to other indications for which the Canadian RBD is approved. Various aspects of clinical trial design may impact whether the data are adequate to support extrapolation. These design features include the population being studied, duration of the trial, route of administration, dose, monotherapy versus combination therapy, concomitant medications, and immunogenicity profile. A PK/PD bridging study in the relevant patient population is also required.

Dr. Wang elaborated that extrapolation of indications may not be possible in some cases. For example, RITUXAN[®] has indications in rheumatoid arthritis, oncology, and vasculitis due to the involvement of CD20 in all of these diseases; however, the underlying pathophysiology and mechanism of action may not be the same, making extrapolation of indications for this product very challenging. He added that extrapolations in the following cases may be difficult to justify: different routes of administration (from intravenous to subcutaneous), from pharmacodynamic biomarker to clinical endpoint, from short to long-term use, from combination therapy to monotherapy, from high to low dose, from one to both genders, and from healthy subjects to a disease population. It may be more acceptable to extrapolate from monotherapy to combination therapy once comparable safety and efficacy of SEB monotherapy has been established. A particular area of concern is the immunogenicity of the subcutaneous route of administration; it may be more acceptable to extrapolate from subcutaneous administration to indications requiring intravenous administration, rather than the reverse.

Dr. Keystone (rheumatologist, Mount Sinai Hospital/University Health Network, University of Toronto) considered that even

though they are different molecules, the TNF α antagonists adalimumab, etanercept, golimumab, and infliximab exhibit similar clinical efficacy in terms of their main clinical trial endpoints in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. Therefore, he reasoned that the typical clinical trial endpoints for these indications (e.g., ACR20, ASAS20, and PASI75) are inadequate to assess differences between SEBs and their respective RBDs, and highlighted the importance of conducting clinical trials for SEBs in a sensitive clinical population.

Dr. Keystone highlighted that different doses of etanercept are used to treat rheumatoid arthritis and plaque psoriasis. He also drew attention to the differences in approved indications between the anti-TNF α mAbs, and that etanercept, unlike adalimumab and infliximab, has not demonstrated efficacy in Crohn's disease. The reason for this discrepancy, besides their molecular differences, is unknown. Dr. Keystone summarized the differences in sequence and structure among the anti-TNF α agents. Certolizumab pegol, a pegylated Fab' fragment [34], lacks an Fc domain (which has been proposed to contribute to the mechanism of action of anti-TNF α drugs in Crohn's disease) and yet still exhibits efficacy in Crohn's disease. Taken together, the issues with certolizumab pegol and etanercept suggest that the mechanism of action of anti-TNF α agents in Crohn's disease is not completely understood.

Dr. Keystone stated that the immunogenicity of TNF α antagonists can negatively impact safety, efficacy, drug levels and potency, and therapeutic switching strategies. As observed in the ATTRACT and ACCENT I trials of infliximab in rheumatoid arthritis and Crohn's disease, respectively, the presence of anti-drug antibodies was associated with a higher proportion of infusion reactions [35,36]. Also, the presence of antibodies to adalimumab has been associated with lack of response and lower trough levels of drug in serum in patients with rheumatoid arthritis, as well as lack of PASI response in patients with psoriatic arthritis [37,38]. Similar effects have been reported in patients with Crohn's disease treated with infliximab. Dr. Keystone also mentioned a recent study suggesting that anti-drug antibody responses to infliximab are associated with a higher level of anti-drug antibody response after switching to adalimumab, even though these anti-drug antibodies are not cross-reactive [39]. Dr. Keystone suggested that patients losing response to one therapy could be monitored for anti-drug antibodies to guide decisions about the next course of therapy. A similar approach could be developed for SEBs.

6. Clinical perspectives: pharmacokinetics, pharmacodynamics

Dr. Mould (Projections Research Inc.) reviewed the requirements for comparative PK and PD studies as described in Health Canada's guidance document. She commented that human PK and PD profiles cannot always be predicted from functional assays and/or animal studies, and cautioned that animals may not always be suitable models of human antibody salvage pathways (through interaction with FcRn), target receptor interactions, or cytokines. A human PD study demonstrating similar effects on a clinically relevant PD measure could provide strong support for biosimilarity; however, with respect to the inflammatory diseases treated with anti-TNF α mAbs, the biomarkers of disease, including C-reactive protein, are not well-correlated to clinical efficacy and thus are not considered appropriate surrogate endpoints.

Dr. Mould discussed the selection of suitable subjects (patients or healthy volunteers) for PK and PD studies. Dr. Mould suggested that for alemtuzumab (CAMPATH[®], anti-CD52 antibody), which is used to treat B-CLL, PK in healthy volunteers and patients would be quite different. In healthy volunteers who express low levels of the target receptor, PK would appear to be linear and exhibit a half-life

typical of IgG antibodies. In contrast, patients in blast crisis would exhibit low levels of drug soon after administration because of receptor mediated clearance [40]. Dr. Mould noted other examples of the variable PK of anti-TNF α antibodies in different patient populations, including patients who develop anti-drug antibodies.

Dr. Mould suggested that disease-PK interactions, whereby levels of drug can vary in different disease states, may complicate extrapolation of PK data from one disease state to another [41]. She stated that it would be a very rare case that a demonstration of biosimilarity could be made on human PK and PD data alone, and that comparative safety and efficacy studies may be necessary to resolve any residual uncertainties about the similarity of two products. Dr. Mould suggested that the following factors could influence the type and extent of comparative clinical safety studies required: the nature and complexity of the reference product; limitations in comparing structural and functional characteristics; the findings of non-clinical testing; the extent that differences in structure, function, and non-clinical pharmacology and toxicology can predict clinical outcomes; the degree of understanding of mechanism of action of the reference product and disease pathology; the extent that human PK/PD can predict clinical outcomes; and the extent of clinical experience with the RBD including safety, efficacy, and relevant biomarkers.

Dr. Mould discussed the example of pegfilgrastim (NEULASTA[®]). While manufacturing controls are in place, variability in the extent of pegylation and types of pegylation in the product can affect clinical PK and PD. Pegylation reduces the recognition of the product as a foreign protein and slows proteolysis but also interferes with the analysis of drug levels. For these reasons, demonstrations of comparability for a pegylated SEB product may be difficult.

Dr. Mould reiterated previous comments that due to partial understanding of the mechanism of action of products such as TNF α antagonists in different disease states, data in one indication may not apply to other indications. Dr. Mould also identified the example of cetuximab (ERBITUX[®], anti-EGFR), which has activity in several solid tumor types, and even in tumors where the target of the antibody has not been detected [42].

Dr. Mould added that antibodies engineered to bind very well with FcRn will have longer half-lives. She commented that FcRn expression and receptor mediated clearance of antibodies can vary among different subjects and disease states. For example, in patients with multiple myeloma in whom IgG levels are high, FcRn receptors are saturated, compromising the salvage pathway, which can result in a very short IgG half-life. Also, expression levels of antibody targets can vary in different patient populations. Dr. Mould described an example in which levels of a targeted mAb in a patient with B-cell lymphoma were very low early during the course of treatment when white blood cell (WBC) counts were high; once WBC levels decreased in response to drug, the mAb could then be readily detected in serum [40]. In these circumstances, subcutaneous administration of such a drug would not result in detectable levels in serum until the patient achieved good response.

Dr. Mould emphasized that it would be challenging to extrapolate PK for a mAb in one patient population to another, and that switching routes of administration even for the same drug in the same patient population can result in markedly different PK and PD.

Dr. Mould concluded that the determination of similarity is a complex process. It is important to understand the pharmacology and the impact of disease on PK/PD. Dr. Mould suggested that sponsors should incorporate information about endogenous factors that can affect PK and PD.

Dr. Wang reviewed the differences in Health Canada's requirements for small molecule generics and SEBs. For generic

compounds, a bioequivalence study may be waived if the drug is administered intravenously. In contrast, an SEB application requires bioequivalence and PD/clinical comparability studies as part of the stepwise comparability assessment. Generics receive a claim of equivalence in the product labeling, whereas SEBs, which are not identical to their RBDs, will be labeled as similar. Furthermore, it is not appropriate to refer to SEBs and RBDs as pharmaceutically equivalent.

Dr. Wang reviewed the potential uses of PK/PD studies in an SEB application: to support a demonstration of similarity between an SEB and RBD, to monitor immunogenicity, to quantify the effects in patient populations, to compare different formulations of an SEB, or to compare different routes of administration of an SEB. Furthermore, Dr. Wang reviewed factors to consider when designing PK/PD studies, such as half-life, linearity of PK, endogenous levels and diurnal variations of the protein under study (comparability testing would be specific to exogenous levels of a biologic drug), the disease being treated, route of administration, the indications for which the sponsor is applying, and, particularly for mAbs, elimination pathways including target-mediated pathways (which depend on the expression levels of the target).

Dr. Wang stated that comparative PK studies should be conducted to detect potential differences between the SEB and RBD by performing single-dose, cross-over studies in sensitive, homogeneous populations using a dose that is most sensitive to detect differences through subcutaneous or intramuscular routes of administration. For cross-over studies, sponsors need to justify that drug half-life is not an issue and that formation of antibodies does not impact the PK/PD profile. Dr. Wang added that a parallel group design should be considered for SEBs with a long half-life, and that the two groups should be balanced. He emphasized that parallel PK study designs require more subjects than cross-over designs in order to achieve statistical power. For drugs with a long half-life or that are administered intravenously, a demonstration of similarity in absorption or bioavailability may not be available or sufficient. Furthermore, a demonstration of similarity in clearance and half-life may be required for assessing the risk of differences in elimination rate for these products.

Dr. Wang advised that PK studies should generally be conducted in the relevant patient population, since a number of factors such as receptor expression, receptor internalization rate, and patient condition can affect the clearance of the medicinal product. He further clarified the limitations of conducting studies in healthy patients although sometimes this approach could be justified. Healthy subjects would not likely support data extrapolation to disease states, and healthy subjects may not be considered the most sensitive population because a clinically relevant dose may induce a ceiling effect. Also, target-mediated effects on PK cannot be fully assessed in healthy subjects.

With respect to the parameters for PK comparability, Dr. Wang stated that the principles for small molecules (for example, 90 percent confidence interval for AUC_T and ratio of test to reference C_{max} to be within 80–125 percent) may not always apply to biologic products. For PD studies, biomarkers or clinically relevant and validated surrogate markers can be used. Dr. Wang stated that combined PK/PD studies may provide useful information on the relationship between dose exposure and effect, and could be used to support extrapolation of indications. He highlighted that the PD parameters could be investigated in the context of combination PK/PD studies. Dr. Wang clarified that Health Canada recommends 95 percent instead of 90 percent confidence intervals for PK/PD studies when determining similarity for SEBs. He also stated that well-designed comparative PK/PD studies may be sufficient to demonstrate clinical comparability in cases where sufficient justification is provided.

7. Post-market: payer perspective

Dr. Guirguis (Alberta Blue Cross, presenting his personal view, not that of his employer) expressed concern about the challenges that face prescribers and payers to ensure the safe and effective use of SEBs. While these important stakeholders are aware that SEBs are not generic products, there remains a degree of uncertainty about them in general, which is reflected by the terminology used and the complexity of discussion. Dr. Guirguis stated that given the current knowledge gap regarding substitution and interchangeability of SEBs, payers and governments would be hesitant to impose restrictions on physicians and patients.

Dr. Guirguis perceived a lack of understanding among prescribers and payers about differences in manufacturing, PK and PD between SEBs and their respective RBDs. He pointed out that regulators are trying to quantify this variability and define acceptable levels of risk. For example, statistical intervals are used as goalposts for PK and PD measurements, and release tests for manufacturing variability. He questioned the understanding at the prescriber level of risk associated with differences between SEBs and RBDs, and how that could be communicated and managed. He raised the issue that long-term safety data should be required to determine whether SEBs and RBDs will be comparable over time. Other factors for consideration by physicians are whether an SEB comes with a different delivery device, whether it has a similar patient support program as the RBD, and whether patients will require more frequent follow-up. He discussed the uncertainty a physician could face in the event of lack of efficacy in a patient receiving an SEB, as well as the lack of clinical data on whether the patient could benefit from a switch to the innovator product.

Dr. Guirguis stated that as costs for biologics increase, entry of SEBs into the Canadian market may result in significant cost savings for payers and insurers. However, he commented that the market penetration of follow-on proteins and biosimilars in other markets has not been very high and suggested several possible explanations: issues related to specific products, cultural issues, and actions/perceptions of prescribers and patients. He reasoned that there is a need, while not dictating prescribing practices, to provide patients and physicians with information so that they can make informed treatment decisions.

8. Post-market: pharmacovigilance and safety monitoring

Dr. Klein (Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, Health Canada) remarked that Health Canada takes a scientific approach to reviewing SEBs. She emphasized that an SEB is not identical to its RBD. At the time of marketing authorization, as much if not more information will be available for an SEB than for other newly approved products; however, important concerns such as immunogenicity and other safety issues remain unknown and need to be defined for the SEB. Hence, there is a need for post-marketing pharmacovigilance for SEBs.

The pharmacovigilance requirements for SEBs will be similar to those for novel biologic products with respect to adverse event reporting, Periodic Safety Update Reports (PSURs) and additional post-marketing surveillance activities. Sponsors are required to submit a Risk Management Plan (RMP), which is a prospective set of safety mitigation standards tailored to concerns about the product. The content of the RMP should be agreed upon by the Regulator and the sponsor before marketing authorization is granted. The requirements for ad hoc reporting and other regulatory actions are the same as those for novel innovator products.

Like any new medicinal product, SEBs will be closely monitored in the post-marketing phase due to incomplete information at the time of marketing authorization. The objective of post-market

monitoring is to understand differences versus the RBD in the immunogenicity profile and local reactions. Since SEBs and RBDs are not identical, their properties could differ widely. Dr. Klein highlighted that biologic products vary from time to time and cannot be reproduced in an identical manner over time. Thus, Health Canada is taking a lifecycle management approach to the regulation of medicinal products, allowing the knowledge about particular products to be less static than it has been in the past.

Dr. Klein clarified Health Canada's position on substitution and interchangeability: SEBs and RBDs are not substitutable products. Secondly, matters of interchangeability and substitutability are under the jurisdiction of the Canadian provinces, not that of the federal government.

9. Discussion

The following section is an edited synopsis of key issues discussed during several discussion periods interspersed between the presentations.

9.1. Defining biosimilarity

Dr. Kay asked Health Canada to clarify the distinction between biosimilars and members of the same product class. For example, golimumab and adalimumab are both human IgG anti-TNF α antibodies, they have similar biological activities, bind the same ligand, and bind the same Fc receptor. They are members of the same product class but are not biosimilars or SEBs. Dr. Klein replied that once an SEB is approved, it becomes a member of the same product class as the RBD. Product labeling for SEBs will contain class-specific warnings and precautions. As different products within the same class, SEBs and RBDs have similar activities but are not used interchangeably because they do not necessarily work the same way in the clinical setting. Dr. Ridgway continued, stating that monoclonal antibodies in the same product class that have similar targets and classes of immunoglobulin can have different clinical effects. Health Canada is not intending to consider all products of the same class roughly similar. Biosimilarity will be assessed on a product-by-product basis. A sponsor would have to request the review of a product as an SEB, and provide a substantial data package to show biosimilarity to the RBD, including head-to-head clinical data. In some circumstances the challenge of demonstrating biosimilarity may be so great that it may be easier and less expensive for a sponsor to request approval as a stand-alone product via the New Drug Submission route rather than attempting to follow the route for SEBs.

Dr. Kay asked Health Canada whether it would be easier to demonstrate biosimilarity for a smaller protein with good biomarkers than for a large, complex monoclonal antibody. He reviewed that glucagon and somatropin, which were approved through the 505(b)(2) regulatory pathway in the US, have reliable biomarkers, whereas many large biopharmaceuticals such as TNF α inhibitors do not. Dr. Ridgway acknowledged that it will be very challenging for monoclonal antibody or factor VIII/IX SEBs to follow the SEB pathway due to the lack of understanding of how molecular attributes impact clinical efficacy; however, as science evolves it may be possible to produce enough data to show that many of the variations between two molecules are not critical for safety or efficacy, allowing a focus on those that are.

Dr. Ridgway stated that SEBs using different manufacturing processes than their respective RBDs are less likely to meet the criteria for biosimilarity. Also, SEBs made in different host cell systems may not be able to reference the safety record of their respective RBDs due to differences in process-related and product-related impurities.

9.2. Clinical PK/PD studies

Dr. Kay asked whether conducting the PK/PD studies for SEBs and RBDs in the same patient population would allow for a reliable assessment of comparability. Dr. Mould replied that the reliability of the data would depend on the importance of receptor expression levels for PK outcomes; highly variable responses in a subset of patients in a small study could invalidate a determination of similarity. This concern could be alleviated by using a large number of subjects, or accounting for PD outcomes. For example, accounting for differences in receptor expression levels over time or between subjects may clarify the interpretation of PK data.

The types of single-dose or steady-state PK studies were also discussed. Dr. Wang indicated that single-dose cross-over studies are preferred, but that other study designs may be needed depending on the properties of the molecule. For example, testing in patient populations may require continued dosing for ethical reasons. Dr. Mould asked if confidence intervals for PK parameters could be widened or narrowed depending on the therapeutic index of the product being studied. Dr. Wang replied that, so far, wider confidence intervals have not been accepted. When asked by Dr. Keystone about the lack of validated surrogate pharmacodynamic markers of efficacy in diseases such as rheumatoid arthritis, Dr. Wang replied that, in such diseases, clinical trials would be required for approval of an SEB.

9.3. Clinical safety and efficacy studies

Dr. Wang stated that Health Canada recommends an equivalence design for SEB clinical trials. Sponsors intending to use other designs (e.g., non-inferiority) would have to provide justification. A non-inferiority approach would require the sponsor to test whether the SEB demonstrated superiority, in which case it would not be considered biosimilar. Dr. Feagan and Dr. Trudeau (oncologist, Sunnybrook Health Sciences Centre, University of Toronto) expressed concern regarding the large number of patients required for equivalence trials and the capacity to conduct large clinical trials in limited patient populations. With more companies shifting clinical trials outside of North America, Dr. Kay asked whether data obtained in such trials could be applied to North American populations. Health Canada panelists confirmed that clinical trial data from outside Canada for new compounds and biosimilars is acceptable, but justification should be provided that the study populations are relevant to the Canadian population. Dr. Mould reminded the panel of the heterogeneity of clinical response that can be observed in various racial backgrounds due to, for example, variable expression of cytochrome P450 proteins, and that genetic differences in the receptors targeted by biologic drugs have been largely unexplored.

Dr. Feagan and Dr. Kay discussed suitable clinical trial endpoints, and suggested that continuous outcomes (e.g., change in DAS28 over time in rheumatoid arthritis) rather than dichotomous outcomes (e.g., ACR20 in rheumatoid arthritis or a fall of the Crohn's Disease Activity Index (CDAI) of >70 points defining response in Crohn's disease) may be more sensitive for the determination of clinical comparability.

9.4. Indication extrapolation

Dr. Trudeau asked Health Canada to clarify the clinical trial requirements for a sponsor seeking approval of an SEB for different disease states such as rheumatoid arthritis and ulcerative colitis. Dr. Wang replied that Health Canada will not consider automatic extrapolation. Indications will be considered on a case-by-case basis according to data and scientific justification provided by the

sponsor. Dr. Mould suggested that differences in PK/PD in different disease states may pose a challenge to extrapolation of indications.

Health Canada was asked to comment on specific examples of extrapolation of indications. In response to Dr. Trudeau, Dr. Wang replied that it may be possible to extrapolate clinical data for trastuzumab in the setting of metastatic disease to its use as adjuvant therapy. However, the use of monotherapy or different combination therapies in these settings would be important considerations. In response to Dr. Keystone, Dr. Wang replied that it may not be possible to extrapolate clinical data for a monoclonal antibody in one rheumatologic indication to other rheumatologic indications because of differences in dose, duration of therapy, efficacy of monotherapy vs. combination therapy, and stated claims of efficacy for those indications. However, extrapolation of indications may be granted if a sponsor provides sufficient scientific justification and PK/PD data in the patient population of interest. Dr. Feagan stated his opinion that efficacy data in patients with rheumatoid arthritis might not provide adequate justification for extrapolation to Crohn's disease.

9.5. Manufacturing drift

Incremental differences between products may occur following changes in manufacturing. Consequently, according to Dr. Ridgway, after a thorough demonstration of biosimilarity at the time of approval, an SEB and RBD may diverge to the point that they will no longer be deemed biosimilar. Based on the potential for manufacturing drift, the panel voiced concern regarding substitution or switching of products for individual patients.

Dr. Ridgway emphasized that regulatory controls are in place to ensure comparability of stand-alone products before and after manufacturing changes. Manufacturing changes to SEBs that occur following approval will require the manufacturer to compare the post-change SEB to the pre-change SEB to demonstrate that the product has not changed significantly. Innovator manufacturers must meet the same requirements. Manufacturing changes to the SEB will not trigger repeated comparability testing with the RBD; therefore, a standard of comparability or biosimilarity that is achieved at the time of approval of the SEB may not be maintained over time. Dr. Ridgway stated that physicians will need to consider the appropriate medication for their patients because the outcomes of an SEB and RBD can be different.

Dr. Keystone expressed the need to educate physicians about product drift due to changes in manufacturing and the importance of pharmacovigilance for biologic products.

9.6. Interchangeability

During the discussion on interchangeability it became clear that Health Canada is taking a different approach from that of the FDA, which is considering allowing interchangeability. Clarification was requested by the panelists regarding the potential risks of interchangeability as a result of manufacturing drift.

Dr. Ridgway voiced that Health Canada does not support automatic substitution of an SEB for its RBD and recommends that physicians be involved in making decisions about substitution or interchange. Physicians who switch a patient from an RBD to SEB (or vice versa) would be advised to monitor the patient for adverse effects. Physicians should be aware of patient-specific differences in outcomes; therefore, a switch from innovator product to SEB should be considered similar to switching between two innovator products. Dr. Trudeau expressed concern about the potential pressure from payers to prescribe lower-cost biologics once SEBs enter the market, and emphasized that Health Canada should ensure that SEBs meet high standards so that physicians can feel confident using them.

Dr. Ridgway commented that the decision to allow substitution is in the hands of the provinces and territories which decide what they will pay for. The colleges of pharmacy decide what their pharmacists are allowed to do within a province. Dr. Guirguis asked how Health Canada would respond if interchangeability and substitution were to occur at the provincial or pharmacy level. In response, Dr. Nyarko emphasized the need for education about SEBs and biologics. For the only biosimilar product currently approved in Canada (OMNITROPE[®]), Health Canada issued a letter that the product is not a generic drug and not deemed bio-equivalent. Dr. Guirguis added that the provincial government of Alberta has published a statement that SEBs will not be reviewed as interchangeable products [43], SEBs will go through the Common Drug Review, and decisions from that review will be evaluated by Alberta Health and an expert committee.

Dr. Keystone believed that physicians may not be aware of the non-interchangeability of SEBs, and cautioned that product interchange or substitution may still occur in clinical practice or at the pharmacy level unless there is regulatory guidance to prevent that from happening. Panelists encouraged Health Canada to provide clear guidance to clinicians and payers about the issue of interchangeability.

9.7. Pharmacovigilance and nomenclature

Dr. Feagan asked Health Canada about the regulatory requirement for sponsors to maintain a database of patient exposure for SEBs, as has been required for other biologic products. Dr. Wang emphasized that the approach will be similar to that as described in ICH guidance, whereby the safety exposure required prior to approval of a product will be a minimum of 100 patients for one year. This requirement may increase depending on the post-marketing safety record of the RBD, and the number of patients required to ensure adequate statistical power for conclusions of clinical biosimilarity.

Numerous concerns were raised regarding naming of SEBs, and how post-approval adverse events would be attributed to SEBs or RBDs. Dr. Kay suggested that unique names may be appropriate for stand-alone products, and that unique names would be needed in circumstances when using brand names is discouraged or prohibited, such as in continuing medical education settings. Dr. Keystone commented that an SEB and its RBD, which are not identical, substitutable or interchangeable, could not be distinguished by using only the generic name.

Dr. Nyarko stated that SEBs would have unique brand names, which can be used to identify products for pharmacovigilance activities. For the purpose of differentiating between brands, the WHO system for International Non-proprietary Names (INN) was discussed [44], but Dr. Nyarko stated that this system poses a number of challenges. Dr. Klein added that Health Canada continues to consider the nomenclature of SEBs and is following developments in other jurisdictions.

10. Closing remarks

This meeting provided Canadian stakeholders an opportunity to gain clarity on Health Canada's science-based guidance policy on SEBs, and to discuss issues of concern from their perspective. Although Health Canada, EMA, FDA and health agencies in other regulatory jurisdictions take similar approaches to evaluating biosimilars, there are requirements and policy positions specific to Canada that Canadian stakeholders are beginning to appreciate. It is hoped that this knowledge gap will continue to be bridged through ongoing education and sharing of information among key Canadian stakeholders and their international counterparts.

Conflict of interest

- Panelists (except those from Health Canada) were offered compensation from BIOTECCanada for their travel and time to participate in this summit.

Jonathan Kay, MD, FACP

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- Speakers bureau: UCB, Abbott, J&J/Janssen
- Member, scientific advisory board: Astra Zeneca, Elan/Biogen, Celltech, Merck, Celgene, Novartis, Given Imaging Inc., UCB Pharma, Salix Pharmaceuticals, Abbott Laboratories, Centocor Inc. Pfizer, Axcan, Tillotts Pharma AG, Prometheus Laboratories

Micheal S. Guirguis, PhD

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Agnes V. Klein, MD, DPH

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Anthony S. Lubiniecki, ScD

- Dr. Lubiniecki is an employee and a stockholder of an innovator pharmaceutical company.

Diane R. Mould, PhD, FCP

- No conflicts to disclose.

Kwasi A. Nyarko, PhD

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References

- [1] Reichert JM. Next generation and biosimilar monoclonal antibodies: essential considerations towards regulatory acceptance in Europe. February 3–4, 2011, Freiburg, Germany. *MAbs* 2011;3:223–40.
- [2] Wadhwa M, Kang HN, Knezevic I, Thorpe R, Griffiths E. WHO/KFDA joint workshop on implementing WHO guidelines on evaluating similar biotechnological products, Seoul, Republic of Korea 24–26 August, 2010. *Biologicals* 2011;39:349–57.
- [3] Committee for Medicinal Products for Human Use, European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. EMEA/CHMP/BWP/49348/2005. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf; 2006 [accessed 03.07.12].
- [4] Committee for Medicinal Products for Human Use, European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BWP/42832/2005. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf; 2006 [accessed 03.07.12].
- [5] World Health Organization. Guidelines on evaluation of similar biotechnological products (SBP). http://www.who.int/biologicals/areas/biological_therapeutics/BIO_THERAPEUTICS_FOR_WEB_22APRIL2010.pdf; 2009 [accessed 18.08.12].
- [6] Health Products and Food Branch, Health Canada. Guidance for sponsors: information and submission requirements for subsequent entry biologics (SEBs). http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2010-eng.pdf; 2010 [accessed 03.07.12].
- [7] Food and Drug Administration. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product (draft). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>; 2012 [accessed 03.07.12].
- [8] Food and Drug Administration. Guidance for industry: quality considerations in demonstrating biosimilarity to a reference product (draft). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>; 2012 [accessed 03.07.12].
- [9] Health Canada. Summary basis of decision for OMNITROPE, http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/sbd-smd/phase1-decision/drug-med/sbd_smd_2009_omnitrope_113380-eng.pdf; 2009 [accessed 18.08.12].

- [10] Klein AV. The first subsequent entry biologic authorized for market in Canada: the story of Omnitrope, a recombinant human growth hormone. *Biologicals* 2011;39:278–81.
- [11] Kay J. Biosimilars: a regulatory perspective from America. *Arthritis Res Ther* 2011;13:112.
- [12] Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology—“O Brave New World”. *Nat Rev Rheumatol* 2012;8:430–6.
- [13] Committee for Medicinal Products for Human Use, European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies (draft). EMA/CHMP/BMWP/403543/2010, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf; 2010 [accessed 03.07.12].
- [14] Casadevall N, Dupuy E, Molho-Sabatier P, Tobelem G, Varet B, Mayeux P. Autoantibodies against erythropoietin in a patient with pure red-cell aplasia. *N Engl J Med* 1996;334:630–3.
- [15] Boven K, Stryker S, Knight J, Thomas A, van Regenmortel M, Kemeny DM, et al. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. *Kidney Int* 2005;67:2346–53.
- [16] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Specifications: test procedures and acceptance criteria for biotechnological/biological products: Q6B, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf; 1999 [accessed 03.07.12].
- [17] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Comparability of biotechnological/biological products subject to changes in their manufacturing process, Q5E, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf; 2004 [accessed 03.07.12].
- [18] 2012 APEC Harmonization Center Biosimilar Workshop. (April 3–5, 2012) Seoul, Korea. <http://www.apec-ahc.org/contents/page.jsp?mcode=3021001>; [accessed 03.07.12].
- [19] Burg J, Sellinger KH, Haselbeck A, Koll H. Erythropoietin with high specific activity, European Patent. PCT/EP/98/07876.
- [20] Storrer PL, Tiplady J, Gaines Das RE, Stening BE, Lamikanra A, Rafferty B, et al. Epoetin alfa and beta differ in their erythropoietin isoform compositions and biological properties. *Br J Haematol* 1998;100:79–89.
- [21] Skibeli V, Nissen-Lie G, Torjesen P. Sugar profiling proves that human serum erythropoietin differs from recombinant human erythropoietin. *Blood* 2001;98:3626–34.
- [22] Schellekens H. Biosimilar epoetins: how similar are they? *Eur J Hosp Pharm Sci* 2004;3:43–7.
- [23] Jiang H, Wu SL, Karger BL, Hancock WS. Characterization of the glycosylation occupancy and the active site in the follow-on protein therapeutic: TNK-tissue plasminogen activator. *Anal Chem* 2010;82:6154–62.
- [24] Xie H, Chakraborty A, Ahn J, Yu YQ, Dakshinamoorthy DP, Gilar M, et al. Rapid comparison of a candidate biosimilar to an innovator monoclonal antibody with advanced liquid chromatography and mass spectrometry technologies. *MAbs* 2010;2:379–94.
- [25] European Medicines Agency. Questions and answers on recommendation for refusal of marketing application for Alpheon, http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/000585/WC500017451.pdf; 2006 [accessed 18.08.12].
- [26] European Medicines Agency. Questions and answers on the withdrawal of the marketing authorization application for insulin human rapid Marvel, insulin human long Marvel, insulin human 30/70 mix Marvel, http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500015341.pdf; 2008 [accessed 18.08.12].
- [27] Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. *Nat Biotechnol* 2011;29:310–2.
- [28] Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;348:601–8.
- [29] Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterol* 2009;137:1628–40.
- [30] Sandborn W, Rutgeerts P, Reinisch W, Mantzaris G, Kornbluth A, Rachmilewitz D, et al. SONIC: a randomized, double blind, controlled trial comparing infliximab and infliximab plus azathioprine to azathioprine in patients with Crohn's disease naïve to immunomodulators and biologic therapy. *Am J Gastroenterol* 2008;103:1117 [Late-breaking abstract 29].
- [31] Afif W, Loftus Jr EV, Faubion WA, Kane SV, Bruining DH, Hanson KA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010;105:1133–9.
- [32] Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006;144:865–76.
- [33] Nesbitt A, Fossati G, Bergin M, Stephens P, Stephens S, Foulkes R, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor alpha agents. *Inflamm Bowel Dis* 2007;13:1323–32.
- [34] Weir N, Athwal D, Brown D, Foulkes R, Kollias G, Nesbitt A, et al. A new generation of high-affinity humanized PEGylated Fab fragment anti-tumor necrosis factor- α monoclonal antibodies. *Therapy* 2006;3:535–45.
- [35] Data on file. Janssen Biotech Inc.
- [36] Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541–9.
- [37] Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis* 2007;66:921–6.
- [38] Lecluse LL, Driessen RJ, Spuls PI, de Jong EM, Stapel SO, van Doorn MB, et al. Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. *Arch Dermatol* 2010;146:127–32.
- [39] Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naïve patients: a cohort study. *Ann Rheum Dis* 2010;69:817–21.
- [40] Mould DR, Baumann A, Kuhlmann J, Keating MJ, Weitman S, Hillmen P, et al. Population pharmacokinetics-pharmacodynamics of alemtuzumab (Campath) in patients with chronic lymphocytic leukaemia and its link to treatment response. *Br J Clin Pharmacol* 2007;64:278–91.
- [41] Kapel N, Meillet D, Favennec L, Magne D, Raichvarg D, Gobert JG. Evaluation of intestinal clearance and faecal excretion of alpha 1-antitrypsinase and immunoglobulins during Crohn's disease and ulcerative colitis. *Eur J Clin Chem Clin Biochem* 1992;30:197–202.
- [42] Custodio A, Feliu J. Prognostic and predictive biomarkers for epidermal growth factor receptor-targeted therapy in colorectal cancer: beyond KRAS mutations. *Crit Rev Oncol Hematol* 2012 [Epub ahead of print].
- [43] Government of Alberta. Alberta health and wellness drug benefit list, https://www.ab.bluecross.ca/dbl/pdfs/ahwdbl_april_list.pdf; 1 April 2012 [accessed 03.07.12].
- [44] Program on International Nonproprietary Names (INN), World Health Organization. Guidelines on the use of international nonproprietary names (INNs) for pharmaceutical substances, http://whqlibdoc.who.int/hq/1997/WHO_PHARM_S_NOM_1570.pdf; 2007 [accessed 20.08.12].