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CONSULTATION ON THE REGULATORY FRAMEWORK FOR SUBSEQUENT ENTRY BIOLOGICS – SUMMARY REPORT

June 5 - 6 2008
Chateau Cartier, Aylmer, Quebec

HEALTH CANADA
CENTRE FOR POLICY AND REGULATORY AFFAIRS
BIOLOGICS AND GENETIC THERAPIES DIRECTORATE

Canada

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Consultation Summary

In twelve hours of meetings over two days in early June 2008, 105 government and stakeholder representatives enjoyed the opportunity to exchange information and views with regard to Subsequent Entry Biologic products (SEBs). A series of presentations were followed by intensive table discussions around the key issues, including fundamental concepts, quality requirements, clinical requirements, intellectual property, comparability, and post-market measures.

Overall, the sessions saw a significant amount of consensus and also highlighted a number of key areas of divergence.

Consultation Objectives

In bringing together a diverse group of stakeholders, the Biologics and Genetic Therapies Directorate (BGTD) of Health Canada hoped to accomplish four key objectives:

1. To impart comprehensive information on issues and options with regard to SEBs
2. To stimulate broad-based discussion on SEBs involving innovators, generics and government.
3. To seek feedback on the draft Guidance Document.
4. To hear suggestions from participants regarding the way forward.

Given the preliminary nature of the discussion, there was no expectation that the consultations would lead to consensus regarding how Health Canada should manage SEBs.

Consultation Process

In early June 2008, BGTD of Health Canada brought together a range of industry stakeholders for a two-day meeting about SEBs.

An SEB is a biologic product that would enter the market subsequent to, and similar to, an approved innovator biologic, which would rely, in part, on prior information deemed relevant to demonstration of similarity. (Note: It is the demonstration of similarity that makes the prior information relevant).

The sessions were held on June 5 and 6, 2008. The consultation comprised a number of presentations to the full group, as well as six separate breakout sessions to discuss a number of issues in more detail. The agenda for the sessions is appended to this report.

Most presentations on Day 1 were provided by representatives of Health Canada, but there were also presentations by a representative of the World Health Organization and two manufacturers (one innovator and one generic[1]).

Breakout sessions on Day 2 involved focused discussions by tables of 6 to 8 people who responded to workbook questions designed by Health Canada. One individual at each table recorded the collective response to the questions in the workbook, including any dissenting opinions.

Approximately two-thirds of the consultation was devoted to presentations and questions from the floor, while one-third was devoted to the break out discussions.

Participants in the consultations were representative in nature. Innovator and generic industry participation was balanced. Invitations were sent based primarily on an expression of interest in response to an online posting. Provincial and patient group participation was actively sought although the response from these groups was low. The approximate breakdown of the participants is shown in the following table.

Stakeholder Group	Participants
Innovator	39 %
Generic	35 %
Innovator/Generic	10 %
Patient Groups	2 %
Non- Health Canada Federal Government	2 %
Provincial Government	1 %
Other (law firms, suppliers, consultants, etc)	11 %

Participants were assigned seats during the main sessions to ensure a mixture of viewpoints at each table. This approach was explicitly praised by a number of participants in the evaluation comments.

At the close of the session, participants were asked to complete an evaluation form which included 12 closed-ended questions and an opportunity to provide comments. These evaluations, which were very positive overall, are summarized and discussed in Appendix B.

Key Themes

The detailed discussions are reported in the following sections of this report, but a number of points emerged as key themes throughout the discussions.

[1] Unlike pharmaceuticals, biologic products cannot be separated clearly into *innovators* and *generics*, primarily because the high degree of variation inherent in these products makes identical products impossible. Nonetheless, the terms *innovator* and *generic*/*SEB* are used in this report to distinguish between entirely new biologic therapies and subsequent-entry products which are intended to mimic or replace previously-approved innovator products.

There is wide agreement from all participants that criteria for SEBs should be based on good science and with patient safety foremost. Although definitions of these terms vary somewhat between different stakeholders, they agree that these ideas should be paramount. Issues such as data protection, patents and economic impact are important but secondary considerations.

There was clear agreement among participants that SEBs, while in some ways analogous to Second Entry pharmaceuticals ('generics'), cannot be treated in the same way within the existing regulatory framework. SEBs are expected to face a more demanding approval process than pharmaceutical 'generics' because they cannot claim to be identical to the biologics used as reference products. While SEB submissions may be allowed to use an abbreviated data package, there was wide consensus that, once approved, they will be treated in a manner similar to innovator products in terms of pharmacovigilance and risk management.

Related to the analogy to generic pharmaceutical drugs, there is an underlying concern that physicians and patients will view SEBs and innovator drugs as interchangeable and substitutable. This is of real concern because of potentially significant differences between the products.

While most of the evaluation criteria for SEBs appeared to be acceptable to most participants, the issue of use of foreign reference products was a clear point of contention. Innovator companies at the sessions generally rejected the idea that a biologic product could enter the Canadian market as an SEB and benefit from using an abbreviated data package if the reference product was not already approved/marketed for sale in Canada. In contrast, many participants from the generic industry felt that biologics approved in some foreign countries should be accepted as reference products for an abbreviated submission data package.

There is an inevitable tension among stakeholders between the desire to avoid inflexibility when regulating an emerging area such as SEBs and the possibility of developing a somewhat *ad hoc* process which is insufficiently clear or predictable. While stakeholders often suggested a case-by-case approach, they also expressed some frustration that too much was being left undefined in the draft *Guidance Document.*

Stakeholders are also somewhat split on the relative role of the *Guidance Document* and the *Regulations*. While some are content to move forward based on a guidance document, others feel that any guidance document should be based on revised regulations.

Fundamental Concepts and Underlying Philosophy

During the opening plenary, Dr. Kwasi Nyarko (BGTD) gave a presentation on fundamental concepts and underlying principles related to SEB's. A breakout session on this topic included four tables. Dr. Nyarko was present to answer questions. The workbooks contained six questions, but most tables only had time to answer two or three questions.

Question 1: What SEBs fall outside the scope of the draft guidance document and/or are there any products that you anticipate will be inadvertently included because of the proposed definition?

There is consensus that blood products and vaccines would necessarily be excluded from the SEB pathway because these products cannot be adequately characterized. Conversely, there is support for the inclusion of any biologic product which can be well characterized. Nonetheless, some ask if the proposed definition might inadvertently exclude small molecule heparins or synthetic version of biologic products, such as synthesized peptides. One table specified that any biologic products currently managed by TPD (as opposed to being managed by BGTD) should be reclassified to align with the SEB guidance.

Within this discussion, two of four tables tackled the question of regulations versus guidance. Innovators tend to feel that the regulations should be amended to reflect the new environment and provide specific pathway for SEBs. This would, they argue, provide consistency, fairness and a needed link to the PM (NOC) regulations. SEB producers tend to feel that the current regulatory system is adequate to support guidance on SEBs.

Within the question of the regulations, a number of participants expressed a desire to see product-specific or class-specific guidance documents. The EMEA is seen to provide a good example in this regard.

Question 2: What considerations should be taken into account in the choice of a reference product and why?

This question tends to focus respondents on the issue of a foreign reference product. There is disagreement on this issue, as discussed below, but there is also agreement on several key points:

- Most agree that Health Canada must evaluate all SEB's, regardless of their status elsewhere. Use of foreign *data* should not equate with reliance on foreign regulatory *decisions*.

- There is unanimity that the SEB pathway should require equivalent levels of scientific certainty as is required by innovator products. Thus, reference products must be known to Health Canada and have sufficient duration and volume of use. (The differences on this issue relate to acceptable sources and types of data.)

- There is interest in a global data package acceptable to Health Canada.

Some argue that SEBs should only use biologics approved/marketed in Canada as reference products. This is based primarily on the view that such reference products are already known to Health Canada and have produced, by definition, 8 years of safety and efficacy data before an SEB can enter the market.

This group appears to accept the use of a foreign reference product if a substantially identical product is already marketed in Canada. However, there is a general belief that SEBs should be

required to provide clinical data to support specific indications unless there is a *scientific* rationale why this cannot be done.

Others argue that reference products from other jurisdictions should be allowed, even though Canadian reference products would be preferred. This is motivated by the belief that Canadian regulators should be able to consider foreign experience in evaluating an SEB and a belief that an SEB should not be kept from the Canadian market because the Innovator never sought approval for the reference product in Canada.

Within both groups there were questions about a number of factors which could affect the choice of reference product. If only Canadian reference products were used, must they be marketed or simply approved? And what would be the impact of a market withdrawal unrelated to safety?

One table of four specifically affirmed that SEBs should not themselves serve as reference products for other SEBs.

Another table felt that the current sharing of information through Memoranda of Understanding is 'not satisfactory'. They also noted that there are intellectual property implications of international data sharing.

Question 3: How should the existing regulatory pathway for generic pharmaceuticals (abbreviated new drug submission – ANDS) be used in the development of the proposed regulatory framework for SEBs?

Three tables addressed this question, two of which suggested that SEBs should have their own pathway in the regulations rather than an SEB version of the ANDS.

As in other discussions, some Innovators suggested that there should be new regulations to cover SEBs, while SEB producers tended to feel that the process could move forward based on guidance documents alone.

One table suggested that the SEB should have a unique brand names rather than using INN names. Another table stressed the importance of better definitions in the guidance document.

Quality Requirements

Dr. Anthony Ridgway (BGTD) gave a presentation during the opening plenary on quality requirements for SEB's. He was present to answer questions during a subsequent break out discussion session which included four tables that completed workbooks on this topic.

Question 1: What is considered a suitable starting material for a SEB?

Most tables concluded that starting material used for a biologic was not directly relevant to whether it is accorded SEB status or not. They believe that clinical requirements and the requirement to demonstrate *biosimilarity* are the issues of importance. While a SEB sourced

from a very different source than the reference product would likely face significant hurdles, few thought this should automatically be the basis for exclusion.

One table, however, pointed out that an innovator which changed to a different starting material would be required to submit an NDS. They therefore felt that subsequent entry biologics using different starting material should be required to submit a NDS rather than use the SEB pathway.

Question 2: How closely matched should the manufacturing process be?

All four tables discussing this issue point out that manufacturing processes for innovator products are not known and are closely guarded secrets. Even where the source material is known, other steps such as filtering are not in the public domain. What is more, processes change over time so information may no longer be current. It is therefore impossible, they say, to judge the similarity of processes between an SEB and its reference product. Furthermore an emphasis on comparable processes might discourage innovation in the production of SEBs.

Instead, participants stressed that the *products* should be compared, rather than the *processes*.

Question 3: What is a suitable end-point or goal for demonstration of similarity?

The three tables which addressed this question offered disparate answers.

One table asserted that pre-set criteria are needed, possibly based on monographs but going further. The further from the reference characterization the SEB is, the more clinical data should be required.

A second table stated simply that differences in impurities are not suitable endpoints, but that the actual end-point would depend on the complexity of the product and the potential consequences of all differences.

Another table pointed to the "whole package" as the end-point, specifically physicochemical characteristics, characterization, pre-clinical data, and clinical data, all obtained in a stepwise approach. They referred to a "complete Module 3 and comparability." They also suggested that a pre-defined list of criteria for assessing comparability would be useful to industry.

Question 4: How much clinical data should be permissible in the demonstration of a structural similarity (given that physicochemical/biological/immunological similarity is the foundation/premise for the SEB pathway)?

Most tables agree on two points related to this question.

First, they feel that clinical data is not the best or primary way to demonstrate structural similarity between an SEB and a reference product. In their view, clinical studies are to be used to demonstrate comparable *effect*, while physicochemical data is used to demonstrate *structural* similarity.

Second, they avoid proposing general requirements for data requirements and instead say that there should be requirements for specific classes or specific products. Some say that much depends on the molecule itself and the complexity of the product. One table suggested Health Canada should indicate at the pre-submission stage the amount of clinical data required. Another table expressed concern, however, that the guidance document is too open to a case-by-case approach, leaving potential sponsors uncertain regarding Health Canada's expectations.

Immunogenicity data was of particular interest to one table, which noted that immunogenicity cannot be predicted without clinical data.

Question 5: Once a SEB is on the market, what is more important following a manufacturing change: internal comparability or similarity to a comparator?

All participants agreed that, once approved, an SEB should only be compared to itself after a manufacturing change. Their position is premised on the assumption that the SEB and reference product are not *substitutable* although they may be considered *interchangeable*. In support of this view, they note that innovator products will also change over time. Thus, once an SEB is approved, it should no longer be judged in comparison with the reference product.

Question 6: What type of stability studies would be needed for SEB products?

Only one table tackled this question. They felt that, in keeping with ICH guidelines, studies should generate data that compares the degradation of the SEB and the reference product.

Clinical Requirements

Dr. Agnes Klein (BGTD) provided an overview of clinical requirements for SEBs during the opening plenary. Dr. Klein was also present as four tables participated in a break out session on this issue. Each table discussed the issues and completed a workbook on the subject.

Question 1: What is the optimal way to design clinical trials for SEBs that provide a reasonable confidence in the data from the point of view of both safety and efficacy?

While all four tables agreed that clinical trials should be rigorous and based upon good science, there are few other common threads in the discussion. The tables do appear to agree, however, that the studies should be equivalence (preferably) or non-inferiority studies and that superiority studies are not appropriate for an SEB.

Two tables stressed the value of using non-Canadian reference products, given the size of the Canadian market.

Two tables noted that the pre-clinical component of the SEB guidance is too "light."

The following points were made by individual tables.

- Studies should be double-blind parallel comparative clinical trials of sufficient duration, to be agreed upon by a pre-CTA meeting.
- If PK/PD shows bioequivalence, efficacy requirements might be reduced.
- Studies should last at least six months, but length should be determined on a case-by-case basis.
- Immunogenicity studies should be required and take patient safety into account.
- Toxicity trials should include at least two species (rodent and non-rodent.)

There is disagreement about how well-defined the criteria should be. While one table feels that study criteria should be set on a case-by-case basis at a pre-CTA meeting, another table argued for greater specificity in guidance.

Question 2: Do you concur that a pathophysiologic approach would be a good way to group indications for SEBS?

Two tables believe that the grouping of indications should be done on a case-by-case basis. Two tables also placed importance on including the most sensitive populations in the studies. One suggested that PK/PD is a reasonable approach to grouping indications.

Question 3: What would clinical requirements look like if and when there is a change in API manufacture?

Only three tables briefly addressed this question. Their responses were as follows:

- The same requirements should apply to both the SEB and the innovator according to the appropriate Health Canada requirements.
- There should be a PK/PD equivalence study followed by discussion with Health Canada before proceeding with a clinical trial if applicable.
- This is outlined in ICH.

Intellectual Property, Data Protection and Patents

A presentation by Anne Bowes (TPD) during the opening plenary session provided information on patent and data protection related to SEBs. In a subsequent breakout discussion session, three tables held separate discussions on this topic and completed workbooks. Mr. Waleed Jurban (TPD) was present to answer questions during the breakout discussion session.

Question 1: What type of comparative data should be considered to determine when the data protection provisions will be triggered?

There is divergence of opinion regarding the triggering of data protection provisions. All participants would agree that data protection is triggered if some of the innovator comparison data used by an SEB is not in the public domain. Some believe that data protection should apply even if the innovator product data is in the public domain. Others believe that the use of public

domain data (alone or with SEB-owned data) should not trigger data protection. Overall, the latter opinion appears to have been the common of the two.

There is clearly uncertainty on this point and two tables specifically suggested greater clarity is needed.

Question 2: With regard to biologics, what variations should or should not be considered to be eligible for data protection (E.g. pegylated products, fragments of previously approved proteins)?

Several tables struggled with this question, and a number of sub-questions emerged:

- What is the definition of an "innovative biologic"?
- On what bases would exclusions from "innovative" status be used?
- Do we consider mechanism of action or immunogenicity?
- What signals a sufficient variation to justify data protection?

Two tables suggested that a clinically significant difference in clinical outcomes (to be defined) might be considered sufficient. They suggested that this question is difficult to answer in the abstract and could more easily be tackled by class.

Another table suggested that the EU definitions for biologic variations that trigger new periods of exclusivity for orphan drugs might form a basis for determining what variations in biologics should be eligible for data protection.

Methods in Comparability

A key aspect of the proposed approach to SEBs is the comparability of the SEB and a reference product. During a breakout discussion session, four tables held separate discussions on comparability and completed workbooks. These sessions were supported by presentations during the opening plenary by two industry participants, Dr. Andrew Fox (Amgen) and Dr. Bruce Clark (Apotex). Mary Alice Hefford (BGTD) was was present to answer questions during the breakout discussion session.

Question 1: What might a demonstration of similarity look like?

Sub-question I: What kinds of methods (at a minimum) would be needed to demonstrate similarity of primary structure, secondary structure, tertiary structure?

There is general agreement that modern, state-of the art methods should be used to demonstrate similarity, including secondary and tertiary approaches where possible. There is further agreement that the methods required should reflect the complexity of the protein molecule.

There is disagreement, however, as to whether requirements should be the same as used by the innovator. Indeed, several tables suggest that requirements should be set for specific classes, possibly modeled on EMEA guidelines.

Sub-question II: Is there a need for redundancy/orthogonal methods?

There is general agreement that redundancy and/or orthogonal methods are valuable and should be included. However, orthogonal methods are only needed, according to several tables, if sufficient redundancy cannot be achieved. This would be determined on a case-by-case basis. One table suggests that additive methods may be of further value.

Sub-question III: Should there be requirements for sponsors to use particular state-of-the-art methodologies (capillary electrophoresis, NMR, etc.) for certain classes of compounds?

Only two tables addressed this question directly, but both endorsed the use of state-of-the-art techniques for some classes, especially if the class has unique specificity to a particular test. However, one table cautioned against referencing specific technologies in the guidance because such references might become quickly outdated.

Sub-question IV: Does one need to test proteins under stress conditions to tease out difference?

There is wide agreement that side-by-side stress testing is a valuable tool, although only one table suggests that it should be *required*.

Sub-question V: Do product-related impurity profiles need to be similar?

Of the three tables which addressed this question, two felt that impurity profiles do not need to be similar, while the third table thought this was necessary for chemical comparability. All tables agreed, however, that impurity differences should be justified and demonstrated to have no clinical impact.

Sub-question VI: What would be the role of bioassays?

Bioassays are seen as useful to demonstrate comparability, through confirmation of 3D, consistency in manufacturing, and comparability of biological activity.

Sub-question VII: What role should PK and PD studies play?

Participants say that PK/PD studies may detect any difference that affect absorption or disposition. If PD is a surrogate endpoint, then a PK/PD will provide critical information on comparable efficacy.

Sub-question VIII: How much can physico-chemical methods tell you about biology?

Physico-chemical methods have limited power to explain biology, according to participants. They can, however, indicate the presence of issues requiring additional exploration or offer additional confidence when moving to *in vivo* testing.

Sub-question IX: How many lots of innovator products would need to be tested?

The number of lots to be tested depends on the tests planned and their variability. Participants suggest a minimum of three lots. One table suggested that the number of lots must be justified by the sponsor.

Question 2: What are the pros and cons of "de-formulation" of a drug substance?

Participants agree that this process is helpful and adds confidence to the process. Although it is not completely reliable, there are no evident alternatives. Two of three tables specified that de-formulation is unnecessary if a biologic can be adequately characterized in formulation, possibly through a bioassay.

There is consensus that albumin formulations create challenges for de-formulation, as they may change the active protein. Participants offer no solutions to this challenge other than to suggest reliance on methods other than de-formulation.

Question 3: What type of non-clinical studies might help address issues of immunogenicity?

Three tables responded to this question. Two tables suggested that non-clinical trials (including animal tests) are incapable of predicting immunogenicity. A third table stated that animal tests of sufficient duration would elicit an immunogenic response, which would form part of a toxicokinetic study. That table noted their agreement with the combination of toxicokinetic study and immunogenic monitoring suggested in the *Guidance Document.*

Post-Market Requirements

Dr. Souleh Semalulu (MHPD) gave a presentation overview of post-market issues related to SEBs during the opening plenary and was present to answer questions during a subsequent break out discussion session on this subject. Five tables held separate discussions and completed workbooks.

Question 1: What are the desired risk evaluation and mitigation strategies (REMS) for SEBs?

A number of risk management strategies were raised by most or all of the tables.

- Registries of patient AEs/ARs, possibly including patient-reporting.
- Periodic Safety Update Reports (PSURs), same frequency as reference product.
- Tracking of specific products in case of adverse reaction
- Education of patients and health care professionals about meaning of 'similarity'.

A number of suggested REMS components relate to the labelling and naming of SEB products. Participants want to avoid rapid switching or substitution between SEBs and innovators because this may create immunogenicity issues or inhibitors across a class of products. Participants propose to avoid this situation by providing clear warnings on labels, requiring SEBs to have a unique brand names and ensuring that patient prescriptions specify a brand name. One table suggested that the NOC should specify that Health Canada has not made a determination of interchangeability.

There is no consensus as to whether SEB REMS should be linked to the REMS of the reference innovator product.

Two tables raise the possibility that clinical trials might continue after approval of the SEB, specifically to close any data gaps in the submissions and track immunogenicity. These would be decided in advance on a case-by-case basis.

Question 2: When should sponsors of SEBs be required to submit REMS?

Among the three tables which answered this question, there is agreement that REMS should be submitted before approval and that they should be in development throughout the product development cycle. They believe that there should be ongoing discussion between manufacturers and Health Canada to design the REMS, taking into account the innovator product experience. Finally, there is some suggestion that REMS should continue to evolve after approval in response to new science and new signals.

Question 3: What are the pharmacovigilance tools that will be required for SEBS? When? How often?

A priority for participants with regard to pharmacovigilance is the trackability and traceability of specific products. They say it is important to have good records of who is taking which biologics and which patients have switched between different biologics in the same class.

Education of health care providers and patients is mentioned by two tables as an important element of post-market oversight and risk management.

Participants also mention PSURs as important pharmacovigilance tools. Two tables suggest that PSUR frequency should be aligned with ICH requirements and tailored to the risk associated with the product.

Question 4: How will these be aligned with international regulatory partners?

There is overall support for some harmonization/alignment with other jurisdictions. The two key points of alignment would be:

- safety data sharing between governments using compatible data formats; and
- coordination of reporting periods and timelines.

The ICH was specifically mentioned by two tables as the appropriate mechanism for international alignment. One table also stressed the importance of respecting Canadian clinical and legal practice, however.

Additional Issues

Participants raised a number of issues which, although they fell outside the agenda of the sessions, evidently sparked interest and discussion in the room. These are presented below as areas deserving further attention.

Given that the majority of stakeholders in these sessions represented industry, there is considerable interest in knowing what other stakeholder groups think about the issues around SEBs. This would include patients, health care professionals and the provincial/territorial governments.

One key reason why some stakeholders are anxious to hear what provinces and territories have to say in particular is the fact that substitution and interchangeability will be played out primarily within the provincial formularies. Stakeholders are interested in what those governments (and the CDR) will make of the proposed pathway for SEBs.

Consultation with patients was an issue raised strongly by the patient representatives attending this session. They emphasised the perspective and legitimacy that patient groups can bring to the process of regulatory change.

One Minute with the Minister

At the close of the session, each table was asked to think about what they would say to the Minister of Health on the subject of SEBs if they had one minute. This allowed each table, comprising diverse stakeholders, to sum up the accumulated consensus from the session, identify divergences, and provide a suggested way forward. The following bullets provide those comments, in verbatim form.

- *This was a successful international meeting, we achieved consensus on a number of issues, and we look forward to a finalized guidance on SEBs by October.*
- *Patient safety should be the overriding concern. Some of us feel the regulations are currently adequate to support guidance, but others believe that new regulations are needed.*
- *There is an international will to proceed forward on this file. There is a careful balance between timeliness and moving forward carefully with all our ducks in a row, keeping patient safety foremost in our mind.*
- *Patient safety and good science are the most important things. We were not sure that the bottom up approach is best – producing guidance first - or if regulations should come first.*

- *There was a lot of consensus. There is a way forward. There are items which still need to be settled, however, and they must be settled in a rigorous scientific manner with patient safety as a priority.*
- *We need a predictable and reliable process. We need the provinces at the table. We hope that SEBs will not be delayed by the progressive licensing process.*
- *Do not proceed with anything until you have involved patient groups at every step of the way.*
- *There is a way forward. There are issues with IP, the pathway, the definitions. But keep up the momentum. Take the time to get it right and consult with patients.*
- *We are not sure if the regulations should be changed first or the guidance is adequate. Consultations with provinces and other stakeholders should also be held.*

Definitions

AEs/ARs	adverse events/ adverse reactions
CTA	Clinical Trial Application
ICH	International Conference on Harmonization
IP	Intellectual Property
MHPD	Marketed Health Products Directorate (Health Products and Food Branch, Health Canada)
NDS	New Drug Submission
BGTD	Biologics and Genetic Therapies Directorate (Health Products and Food Branch, Health Canada)
PK/PD	Pharmacokinetics and Pharmacodynamics
PM/NOC	Product Monograph/Notice of Compliance
PSURs	Product Safety Update Reports
REMS	Risk Evaluation and Mitigation Strategies
SEBs	Subsequent Entry Biologics
TPD	Therapeutic Products Directorate (Health Products and Food Branch, Health Canada)

Appendix A: Agenda

Day 1 (June 5)

Time	Activity	Details
8:30 am	Welcome Address	Dr. Siddika Mithani Associate Assistant Deputy Minister, Health Products and Food Branch (HPFB), Health Canada
8:40 am	Canadian Approach for SEBs	Dr. Elwyn Griffiths Biologic and Genetic Therapies Directorate, HPFB, Health Canada
8:55 am	Consultation Overview	Mr. Frank Van Gool Certified Professional Facilitator GROUPE INTERSOL GROUP
9:00 am	Global Guidance for Evaluation of SEBs – update	Dr. Ivana Knezevic Quality, Safety, Standards Team, World Health Organisation
9:30 am 9:50 am 10:00 am	Fundamental Concepts and Underlying Principles for SEB Regulatory Framework ▪ Table Discussions: o Key Messages o Reactions o Questions of Clarification and Understanding ▪ Questions and Answers	Dr. Kwasi Nyarko Centre for Policy and Regulatory Affairs, BGTD, HPFB, Health Canada
10:20 am	**BREAK**	
10:30 am 10:50 am 11:10 am 11:25 am	Quality Requirements Clinical Requirements ▪ Table Discussions	Dr. Anthony Ridgway Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, BGTD, HPFB, Health Canada Dr. Agnes Klein Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, BGTD, HPFB, Health Canada

	▪ Questions and Answers	
12:00	**LUNCH**	
1:00 pm 1:20 pm	Progressive Licensing Project and Regulatory Framework for SEBs ▪ Questions and Answers	Mr. David Lee Progressive Licensing Project, HPFB, Health Canada
1:30 pm 1:50 pm	Post-Market Requirements ▪ Questions and Answers	Dr. Souleh Semalulu Marketed Biologicals, Biotechnology and Natural Health Products Bureau, Marketed Health Products Directorate, Health Canada
2:00 pm 2:20 pm	Patent and Data Protection ▪ Questions and Answers	Ms. Anne Bowes, A/ Director, Office of Patented Medicines and Liaison, Therapeutic Products Directorate, HPFB, Health Canada
2:30 pm	**BREAK**	
3:00 pm	Patient Safety, Immunogenicity and the regulation of SEBs	Dr. Andrew Fox, Director, Regulatory Affairs Amgen - Corporate Headquarters - USA
3:30 pm	Comparability and Regulation of SEBs	Dr. Bruce Clark, VP Regulatory and Medical Affairs, Apotex Inc.,
4:00 pm	Closing and Sign-up for Day 2 Facilitated Breakout Sessions	Dr. Kwasi Nyarko Centre for Policy and Regulatory Affairs, BGTD, HPFB, Health Canada

Day 2 – (June 6)

Time	Activity	Details
8:30 am	Welcome and Introduction to Day 2	Ms. Catherine Parker Centre for Policy and Regulatory Affairs, BGTD, HPFB, Health Canada

TIMESLOT #1 – Facilitated Breakout Sessions	
8:45 am	(1) Fundamental Concepts and Underlying Philosophy
	(2) Quality Requirements
	(3) Clinical Requirements
10:15 am	**BREAK**
TIMESLOT #2 – Facilitated Breakout Sessions	
10:30 am	(4) Intellectual Property, Data Protection and Patent
	(5) Methods in Comparability
	(6) Post-Market Requirements

12:00 pm	**LUNCH**	
1:00 pm	One minute message to the Minister	Session Facilitators
1:30 pm	Closing	Dr. Elwyn Griffiths

Appendix B: Participant Evaluations

At the close of the sessions on Day 2, consultation participants were asked to complete a one-page evaluation form contained in their meeting binders. 30% of participants completed their forms.

As the table shows, participants were generally very positive about all aspects of the sessions, with negative assessments limited to between zero and seven participants at most.

Participant Evaluations of the SEB Consultation Session

	Total Agree	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Total
Background materials contained sufficient information to prepare you to participate in the Consultation.	33	13	20	1	0	0	34
The participants in this Consultation represented those who will be affected by the proposed Regulatory Framework for Subsequent Entry Biologics.	27	13	14	0	7	0	34
Sufficient information was provided about how the results of this Consultation will be used in the decision-making process.	25	6	19	3	6	0	34
The objectives of the Consultation were clearly defined upfront (i.e. you understood the purpose of the Consultation).	33	14	19	0	1	0	34
The Consultation provided you with a better understanding of the proposed Regulatory Framework for Subsequent Entry Biologics.	31	17	14	3	0	0	34
The Consultation allowed for adequate discussion of the Guidance document policy statements.	30	15	15	3	1	0	34
The Consultation allowed for adequate discussion of the Quality submission requirements?	28	7	21	6†	0	0	34
The Consultation allowed for adequate discussion of the Clinical submission requirements?	26	9	17	7	1	0	34
The Consultation provided sufficient opportunity for you to give feedback on the issues of importance to you/your organization?	31	9	22	1	2	0	34
Based on your participation in this Consultation, your understanding has increased regarding what could be asked of your organization, in order to comply with the Guidance document and for the proposed Regulatory Framework for Subsequent Entry Biologics.	28	6	22	3	3	0	34

The facility for this Consultation was adequate.	29	7	22	3	1	1	34
	Total Agree	**Strongly Agree**	**Agree**	**Neutral**	**Disagree**	**Strongly Disagree**	**Total**

† Includes one evaluation which was blank for this question.

A few findings from the evaluations stand out and may prove useful for future consultations.

- One area of lower enthusiasm was the information provided on how the session feedback would be used in decision-making. Some felt this was not adequate.

- Another area where there was some dissatisfaction relates to the representation of all groups in the sessions. It was evident from the written comments that some felt that two groups were notably absent: patients and the provinces.

- Participants are less likely to *strongly agree* that the sessions provided adequate time for them to provide feedback on issues they consider important. In this regard, it should be remembered that the format of the sessions emphasized collective discussion in break out groups rather than individual statements in plenary.

- Although the consultation rooms were excessively warm at times, most participants offered a positive assessment of the facility.

Twenty of the thirty-four participants that provided evaluations took the opportunity to expand on their ratings in their own words and/or offer additional suggestions[2]. Those comments are presented verbatim below. Evidently, these participants were enthusiastic about the sessions and especially about the opportunity to meet face to face with other stakeholders.

- *Absolutely, face to face is needed to inform stakeholders. More consultation should be established prior to finalizing this. Regulations are needed for SEBs. Should be established sooner rather than later.*
- *Background materials need to be provided earlier. Should have had more representation from patients. Where were the provinces? Questions could have been provided in advance.*
- *Excellent for understanding and exchange of ideas. Face to face brought more consensus to good science. More consultations needed to continue this effort as things progress.*
- *Excellent forum for discussion with colleagues. Very glad to get international input and perspective as we live in a global world.*

[2] The open-ended question in the evaluation actually asked about the value of face to face meetings such as this one. Some participant answered that question while others offered other comments.

- *Excellent meeting. More work to be done as multidisciplinary issue. Patient safety first and foremost. Good science is that which understands there are unknowns. It was great to hear at a personal level, independent of innovator/generic affiliation, that there are issues with biologics and it is not the same as generics. There shouldn't be a push; it should be based on right thing to do.*
- *Excellent opportunity for dialogue with Government, Industry and International Stakeholders on this important issue. Would have been useful to have short sessions from each stakeholder group (patient advocacy, innovators, generics, lobby groups). Thanks.*
- *Face to face consultation pre-submission meeting on special requirements would be helpful. Thanks for organizing this event.*
- *Face to face is an excellent complement to written submissions. Also it was good to have a mixed representation at each table.*
- *Face to face is key when wanting to move forward. Excellent means to highlight consensus but also differences.*
- *Face to face is very useful. Format of mixing stakeholders with assigned seats was very beneficial. Provincial participation would have been helpful at a common consultation.*
- *Good meeting.*
- *Great meeting. Thank you!*
- *I have been to similar meetings held by FDA and EMEA. This meeting was the most successful one. The interaction between people was great, the atmosphere was superb. This is the best process: face to face with people from all disciplines. Thank you!*
- *I recommend that the SEB pathway be first enshrined in the FDR the same way as ANDS were done. This would give backbone for this Guidance which can then be finalized; I recommend that any interchangeability and substitution be removed from the guidelines. I recommend that the option of a non-Canadian reference product be removed.*
- *I think this is useful and should be used more often. The table set-up with people from different perspectives was very useful generating true discussions and debates. Consensus was tough or impossible but points were well taken.*
- *Need to involve patients, provinces, health care providers. Need to take a robust and top-down approach: Regulations <u>then</u> guidance. Current regulations are inadequate.*
- *The meeting was very well organized. The ramifications for Industry globally with an interest in Canada are significant. Unique elements to Canada (payers and provinces) need to be engaged since they have increased confidence in decisions from Health Canada and its decisions regarding generics.*
- *This is a useful approach having Industry and other stakeholders meet with regulators to better understand the implications associated with the regulations/guidance.*
- *Workshop approach worked well. Disappointing that there was no time for questions after the Industry speakers on Day 1. This was the first opportunity for innovator and SEB manufacturers to hear each other's positions and it would have been important for Health Canada to hear questions and answers for each.*