Association Bilateral Meeting
Health Canada (HC) - Health Products and Food Branch (HPFB) –
Biologics and Genetic Therapies Directorate (BGTD)
Record of Decisions

FINAL

Cell Therapy Stakeholder Group (CTSG)

100 Eglantine Driveway, Boardroom 1278, Ottawa, Ontario

Tuesday April 30, 2019
(1:00 p.m. to 3:55 p.m.)

Cell Therapy Stakeholder Group Participants

Sowmya Viswanathan, CellCAN, International Society for Cell & Gene Therapy (ISCT), North America Legal & Regulatory Affairs (NA LRA) Member, CTSG Co-Chair

Siofradh McMahon, Centre for Commercialization of Regenerative Medicine (CCRM)

Steven Keizer, CCRM

David Courtman, CellCAN

Samantha Hodgins, CellCAN (via telecon)

Craig Hasilo, CellCAN

Helen Yu, CellCAN

Leah Kesselman, CellCAN

Friederike Pfau, CellCAN (via telecon)

Erika Kleiderman, CellCAN

Gayle Piat, CellCAN (via telecon)

Martin Giroux, Centre of Excellence for Cellular Therapy (CETC) (via telecon)

Patrick Bedford, ISCT

Michael Mendicino, ISCT (via telecon)

Karen Nichols, ISCT (via telecon)

Olive Sturtevant, ISCT (via telecon)

Jodie Garner, Ontario Institute for Regenerative Medicine (OIRM)

Jonathan Draper, Stem Cell Network

Health Canada Participants

Celia Lourenco, Director General (DG), BGTD, HPFB, Co-Chair

Kelly Robinson, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB), BGTD, HPFB

Liz Anne Gillham-Eisen, Office of Policy and International Collaboration (OPIC), BGTD, HPFB

Megan Bettle, Regulatory Review of Drugs and Devices (R2D2), BGTD, HPFB

Francisca Agbanyo, Centre for Biologics Evaluation (CBE), BGTD, HPFB

Jessie Lavoie, CBE, BGTD, HPFB

Anthony Ridgway, CERB, BGTD, HPFB

Kyle Norrie, OPIC, BGTD, HPFB

Nadine Kolas, OPIC, BGTD, HPFB

Andrew Henderson, OPIC, BGTD, HPFB

Lise Cobitz, OPIC, BGTD, HPFB

Christopher Antonio, Office of Regulatory Affairs (ORA), BGTD, HPFB

Suzanne Lecour, Office of Business Integration and Risk Management (OBIRM), BGTD, HPFB

Beth Beaulieu, OBIRM, BGTD, HPFB

Tonja Stothart, Marketed Biologicals, Biotechnology and Natural Health Products, Marketed Health Products Directorate (MHPD), HPFB

Julie Chateauvert, Environmental Impact Initiative, Policy, Planning and International Affairs Directorate (PPIAD), (via telecon), HPFB

Claire Hughes, Environmental Impact Initiative, PPIAD (via telecon), HPFB

Bogna Lasia-Szkaradkiewicz, Health Product Inspection and Licensing, Health Canada, Regulatory Operations and Enforcement Branch (ROEB)

Danielle Lozon, Health Product Inspection and Licensing, ROEB (via telecon)

Mimi Lin, Health Product Compliance and Enforcement, ROEB

Deborah Ashby, Emerging Sciences Division, New Substances Assessment and Control Bureau (NSACB), Healthy Environments and Consumer Safety Branch (HECSB)

Joelle Pinsonnault Cooper, Food & Drugs Act (F&DA) Substances Assessment Division, NSACB, HECSB

Valar Anoop, Emerging Sciences Division, NSACB, HECSB (via telecon)

1. Welcome and Introductions

Kelly Robinson, Director, CERB, opened the meeting on behalf of Celia Lourenco, DG, BGTD, HPFB, as she was in a meeting and would be joining the group later. Kelly welcomed everyone to the meeting and a round table of introductions followed.

An update on organizational changes within BGTD were provided. Kelly noted Cathy Parker's retirement as of December 24, 2018, and Celia Lourenco as the new DG for BGTD. She also introduced Marianne Tang as the new director for the Office of Regulatory Affairs (ORA), with Georgette Roy's retirement in December 2018. With Lindsay Elmgren's departure in September 2018, Michael Rosu-Myles became the new director of the Centre for Biologics Evaluation (CBE). Beth Beaulieu was introduced as BGTD's new Bilateral Meeting Program Coordinator, taking over from Ashley Baer.

Kelly notified CTSG that in early 2019, the Regulatory, Operations, and Regions Branch was renamed the Regulatory, Operations, and *Enforcement* Branch.

On behalf of the CTSG, Sowmya Viswanathan expressed the group's satisfaction at being at this meeting and how they were looking forward to hearing updates.
It was confirmed that there were no outstanding action items from our last bilat held on December 4, 2018.

There were no changes to the agenda.

2. Update on the Draft Supplementary Guidance Document for the Notification and Testing of New Substances: Organisms used in Gene Therapy and Immunotherapy

Issue	The New Substances program of Health Canada's Healthy Environments and Consumer Safety Branch (HECSB) provided an update on the draft supplementary guidance document for the Notification and Testing of New Substances: Organism used in Cell and Gene Therapies, and work done to date.
Presenters	Deborah Ashby, Manager, Emerging Sciences Division, NSACB, HECSB Joelle Pinsonnault Cooper, Acting Manager, F&DA Substances Assessment Division, NSACB, HECSB
Response	A supplementary guidance document was drafted and was sent to the CTSG and other relevant stakeholders for comments in March 2018. Comments were received in summer 2018 and a new version of the guidance will be available in summer 2019. The document is intended to complement the Guidelines for the Notification and Testing of New Substances: Organisms. It provides additional guidance on addressing information requirements under Schedule 1 (for release Anywhere in Canada) of the *New Substances Notification Regulations* (Organisms) (NSNR (O)) of the *Canadian Environmental Protection Act*, 1999 for substances that are animate products of biotechnology used in gene therapy, cell therapy or immunotherapy and administered to patients. The Annex of the deck includes NSNR (O) information requirements that align with Clinical Trail Applications (CTA) and information requirements specific to NSNR (O). The New Substances (NS) program has shortened the time taken to review a New Substances Notification (NSN) from 120 days to 30 days for cell and gene therapy substances used in a clinical trial to match the CTA assessment period of 30 days. Sponsors/Notifiers are encouraged to meet with the NS program to discuss submission requirements (can be before or at the same time as the pre-CTA meeting, in person or by teleconference call). They may also submit their environmental assessment package before submission of their CTA package, and should request an early termination of the assessment period, as early as possible to avoid delays. HECSB wanted to know from CTSG: • If they need additional guidance to fulfil information requirements under the NSNR (O)? • Is there interest in a "New Substances Notification (NSN) 101" presentation?

	• Is there interest in developing an industry-led case study on NSN submission for cell and gene therapy substances (e.g., human cells, non-replicating vectors, etc.)? HECSB provided CTSG with some updates and reminders: During the March 2018 workshop, there was support for the development of generalized literature reviews/biology documents. NSNs under the NSNR (O) of the CEPA is independent from the CTA of the F&DA; the NS Program does not have ready access to the CTA. A Pre-Notification Consultation (PNC) is not a prerequisite for the submission of a NSN, but is highly recommended and should be submitted well in advance of the CTA submission. For any questions or to initiate a PNC, CTSG was advised to contact the NS program at: **Environmental Assessment Unit 1** E-mail: HC.eau-uee.SC@canada.ca Telephone: 613-948-3591 or 1-866-996-9913 https://www.canada.ca/en/environment-climate-change/services/managing-pollution/evaluating-new-substances.html
Discussion points	CTSG commented that they have difficulty accessing the relevant types of information needed to complete Schedule 1 of the NSNR. Because of this, CTSG expressed interest in developing test case scenarios with the NS program. BGTD agreed that case studies for completing Schedule 1 would be helpful and will make the process more efficient for both applicant and reviewer. There was a discussion on trying to complete the Schedule 1 Form for genetically modified human cells. BGTD said that their understanding is that if the sponsor provides reasoned explanations to questions (as opposed to just providing a "Not applicable" answer), HECSB has considerable latitude on what is acceptable, adding that CTSG should get this message across to its members and take advantage of the PNC meeting (which can happen at the same time as the pre-Clinical Trials Application consultation meeting). HECSB agreed. CTSG said that they are aware of several clinical trials on hold, and they would like to see some case studies so they have an idea of what responses to provide. BGTD said that it would be ideal to find a way to solve these specific problems quickly. HECSB mentioned they know of one case, and have already gone through the missing information with this organization who was satisfied with the clarifications provided during the PNC meeting. BGTD clarified that HECSB is another Health Canada Branch outside of BGTD. BGTD includes the need for an environmental assessment in the meeting

	confirmation notice. Although the 30-day review policy is laudable, BGTD wanted to remind everyone that stakeholders also have a responsibility to submit their environmental assessment package as early as possible to avoid delays to the start of their clinical trials. BGTD asked HECSB if the stakeholder has to ask for that 30-day review or if it was automatic for CTAs or biologic drugs. HECSB confirmed that stakeholders need to ask HECS for an early termination of the assessment period (and to date, early terminations, under 30 days, have been granted for these files). CTSG said that their academic institutions often act as sponsors and they review the CTA, but were wondering if they should also be reviewing the NSN? HECSB responded that in the case of a NSN, it is the responsibility of the importer of record (as shown on Canadian customs documentation) or Canadian manufacturer is liable for the substance in Canada to sign the NSN reporting form.
Decisions/Action Items	1. Deborah Ashby, HECSB, to coordinate a separate meeting with CTSG, to discuss common "sticking points" and with developing examples of case scenarios for modified human cells and viral vector. Having a previously submitted NSN could be a good starting point (if the confidential business information can be shared publicly). 2. Sowmya Viswanathan to provide the link to the article on the March 2018 workshop outcomes on the NSNR (O): https://www.frontiersin.org/articles/10.3389/fmed.2019.00058/full **(Complete)**

3. Follow up on Previous Agenda Items

Issue	Issue #1: ROEB mentioned that a communication plan is being rolled out to the stem cell clinics as part of AIS "Canadian factors to be considered for same surgical procedures / hospital exemption" during the April 2018 CTSG bilateral meeting. CTSG asked for an update on the effectiveness of this communication plan and its impact on stem cell clinics in Canada Issue #2: At the CellCAN forum meeting on March 15, 2019, many of the CTSG stakeholders met with Celia Lourenco and Dino Petrin. As part of this discussion, CTSG raised questions about the "out-of-specification" numbers at the time of lot release for investigational cell therapy products vs. traditional biologics. CTSG would like to see BGTD's metrics. If there is a trend towards increasing discrepancy, perhaps this may lay the groundwork for future policy decisions around OOS for cell therapy products, especially expensive fresh autologous therapy products with limited shelf lives.
Respondents	**Issue #1**:Mimi Lin, A/Manager, Health Product Compliance and Enforcement, ROEB **Issue #2:** Kelly Robinson, Director, CERB, BGTD, HPFB

Response	**Issue #1:** To date, HC has contacted over 30 clinics in Canada to gather information about the specific activities being conducted related to stem cell therapies. Three clinics were determined to be engaged in, or advertising treatments involving unauthorized imported non-autologous stem cell products. Based on the potential risks posed by these products, Health Canada determined that the appropriate risk mitigation measure was to request an immediate stop to the importation and sale of the products. All three clinics complied with Health Canada's request. HC continues to assess the information gathered from the clinics to determine whether the specific activities being conducted are compliant with federal regulatory requirements. Follow-up is ongoing and the Department will take action should any non-compliance with federal regulatory requirements be identified. **Issue #2:** The BGTD does not systematically collect information related to "out of specification numbers" at the time of lot release. As discussed at the March Forum, BGTD has established a mechanism which could be used in a clinical trial setting to support patient access in cases where (1) the patient's cells do not meet specifications for the authorized CAR-T products and (2) at the discretion of the physician in consultation with the patient, the benefits of doing so outweigh the risks to the patient. BGTD would be interested in better understanding the request for metrics and how this information could be of use to your group.
Discussion points	**Issue #1:** CTSG asked why the three non-compliant clinics were characterized as "high risk", and how that information will be disseminated. ROEB advised the three clinics contacted were determined to be handling unauthorized non-autologous (allogeneic) stem cell products which pose a higher risk. BGTD responded that communication will be published shortly on HC's website. ROEB advised CTSG to send all media questions related to Health Canada's oversight of these products to HC's media relations and provided the following contact information: **Contact Information at Health Canada:** ***Health Product Complaints:*** Should you identify a concern about the safety or quality of a health product, please report this complaint to Health Canada by calling toll-free to 1-800-267-9675, or complete an online complaint form: http://healthycanadians.gc.ca/apps/radar/MD-IM-0005.08.html ***For inquiries from Media Outlets related to actions taken by Health Canada, please refer them to:*** **Health Canada and Public Health Agency of Canada** **Media Relations** Telephone: 613-957-2983 Fax: 613-952-7747

	Email: hc.media.sc@canada.ca ***If CTSG has any other questions, please feel free to reach out to my colleague Chris Simard or myself directly at:*** chris.simard@canada.ca or mimi.lin@canada.ca **Issue #2:** There are a number of reasons why a drug may not meet its lot release specifications. Under some circumstances the potential benefit of patients accessing out-of-specification (OOS) product outweighs the risk. BGTD explained that the situation for clinical trials is not as problematic as for products that are already on the market. For the clinical trials material, there is a Fax Back process and on that Fax Back form there is a checkbox that allows you to indicate if all specifications are not met, and you can provide a rationale as to why you think it's still appropriate to use that drug. Typically, BGTD agrees with the rationale, and it's a very fast turnaround. For some autologous products in particular, under some circumstances, it's often in the patient's interest to have the material administered since they have already undergone a rigorous pre-treatment regime and have few alternative options. A sponsor can always request a special release for an OOS batch if the benefit to the patient is deemed to outweigh the risks. However, autologous-based products from sick patients that may, for example, have undergone variable starting treatment regimes have high potential for variability. HC determined that clinical trials would more easily mitigate the challenge of repeated requests for release of OOS, while supporting patient informed consent and the collection of safety data. Through this mechanism, patients can have access to these products that do not meet the specification requirements of the marketed product, while having safeguards such as informed consent, and ensuring that physicians and patients have that necessary discussion. It's very early days, but one of the benefits of using the clinical trial approach is that sponsors are able to collect safety and/or efficacy data that may eventually inform labelling updates to the marketed products. It is understood that specifications have to be a little broad in clinical trials because it's the information gained in the clinical trials that helps define the specification. It is in phase III of the trial and close to the marketing application that specifications fall into place. Specifications need to be practical and based on manufacturing experience, patient outcomes, and the consistency in manufacturing. However, it's also useful when running a clinical trial to have a "baseline" specification below which it's better not to treat the patients, because if material not likely to generate a response is included, it can have a negative effect on the statistics that you are trying to generate in the trial.
Decisions/Action Items	1. ROEB to provide CTSG with ROEB and HC's Media Relations contact information. **(Complete)** 2. Bogna Lasia-Szkaradkiecz to provide responses to the GMP questions that were originally included for this agenda item. **(Complete)**

Celia Lourenco arrived at the meeting at 1:50 pm, and took over as chair with the following agenda item.

4. Understanding R2D2 and Budget 2019 Implementation Strategies and Timelines

Issue	The use of sandboxes and pilot programs, alignment with international jurisdictions, and a new External Advisory Committee on Regulatory Competitiveness are particularly intriguing to the CTSG. It is not clear to CTSG on how all these initiatives (led separately by Treasury Board Secretariat and PPIAD) fit together with R2D2 initiatives (led by HPFB). They would like to have a clear indication from the BGTD as to who is leading what, and how it fits together. This context will help them ensure they are not speculating and that they are engaged with the right group(s) at the right time.
Presenters	Megan Bettle, Director, R2D2, BGTD, HPFB Liz Anne Gilham-Eisen, Director, OPIC, BGTD, HPFB
Response	R2D2: The Regulatory Review of Drugs and Devices (R2D2) initiative began with Budget 2017 funding targeted at improving access to medicines. Activities under R2D2 are framed around working with health partners (including health technology assessment bodies and international regulators), in building review capacity, streamlining HC processes and policies, creating new review pathways, and enhancing use of real world evidence to support regulatory decision-making. Updates on the R2D2 projects and consultations can be found at: https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices.html The initiatives announced in Budget 2019 around improvements to clinical trials and creating pathways for advanced therapies are separate, but will build on the modernization which continues under R2D2. Regulatory Review and Proposed Amendments to *the Food and Drugs Act*: In 2017, the Advisory Council on Economic Growth published a report entitled Investing in a Resilient Canadian Economy that helped to identify barriers and opportunities to support Canadian innovation. The report helped inform the 2018 Budget where we first saw funding and initiatives around regulatory reviews and reforms. The one that particularly concerns HC and CTSG is the Health and Bio-Sciences Reviews. Once the 2018 budget funding was announced, HPFB initiated horizon scanning with the aim of monitoring advancements in science and technology as they relate to health products and food. The subsequent report highlighted the changing landscape with the rapid advancement of artificial intelligence, gene editing, 3D printing, advanced cell therapies and innovative ways of delivering drugs. Through this initial scan, three regulatory challenges were identified as barriers to growth and innovation: product classification, some of the authorization requirements for clinical trials, and the regulation of advanced therapeutic products.

	The Branch has outlined three key elements for regulatory modernization: 1) the need to remove outdated requirements, 2) increase regulatory flexibility and 3) support access to the most advanced therapeutic products. As a first step towards the modernization of regulatory frameworks, HC has identified some necessary amendments to the *Food and Drugs Act* which are part of the recently tabled *Budget Implementation Act.* The proposed amendments would improve safety and enable innovation, through the following measures: ▪ The ability to classify products that blur the lines of product categories as a food, drug, cosmetic or device; ▪ Provide oversight over the conduct of clinical trials for drugs, devices and foods for special dietary purposes throughout the whole lifecycle of the trial; and, ▪ Introduce a market pathway for novel advanced therapeutic products through the use of regulatory "sandboxes". These initiatives are led by HPFB and BGTD's Celia Lourenco is the DG lead for the innovative products pathway. The Regulatory Review Roadmaps will be posted in the coming weeks, which will further outline the Department's proposals to modernize HC's regulatory frameworks. Over the coming 4-5 years, the Department will carry out further consultation in order to develop and implement the modernization proposals.
Discussion points	CTSG gave the example of a company wanting to develop a 3D printer and asked if this could go on Schedule G of the new Act, and if it would be exempted from some, or all, of the *Food and Drug (F&D) Regulations*. (This could apply to 3D printing or CAR-T cells.) BGTD responded that HC has authorized CAR-T cells through the current pathway so it's not to say that once the Act is in effect, the current pathway is no longer applicable to advanced technologies. The first question that will be asked is whether a product can go through the current pathway. BGTD elaborated that it's the products that are really challenging to HC's current regulatory framework (for example Artificial Intelligence) that will likely go through this new pathway. BGTD added that there is still more foresight work being done through PPIAD and the next roadshow will be a joint effort between BGTD and PPIAD. CTSG asked if they would be included in the foresight roadshow. BGTD said that the foresight work was informed by the consultations that have already occurred, and that HC will work in partnership with industry in the future on this. CTSG asked if there is room in the flexibility being created for technological advancements in manufacturing. For example, if a trial is underway and there is a manufacturing change that is a clear improvement, will there be a mechanism within Schedule G so that it's not a requirement to apply an amendment to the CTA and the NSN? BGTD responded that they don't believe that kind of change would need to go in the "sandbox" or through Schedule G, as there are already approaches HC can use

	within the mechanisms that are currently in place. Perhaps the change can be introduced during the course of the trial, and a standard CTA notification might be submitted instead of an amendment. As well, the review process for an amendment is only 30 days and a notification doesn't need prior approval. There shouldn't be any major impediment for making the kinds of changes CTSG is suggesting. However, if the product becomes, or is judged to be different as a result of the change, then that presents other challenges, and it may need a new CTA. If it's only minor tweaking, there may be ways to build that in at the start so that multiple application are not required. BGTD further clarified that HC has to understand the nature of the materials being used, have some ability to assess the safety of that material and true potential for some clinical outcome. Otherwise there is no point in running a trial, and it's unethical to engage patients in these studies. At this point in the conversation, BGTD clarified that the new authorization/regulatory approach is applicable to the Market Authorization (MA) phase and <u>not</u> the clinical trial phase. HC's goal is capitalize on the clinical trials so they have an idea of how products are going to be regulated when sponsors seek MA. By doing this, HC hopes to identify the gaps in their current regulatory framework. This will involve a lot of policy work. The situation is challenging and a bit hypothetical at the moment, as HC doesn't yet have details on what that framework will look like. BGTD clarified that Schedule G is <u>not</u> an accelerated pathway. It's a customized pathway for products that don't fit in HC's current regulatory pathway. As well, there is no application to get on Schedule G; the Minister decides who goes through this pathway. CTSG asked about the possibility that Schedule G could be influenced by political will (akin to right to try in the US). They also expressed concern, and challenged the fairness of a possible situation whereby you have a product being regulated through the current pathway while competing against a product being regulated through Schedule G. BGTD has had several discussions on this possibility, and would be providing the Minister with recommendations where there will be strict criteria for adding drugs to Schedule G. HC wants to ensure an equal playing field for everybody. It was added that it would be helpful if stakeholders could voice any concerns in a documented fashion, so BGTD can share them with senior management.
Decisions/ Action Items	N/A

5. Advanced Cell and Gene Therapies Action Plan and Working Group

Issue	This update is provided to support common understanding of BGTD policy initiatives related to products of regenerative medicine, including cell therapies, gene therapies, and tissue engineered products.
Respondent	Nadine Kolas PhD, Senior Policy Analyst, OPIC, BGTD, HPFB
Response	Advanced cell therapies, gene therapy, and tissue engineered products are considered part of the burgeoning field of regenerative medicine and personalized

for full response, please refer to AIS form	medicine. It is inclusive of products whereby the therapeutic function is afforded by the introduced or modified gene(s) such as CAR-T therapies and therapies using CRISPR-Cas9 technologies for genome editing purposes. Such advances have recently come to the forefront with global market authorizations for two cell-based CAR-T gene therapies. Newer advanced therapies, particularly stem cell therapies, have been an area of significant policy work in BGTD since 2010. Efforts to date have focused on three main thrusts identified in the BGTD Cell Therapy Action Plan: ongoing policy work and guidance to support safe and effective Advanced Cell Therapy development in Canada, international engagement to support harmonization at an early stage of product development, and stakeholder engagement to promote regulatory capacity of this largely academic community. In the coming months, BGTD will develop a new advanced therapies action plan and launch an HPFB Branch working group to prioritize and address challenges across the lifecycle of advanced therapies. Among the emerging issues expected to be addressed are: (1) the complexities associated with manufacturing safe, reliable products using decentralized manufacturing models, (2) coordinated clinical trial designs, comparability studies, bridging studies and (3) support for products at the interface of different regulatory frameworks etc.
Discussion points	The landscape for regenerative medicine is changing and we are now starting to see the global authorization of CAR-T therapies and the development of the so-called “benchtop” CAR-T manufacturing equipment that is an interface between medical device and drug manufacturing equipment. As such, we are starting to see emerging issues for that group. BGTD said that they are also keeping an eye on the recent announcements by the US FDA as they work to release guidance around the challenges often faced when developing a product in academia (small biotech). Such products face common challenges in being brought to market, regardless of whether they are subsequently sold off to large pharma or developed using an alternate business model. BGTD will be forming a new cross-branch working group (WG) and developing a new action plan on regenerative therapies and the regenerative medicine space (CAR-T, tissue engineered products, etc.). The WG will be looking at both the pre-market and the post-market space, (which would involve MHPD), and new tools available through R2D2 and the BIA, and together they will be prioritizing work to support cell and gene therapy/innovative medicines. BGTD will be looking at different ways to engage with stakeholders, whether it’s through a roadshow or through this bilateral group. CTSG asked what types of input they hoped to gather. BGTD responded that at this time, they are already aware of a number of issues and will focus on the most pressing ones. BGTD will go through their usual channels for consultation. CTSG asked if there was any proposed mechanism for them to engage with this WG. BGTD clarified that this was an internal WG. BGTD assured them there will be consultations at various points.

	BGTD emphasized that CTSG should always reach out to them if they have any questions or concerns.
Decisions/Action Items	N/A

6. Regulatory Sandbox Proposal for Good Manufacturing Practices (GMP) Audits

Issue	It is CTSG's understanding that there have been no GMP audits of cell and gene therapy manufacturing sites conducted by the inspectorate, and no Establishment Licenses requested or issued. There is concern within the manufacturing community that the transition to commercial/late stage manufacture may bring with it issues related to lack of experience and training both at the facility and at ROEB in relation to the interpretation and enforcement of GMP requirements in this highly specialized field of manufacture. CTSG wants to explore whether there is an opportunity to engage ROEB together with the BGTD on a pilot basis (perhaps via a 'regulatory sandbox') earlier during the development of these products to: 1) help to train and educate Canadian manufacturers on processes for GMP audits and establishment licence requirements as they would apply to cell and gene therapies; and 2) to help provide training and learning opportunities for ROEB in this highly specialized area of manufacture and identify challenges and gaps before they become critical bottlenecks to commercialization.
Respondent	Bogna Lasia-Szkaradkiewicz, Senior Corporate Regulatory Compliance and Enforcement Advisor, ROEB
Response	HC is currently assessing the key barriers facing the adoption and implementation of gene and cell therapies in Canada. Gene and cell therapies are subject to existing regulatory frameworks; however, as announced in Budget 2019, the Government of Canada is proposing to create a legislative pathway to accommodate emerging technologies, and a future framework for clinical trials. We are exploring the use of this legislative pathway to create sandboxes to better align our requirements with the realities that industry faces with emerging technologies. The emphasis of these proposed amendments is to foster innovation while continuing to protect Canadians' health and safety. Budget 2019: https://www.budget.gc.ca/2019/home-accueil-en.html (Pages 118-121) ROEB / Health Products Compliance Directorate (HPCD) has been exploring considerations in the application of GMP requirements (Part C, Division 2 of the *Food and Drug Regulations*) to gene and cell therapy products based on questions from external stakeholders. Specifically, elements of the requirements covering testing, storage, transportation, consistency of manufacture and compliance with specifications. In addition, HPCD has been engaged in the review of the design of two manufacturing facilities for cell therapy products to facilitate their GMP compliance. ROEB/ HPCD is looking into important cooperation opportunities with the CTSG in the development of a site visit/ GMP training workshop. The goal of these site

	visits/training workshops would be to hear from industry firsthand regarding the challenges they encounter in the production of their specialized products. Some challenges raised so far include source material variability, different manufacturing models, specific equipment used in gene and cell therapy field, unique manufacturing requirements and difficulties in distribution and comparability between manufacturing sites. These one-day workshops/site visits would enable valuable information exchanges and could be held in two different locations in Canada to facilitate the participation of inspectors located in different regions in Canada. A GMP inspection of a clinical trial could be conducted upon request. The GMP requirements governing clinical trial drugs are mentioned in C.05.010 (j) of the *Food and Drug Regulations*. This subsection of the regulation outlines the requirement for the clinical trial sponsors to ensure that "*the drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices referred to in Divisions 2 to 4 except sections C.02.019, C.02.025 and C.02.026*." Guidance on complying with GMP requirements for clinical trial drugs can be found in our *Guidance Document - Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines Drugs Used in Clinical Trials (GUI-0036)*:https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices/guidance-documents/annex-13-good-manufacturing-practices-guidelines-drugs-clinical-trials-0036.html Manufactured drugs used in clinical trials are not covered by the mutual recognition agreement (MRA) between Canada and the European Community except for sites already holding a manufacturing authorization / establishment licence**:** https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/international/mutual-recognition-agreements/updates/mutual-recognition-agreement-canada-european-community.html
Discussion points	ROEB says they need to figure out how to plan the site visits/GMP training workshop(s). CTSG asked if they had an idea as to when they could start the visits, and ROEB responded that it depends on what is proposed and how many people would be participating. CTSG should contact Bogna Lasia-Szkaradkiewicz (hc.drug.gmp.questions-bpf.medicaments.sc@canada.ca) for continued discussion. BGTD expressed that although not new, the concept is excellent. BGTD has in the past, sent reviewers to sites, as well as on training at a major manufacturer in the United States (US). There is a lot of interest from BGTD reviewers to continue these activities; however, ultimately, it comes down to budget and approvals, and timing wouldn't be likely until well after the election. CTSG can email ROEB at the above email address, to further discuss inspection of buildings engaged in the manufacture of clinical trial drugs.

	BGTD supports the possibility of ROEB looking into inspecting manufacturing sites that supply clinical trials; however, there will need to be important criteria set, as there will be competition regarding who gets to be inspected and who receives the GMP certificate. Having a handful of sites across Canada who have GMP certification, who are the major supplies of clinical trials across Canada would be very advantageous, both from the perspective of BGTD reviewers, and from the patient perspective. CTSG said they would commit to sharing the lessons learnt from a GMP pilot inspection to the greater community and that there was a possibility of having other manufacturers on site during the inspection to make this a shared experience.
Decisions/Action Items	CTSG will follow up with ROEB to set up potential dates (2) for an on-site information exchange and learning experience. This on-site visit would be open to the BGTD policy group and reviewers, ROEB inspectors, members of CTSG, and other interested stakeholders.

7. Examples of minimally manipulated autologous cells for homologous use to be included in guidelines

Issue	CTSG wanted to follow up on the International Society for Stem Cell Research's (ISSCR's) request to HC to include specific examples of minimally manipulation, and specific examples of homologous use to existing guidelines, in alignment with other jurisdictions. CTSG would like BGTD's response on whether an amendment to the cell therapy clinical trial guidelines or a policy statement to provide specific examples will be issued and whether BGTD would like input from the CTSG on generating examples of autologous cells that are minimally manipulated and/or for homologous use.
Respondents	Andrew Henderson, Policy Analyst, OPIC, BGTD, HPFB Francisca Agbanyo, Manager, CBE, BGTD, HPFB
Response *for full response, please refer to AIS form*	A very limited subset of allogeneic minimally manipulated cell therapies intended for homologous use in patients fall under the scope of the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations). All other cell therapies, referred to as advanced cell therapies, including hematopoietic stem cells intended for non-homologous use are regulated as drugs under the *Food and Drug Regulations*. There currently appears to be some confusion regarding the regulatory status of autologous minimally manipulated cell therapies that are intended for homologous use. Autologous, minimally manipulated hematopoietic stem cells intended for hematopoietic reconstitution are the only autologous cell therapy that HC decided not to regulate under the *Food and Drug* Regulations while also purposefully excluding them from the scope of the *CTO Regulations*.

	HC is currently working towards publishing communications to clarify the regulatory status of cell therapies in Canada. (**Update May 15:** BGTD emailed CTSG with a communication regarding HC's Policy Position Paper and information update related to Autologous Cell Therapy products in Canada, for dissemination to the CTSG).
Discussion points	When it comes to some of the tissue products like morselized injectable amniotic membrane and amniotic fluid, HC's inspectorate has been very proactive in identifying these tissue banks at the registration application stage and letting them know that they are non-compliant with the regulations. CTSG commented that many people misinterpret the exclusion of autologous cells and tissues from the *CTO Regulations* as a sign that these cells and tissues are not regulated by HC. As stakeholders, CTSG is often engaged by physicians and patients trying to get precise information on HC's website, but feel there is confusion amongst the general public. BGTD commented that in addition to the forthcoming Policy Paper, HC will be revisiting the CTO guidance document for administrative changes, and there is an opportunity to add in some language to help clarify statements, as well as include a few examples of homologous use and minimal manipulation. CTSG was supportive of this. BGTD added that they would have to make a regulatory amendment to add autologous cells to the *CTO Regulations*. Although there are a number of other priority regulatory amendments at the moment, BGTD assured CTSG that there will be further discussion and policy analysis on this issue. BGTD added that while HC considers all cells to be drugs, autologous minimally manipulated hematopoietic cells that are for homologous use are not subject to the *Food and Drug (F&D) Regulations*. They are however, still subject to *the Food and Drugs Act*. Cells may be minimally manipulated but the autologous cell therapies used in clinics are not homologous use and therefore the *F&D Regulations* would apply to them. HC will clarify that position within the statement that will be released shortly. CTSG asked if ROEB can share the compliance and enforcement letters as does the US Food and Drug Administration (FDA). ROEB replied that they have never publicly shared their non-compliance letters and they aren't sure if there is any intention to do so. It should be noted that if a high-risk issue is identified, ROEB communicates it via a public advisory Furthermore, if there are any concerns with potential non-compliant sale or advertising of health products, CTSG should contact HC online by submitting the Health Product Complaint Form (FRM-0317). CTSG asked about the *CTO Regulations* and if HC can define where the limits to the Edmonton Protocol for islet cell transplantation fall. They asked if it was just a matter of whether the product in the end is equal to or improved while still performing the same function, or if there are changes with which they need to be concerned about?

	BGTD responded that at the time, HC's decision was that they didn't want to subject islet cells to clinical trials if their efficacy had already been proven. Because of this, they were included in the *CTO Regulations.* It has since been determined that the Edmonton Protocol has not worked as well as anticipated, and establishments continue to make changes to this protocol. BGTD's position is that if a sponsor changes the protocol being used at the time islet cells were included in the *CTO Regulations*, they will need to submit a clinical trial with HC. CTSG asked for clarification on what types of changes they should be concerned about. BGTD responded that if the changes could alter the characteristics of the product, it can no longer be considered the same product that was being developed under the Edmonton Protocol. HC wants to know what the impact of the change is on the islet cells. The key consideration is the degree of change being made. For example, BGTD has seen changes where sponsors are adding various substances to the solutions being used during islet cell isolation and preservation to improve the efficacy of the product. HC would like to know about the safety of these substances and what kind of impact they are having on the islet cells. In these cases, and depending on how significant other changes are, companies should submit a CTA to HC, describing the changes they are making to the Edmonton Protocol. CTSG asked how you would graduate into *the CTO Regulations* or the *F&D Regulations*, after the clinical trials are complete? BGTD responded that currently, sponsors provide HC with the changes they intend to make. If HC identifies any issues or concerns, they will respond accordingly. So far, HC has not identified any issues that prevented establishments from implementing their proposed changes.
Decisions/Action Items	BGTD would be issuing a policy statement on autologous cell therapies. (**Complete**)

8. BGTD Pipeline Initiative

Issue	BGTD would like to request and compile pipeline information through associations in order to compile data to enhance planning and forecasting by Centre directors and regulatory review staff.
Presenter	Suzanne Lecour, Manager, Performance and Planning Unit (PPU), OBIRM, BGTD
Response *for full response, please refer to AIS form*	BGTD would like to request pipeline information from associations in order to compile data to enhance planning and forecasting by Centre directors and regulatory review staff. This is not a new initiative. The Therapeutics Product Directorate (TPD) within HPFB has been collecting and compiling pipeline information since 2011. BGTD would like to collect similar information to TPD, but with some additional questions that may be useful including: if a submission is for a biosimilar, for a rare disease, for a pediatric indication, a submission based on real world evidence, and in what other jurisdictions has this been approved.
Discussion points	BGTD clarified that they are seeking information for new drug submissions.

	It was clarified that the CTSG is biologics, so they are not familiar with TPD's pipeline process. BGTD offered to share the template in advance so they can familiarize themselves with it and ask any questions. BGTD will initially request pipeline information once a year, and likely increase to twice a year to be in line with TPD. It was emphasized that the earlier BGTD receives the information, the better our Directorate can prepare.
Decisions/Action Items	BGTD to send pipeline template to CTSG. (**Complete)**

9. Roundtable

a) <u>BGTD's & CTSG's Terms of Reference (ToR)</u>
Liz Anne Gillham-Eisen, Director, OPIC, had reviewed CTSG's comments to the ToR for the bilateral meetings between BGTD and CTSG, and noted that further discussions are required to ensure proper alignment of the stakeholder group. The bilateral meeting is a tool by which BGTD communicates with their stakeholders and needs to be open, transparent and fair to all groups working in this field. BGTD wants to ensure that all groups receive the same information.

BGTD would like to bring the CTSG in line with their other stakeholder groups, as well as broaden the group to include new organizations. Consequently, CTSG will also need to limit the number of representatives around the table at these meetings.

CTSG would like to see BGTD's comments/concerns about the ToR and expressed concern that their group is being seen as restrictive when that is not their intention.

Beth Beaulieu to reach out to CTSG in regards to the ToR, and this item to be included in the fall 2019 agenda.
Action: Sowmya Viswanathan has requested BGTD comments on ToR ahead of the fall 2019 bilat meeting to facilitate and align with internal CTSG discussions about membership.

The meeting was adjourned at 3:55 p.m.