Association Bilateral Meeting – Cell Therapy Stakeholders Group and BGTD-Health Canada - Meeting Minutes - 2018-12-04

Tuesday, December 4th, 2018
1:30 pm to 4:15 pm
100 Eglantine Driveway, Ottawa, Ontario

Attendees

Cell Therapy Stakeholders Group participants
Sowmya Viswanathan (Co-Chair), Friederike Pfau, David Courtman, Jon Draper, Karen Nichols, Craig Hasilo, Martin Giroux, Richard Vaillancourt, Gayle Piat, Siofradh MacMahon, Steven Kaizer, Lucie Germain, Samantha Hodgkins, Olive Sturtevant, Patrick Bedford (via t/c)

Health Canada participants
Catherine Parker (Co-Chair), Celia Lourenco, Georgette Roy, Anthony Ridgway, Agnes Klein, Michael Rosu-Myles, Mary Hill, Kelly Robinson, Kyle Norrie, Marianne Tang, Nadine Kolas, Marie-Noël Deschambeault, Francisca Agbanyo, Ashley Baer, Bogna Lasia-Szkaradkiewicz, Paul Gustafson (via t/c), Thomas Hazle (via t/c), Yen Luc (via t/c), Maya Berci (via t/c), Maria Faraci (via t/c)

1. Welcome and Introductions/Review of Agenda

The meeting was called to order at 1:30 pm. The agenda was reviewed and accepted. Cathy Parker announced her retirement as of December 24th, 2018 and introduced her replacement, Dr. Celia Lourenco who was the Senior Executive Director in the Therapeutic Products Directorate and has worked in radiopharmaceuticals at BGTD in the past. Georgette Roy also announced her retirement and introduced Marianne Tang, the new director of the Office of Regulatory Affairs (ORA).

2. Early Engagement mechanisms between Health Canada, clinical trial applicants and novel device developers

Issue	In cell manufacturing, novel devices are continually being developed. These devices range from simple improvements on clean room operations through to complete closed processing bioreactor systems. Such devices may improve efficiency, safety, product quality, and/or lower product costs, yet the ability to assess the proper use of these instruments can be challenging for individual cell manufacturing centers. From a regulatory stand point, some instruments will clearly need to be evaluated as a medical device, yet others may not. It would be helpful to have a process to clarify how these products devices will be classified before devices are adopted for use.
Presenter	David Courtman, CellCan
Respondent	Thomas Hazle & Yen Luc, Medical Devices Bureau (MDB), TPD

Response	BGTD started by indicating that they do not generally have issues with the use of medical equipment in product manufacturing as long as it is used correctly and for its intended purpose. MDB gave a quick overview of the classes for medical devices. They are concerned with pre-market review for license of devices for sale in Canada. Class 1- lowest risk, no pre-market review Class 2- have to be licensed Class 3 & 4- significant review MDB welcomes engagement from stakeholders and invites communication. BGTD further clarified that equipment does not need to be licensed as a medical device to be used for manufacturing a drug in accordance with the marketing or clinical trial authorization. There are three scenarios: 1. Use of a device that's approved and used correctly. 2. The device is licensed as a medical device but used for different purposes – in this case, information supporting its use for the purpose and associated manufacturing steps must be provided. 3. The device is not approved nor used for its intended purpose – in this case HC would need the required information to evaluate the equipment and the associated manufacturing steps. There is often confusion on what types of claims can be made.; Health Canada is following up with manufacturers, as there have been some recent unsubstantiated claims. It is important for users to know that when manufacturing a drug they can use medical devices for purposes other than those for which they are licensed, as long as there is data to support such a protocol and it is to BGTD. BGTD may contact MDB to consult on a case-by-case basis but a separate review by MDB may not be required.
Discussion points	The Office of Regulatory Affairs (ORA)/BGTD and/or Medical Devices Bureau (MDB)/TPD can be contacted prior to filing for a meeting and will ensure the correct parties are at the table. MDB reiterated that their concern is with the licensing and/or sale of the device.
Decisions/Action Items	N/A

3. The Use of Banked Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) and Samples from Biorepositories for Future Clinical use

Issue	To generate discussion and brainstorm on a variety of issues from a regulatory, and practical perspective as well as patient safety and donor protection when using cells collected and stored for one purpose but being repurposed for a different clinical application.

Presenter	Olive J. Sturtevant, International Society for Cell Therapy (ISCT)
Respondent	Francisca Agbanyo, Centre for Biologics Evaluation (CBE), BGTD
Response	Health Canada has similar expectations as the US and these can be found in our guidance documents. There are three general scenarios: 1) Public banks compliant with CTO regulations in terms of processing cells and tissue. Their cells/tissues are considered safe if they meet regulatory requirements. 2) Private (autologous) banks. They do not need to comply with the regulations. Sponsors can run into a problem if they are not conducting the CTO tests. To generate cell lines, one should ensure they were collected appropriately. There may also be issues of consent that must be addressed. 3) Biobanks. Biobanks are challenging to assess since Health Canada does not know what tests have been conducted. Regulatory requirements apply to all cells/tissues that are used as a source material for manufacturing cell therapy products (details are provided in Health Canada's guidance document on Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans).
Discussion points	Donor consent/testing: - Health Canada focuses on quality and safety - Donor needs to know impact to patient care if donors don't respond to the intake form honestly - Ethical concerns are addressed by research ethics boards - Retroactive testing on cells/tissues that lack initial donor screening can be done but the test methods need to be validated for matrix interference. Record Keeping challenges: - Cells/tissues may have been processed years ago - Difficult to know what standards were applied during screening, testing and processing if record keeping is inadequate. It may be possible to address any gaps/deficiencies identified on a case-by-case basis. - Concerns with traceability – where was the cell/tissue retrieved/collected, and from whom. Health Canada is still working on a draft position paper on future use of bio-banked material.
Decisions/Action Items	N/A

4. Comparability study requirements for process change as sponsors move from early to later phase clinical trials

Issue	As we move from early to late phase trials, there are processing changes. At what point are those processing changes addressed by comparability studies? Do the comparability studies need to be in vitro or in vivo or some

	combination of both? At what point do the processing changes become sufficiently large in Health Canada's experience to require a new clinical trial?
Presenter	Sowmya Viswanathan, CellCAN, ISCT NA LRA
Respondent	Anthony Ridgway, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB), BGTD
Response	The ability to assess comparability at the level of quality is dependent upon the extent to which the biologic can be suitably characterized using appropriate methods and considering relevant quality attributes. If you can't show comparability, then you might have to rethink your process. Knowing what to test for comparability is very difficult for cell therapy.
Discussion points	Health Canada mentioned using small non-clinical and/or clinical bridging studies when necessary to address residual uncertainty remaining after performing quality studies. Health Canada said that it is done on a case-by-case basis and it's important to characterize not only the critical quality attributes but other aspects. There are different methodologies to conduct broader characterization, but even research-based methods should be validated or qualified for their purposes, depending on the risk-benefit analyses. Health Canada also discussed animal studies that may need to be repeated or a bridging clinical study. The "bridge" could potentially be made by a small patient cohort in a new trial, where the first few patients treated would be used to confirm dosing and safety information. CTSG commented that knowing they can use bridging studies might give sponsors confidence to make changes to their trials. It might help eliminate the feeling of being 'locked in' to what was outlined in phase 1. HC doesn't want the regulatory framework to hinder creation/design of better therapy or product. The key is early communication; HC can work with sponsors to achieve a better outcome.
Decisions/Action Items	N/A

5. Development of frequently asked questions from Cell Therapy Stakeholder Group bilateral meetings and BGTD

Issue	The CTSG is seeking support from Health Canada for the creation, review and approval of the FAQ for dissemination and hosting on the CellCAN - Health Canada Working Group webpage. The intent is to launch such an initiative as a joint effort. CellCAN is willing to coordinate this project with network partners. It would be ideal if Health Canada would assign point-of-contact personnel to coordinate the efforts for the regulatory authorities. Health Canada may contribute points to the FAQ from interaction with sponsors, identifying common errors in CTA submissions.

	CTSG believe that an FAQ would be helpful to stakeholders since they are getting the same questions repeatedly, e.g. 'will my pre-meeting interaction with Health Canada be held against me later in my CTA?' Perhaps the website could also include approved minutes from the bilateral meetings. CellCAN has the resources to work on this project and can work in coordination with Health Canada.
Presenter	Craig Hasilo, CellCan
Respondent	Kyle Norrie, Office of Policy and International Collaboration (OPIC), BGTD
Response	Health Canada specified that the information in question can already be found in their guidance documents. If a coordinated project takes place, the key is not to co-brand the document or miss direct information.
Discussion points	It was mentioned that the Canada.ca website can be hard to navigate and so people go elsewhere to find the information they are seeking. This FAQ would be accurate and include up to date information. Cathy Parker agreed that Health Canada would co-lead this project with CellCAN. The BGTD contact would be Kyle Norrie.
Decisions/Action Items	N/A

6. Health Canada's GMP Requirements for Cell Therapy

Issue	Guidance Document: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans states that cell therapies will be held to increasingly stringent manufacturing controls as they are developed from early- to late-stage clinical trials. Since BGTD's pre-market review group determines what attestations made by the sponsor regarding GMP are acceptable, there appears to be a disconnect regarding facility requirements during clinical trials vs. RORB's requirements at the time of licensure.
Presenter	Gayle Piat, CellCAN
Respondent	Bogna Lasia-Szkaradkiewicz, Health Product Compliance (HPC), RORB
Response	Refer to deck presented by RORB and questions and answers document (as of February 5, RORB is still working on finalizing answers)
Discussion points	A question was asked regarding the GMP oversight throughout the product lifecycle. A response was provided to highlight the application of GMP from clinical trial through to marketed drugs. It was noted that the focus of the GMP inspection program is on marketed drugs. When transitioning between clinical trial drugs and marketed drugs, a GMP inspection would be scheduled following receipt of a DEL application. RORB was asked if there were advantages for those that fabricate marketed drugs outside of Canada vs within Canada. The discussion evolved around Canadian fabricators exporting to the US and if they would be subject to inspections from both Canada and the US. Importing from US

	manufacturers importing from the US would require a licensed Canadian importer. GMP evidence for a site located in the USA would need to be aligned with GUI-0080. This may allow for reliance on GMP evidence from a US FDA inspection. RORB provided a short overview of requirements that apply under the two situations. A series of questions collected in advance of the meeting were provided to RORB. RORB will consider these questions in the development of GMP guidance materials to help support stakeholder communications. RORB will share their email contact information with cell therapy stakeholders should they require clarification. Post Meeting Note — The generic email accounts include: • General GMP enquiries: hc.drug.gmp.questions-bpf.medicaments.sc@canada.ca • General DEL enquiries: hc.del.questions-leppp.sc@canada.ca • Fee-related enquiries: hc.criu_ufrc.sc@canada.ca • API-related enquiries: hc.api.questions-ipa.sc@canada.ca • Foreign building GMP enquiries: hc.foreign.site-etranger.sc@canada.ca
Decisions/Action Items	N/A

7. Roundtable

Craig Hasilo mentioned he would like a mechanism to view minutes from other BGTD-stakeholder meetings. Health Canada will look into this request by the next bilat meeting.

Celia Lourenco thanked the group for a great meeting.

Sowmya Viswanathan commented that she's happy to see membership in this bilat growing and welcomed Celia Lourenco to her new role as Director General.

The meeting adjourned at 4:15 pm.