



CELL THERAPY STAKEHOLDERS GROUP – Meeting Minutes

Cell Therapy Stakeholders Group and the Health Products and Food Branch (HPFB)

June 13th, 2017

1:00pm to 4:00pm

100 Eglantine Driveway, Room 1278, Tunney's Pasture, Ottawa, ON

Attendance:

Cell Therapy Stakeholders Group Participants

Sowmya Viswanathan, CellCAN, ISCT, Toronto, ON, University Health Network
Deborah Griffin, ISCT,
David Courtman, CellCAN, Ottawa, ON, Ottawa Hospital Research Institute
Gayle Piat, CellCAN, Edmonton, AB, University of Alberta
Martin Giroux, CellCAN, Montréal, QC, Hôpital Maisonneuve-Rosemont
Craig Hasilo, CellCAN, Montréal, QC, Hôpital Maisonneuve-Rosemont
Friederike Pfau, CellCAN, Québec, QC, Université Laval
Olive Sturtevant (teleconference), ISCT, Boston, MA, Dana-Farber Cancer Institute
Lynn Csontos (teleconference), ISCT, Vancouver, BC, Stem Cell Technologies
Patrick Bedford (teleconference), CCRM, Toronto

Health Canada Participants

Liz Anne Gillham-Eisen, Office of Policy and International Collaboration (OPIC), BGTD
Francisca Agbanyo, Centre for Biologics Evaluation (CBE), BGTD
Ariel Arias, CBE, BGTD
Gina Coleman, CBE, BGTD
Anthony Ridgway, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB), BGTD
Agnes Klein, CERB, BGTD
Georgette Roy, Office of Regulatory Affairs (ORA), BGTD
Nadine Kolas, OPIC, BGTD
Kyle Norrie, OPIC, BGTD
Ashley Baer, OPIC, BGTD
Jessie Lavoie, CBE, BGTD
Melanie Derry, Marketed Health Products Directorate (MHPD)
Paul Gustafson (teleconference), Regulatory Operations and Regions Branch (RORB)

1. Welcome and Introductions

Welcome to the 2017 spring meeting of the CELL THERAPY STAKEHOLDERS GROUP BILATERAL MEETING PROGRAM.

Thank you to Health Canada for hosting the meeting and giving us the great opportunity to bring questions and concerns to this table.

2. Review of Agenda

Agenda is approved, no items added.

3. Ancillary Materials

Lynn Csontos, Senior Director of QA and Regulatory Affairs, STEMCELL Technologies, Inc, presented the different approaches of regulators to address the Ancillary Materials in cellular therapies and regenerative medicine.

The following definition was presented: “A product that is not intended to be in the final product that will come in contact with the product during production.”

The regulations and guidance documents focus on cellular therapies and include the definition of ancillary materials.

Common themes are: safety, identity, purity, stability, activity, potency, performance, packaging, supplier QMS, adventitious agents.

Differences are in the approach and sourcing: The US and Japan use a phased approach allowing more latitude for early phase studies. The European Union does not use a phased approach. The US and the European Union use primary sourcing and Japan secondary.

In Canada, language such as “adequately controlled” or “appropriate control” is used relating to Ancillary Materials.

Question: What is “adequate control”?

Answer: Adequate control is dependent on the type of material: if the Ancillary Material is animal or human derived, contamination with viruses/transmissible spongiform encephalopathies – is a concern and more controls are needed than, for example, for chemical Ancillary Material.

Health Canada follows a risk based approach and criteria detailed in USP 1043.

Follow ICH Q7 for monoclonal antibodies used as ancillary reagents.

Question: Is there a phased approach in Canada?

Answer: Canada is more aligned to the US than the European Union regarding the phased approach. A case-by-case risk-based approach is applied, that deals with animal material first. Safety is important in phase I and II but it is still a phased approach. It is important to work with the suppliers from the start, to let them know what the requirements for the

materials are. The suppliers may be more accustomed with working with R&D customers rather than cell therapy manufacturers.

It is also possible for a product that is GMP-like; such as cytokines that are prepared under GMP conditions but not tested, that the cell manufacturer itself performs certain tests or contracts them out. Also in many cases the tests are done but the documentation has gaps. It is a good practice to qualify more than one supplier if it is possible to find more than one product that will work.

Question: Critical ingredient vs ancillary material: Are cytokines an Ancillary Material? They will be in the cells but at a very low level, whereas gene therapy vectors are in the cell product as well but are more considered a critical ingredient.

Answer: Measure as much as possible how much of the ancillary material remains in the final product. If it is low it would correspond to Ancillary Material. The risk level will be low.

For example, a not yet approved drug is used with cells. If the level is so low that it will not have a pharmacological effect, then it would be considered to be a reagent and would not need to be approved for clinical use. Sometimes the Ancillary Material supplier will supply a CoA and CoO for the material to be the primary support for the CTD filing. Sometimes Health Canada will ask for more information, especially if there is an infectious risk involved.

Question: In absence of a master cell bank undergoing viral clearance studies would adventitious agent testing of the resulting MAb be sufficient? (MAb: Monoclonal Antibody)

Answer: As long as the other two pillars of security are in place: viral testing in process (unpurified bulk) and viral clearing of the manufacturing process. Testing the Master cell bank is a good starting point. The risk can be mitigated. When testing in process, be careful of dilution effects! Test at the right stage especially since virus may have been introduced during manufacturing.

Question: The definition of “raw material” is “any material from outside sources”. Isn’t there an overlap between “raw material” and “ancillary material”?

Answer: Everything is a raw material but then it goes two ways, either to ancillary material or to ingredient depending on what will be found in the final product.

Follow-up: Generally, guidance documents are revised every 5 years. This group can be helpful in identifying issues to be addressed during these revisions. If you find definitions from other jurisdictions that would be helpful, let us know as HC is interested in harmonization.

4. Long Term Monitoring of Patients Who Receive GT Products

A case scenario from the US was presented by Olive Sturtevant to illustrate the need for long term follow up to detect latent off-target adverse events. In this scenario, the sponsor of a clinical trial is no longer in existence. The trial involved genetically modified cellular

products that were administered to patients but never licensed. The problem arose when a long-term survivor developed lymphoma 10 years post-trial.

FDA was asked if they would release the proprietary information related to the genetic sequence of the cellular product. The FDA responded that the consent documents should address long term patient follow-up and they cannot release proprietary information. The inability to conduct long term follow up on patients will be important for the regulators to consider and address as more and more gene therapies patients will be long term survivors who may go on to develop potentially latent off-target adverse events.

Consent forms do in fact include requirements for long term follow-up but not the mechanism.

FDA did a survey in 2000 with gene therapy sponsors and found that, although there was room for improvement, most were meeting the intent of the standards and monitoring programs improved just from the result of conducting a survey. An educational opportunity was identified to train sponsors about long term follow-up.

What are some of the outstanding issues?

- Funding to support tracking and gathering data
- Identify gene therapy patients in health records and network
- National database linked to health and data records
- Ensure public and researcher that info will be available for testing patients if the need arises

The US has some resources for collecting data (GTPTS, GeMCRIS, CIBMTR) but they are not adequate for tracking outcomes since there isn't an automatic way to capture data and there is a need for international databases.

Question: How to identify patients that received genetically modified cells? As noted, the FDA cannot publish/release proprietary information even if the company no longer exists. It is easier to follow patients when the studies are led by an investigator/s. In that case the investigator opens a new file for the long-term follow-up of the patient when the study is closed. For biotech companies, this is different. Nowadays patients sometimes outlive the biotech company. Follow up is difficult once the patient returns home.

Answer: A discussion paper is being developed by the International Pharmaceutical Regulators Forum on Long Term Follow-Up of Patients Receiving Cell Therapy Products. While there are additional considerations for gene therapy products, there is some overlap. The paper can be shared once it is completed. This document could be developed further into an ICH guideline.

Most of the centres that are part of CellCAN (Montréal, Ottawa, Toronto) are conducting gene therapy trials and can speak to these issues. If the FDA has proprietary databases that Canadian researchers cannot access, sometimes the information can be obtained through the European Union where manufacturing is proprietary but not the information on clinical trials including adverse events.

HC - in terms of patient follow up for therapies provided under regular medical care, it is provincial jurisdiction. However, the sponsor can be required to include follow up information for therapies provided as part of a clinical trial if patient's health is at risk.

Example: T-cell clinical trials. They stay in the patient for his/her whole life, but it is still considered a drug. These are new ways to practice medicine..

ICH E18 will be finalized soon, it mentions safety and efficacy. There is international push to make data from clinical trials more available.

Also, the whole sequence is not needed to probe for a vector to be able to link latent off-target adverse events to the original gene therapy. The important thing is to discover that an adverse event is happening. It is also possible that in the future with technological advances it will be possible to make the discovery of differences in sequences easier. Challenges identified are federal vs. provincial jurisdictions, protection of confidential information, bankrupt companies, tracking after market, and follow-up into the next generation.

Action Item: Maybe the stakeholder group could organize a workshop together with Stem Cell Network and CellCan to address this issue. It would be a good idea to involve stakeholders from the European Union too to get more expert input. ISCT is already part of this group and represents the US stakeholders. Health Canada can participate in a workshop. A paper should be prepared in order to assure follow-up.

5. Autologous Cell Therapy Workshop

Sowmya Viswanathan presented the results of the workshop held in Montreal on March 8, 2017 on the gaps in regulation of minimally manipulated autologous cell (MMAC) therapies for homologous use in Canada and provided a current state of regulations in US and EU.

The workshop was by invitation only and recommendations will be made resulting from the workshop's discussions. A survey was conducted among the participants before the workshop. 26 out of 33 participants responded. In Canada, medical practice standards are a provincial matter. A manuscript of the proceedings from the workshop has been submitted to Cell Therapy. The paper is back for review and is nearing completion. The morning session in this workshop discussed how MMAC falls under various regulations: Canadian regulations: FDR, Medical Devices, CTO, Provincial medical practice standards; US regulatory landscape with exemptions and exceptions; EU regulations with substantially manipulated but no minimally manipulated criteria.

The discussion of the MMAC practice of the workshop pointed out certain questions:

- Should MMAC be a federal or a provincial matter?
- If provincial, will private clinics offer this treatment and what concerns does this raise?
- Can certain products with extensive clinical experience be grandfathered into existing regulations such as CTO (e.g. PRP)?

- How should point of care devices used for processing MMACs be regulated?
- Should a GMP production or a standards-based approach be used?
- How should facility vs. bedside MMAC's be handled?
- Need more oversight? Harmonize care practices?
- Long term safety and efficacy is not fully understood or monitored
- An existing standard is CSA Z900
- Control and monitoring: FACT or ISO Standards (ISO 13022:2012)
- MMAC are often not provincially reimbursed so limited incentive to collect long term data
- Tracking at the national level would be ideal
- A national patient registry could be a solution, but examples show that a voluntary contribution registry does not work

Health Canada had, in 2007, decided on a 2-phased approach to the entire field. First phase would include the allogeneic therapies (CTO) and in a second phase autologous products were to be considered, but this has not yet been done. The CTO regulations for allogeneic products were restricted for products with long term established safety as well and the source of cells was limited to 3 sources: peripheral blood, cord blood and bone marrow.

Health Canada is still committed to look into the aspects of phase 2 CTO: include MMAC or not, include other sources and only include therapies that are safe and efficacious (no clinical trial requirements).

Regarding MMAC, they do fit the definition of a drug. If it came to HC's attention that unsafe products were being used, HC could intervene at the level of the Food and Drug Act. Still the colleges view these MMAC as clinical practice and it should be the colleges that intervene in case of adverse events.

The critical points are the definitions of "homologous use" and of "minimally manipulated". Real homologous use with real minimal manipulation should remain clinical practice. The understanding of the cells changes and so are the definitions. Device manufacturers should not be involved in the decision process for decision between a MMAC practice and a regulated product.

Conclusion of the discussion: The MMAC should be added to an existing set of regulations, on the basis of a risk-based approach. There are no donor recipient issues and no tracking issues to be taken into account for MMAC.

6. Master Files

Clarification as to what information would Health Canada like to see in Master Files for Cell Therapies related to 1) ancillary materials, 2) devices and 3) facilities – is there a policy speaking towards this?

A Guidance document has been published on May 1st, 2017. The guidance details the format and the content of what can be included in master files.

A new application form is coming in the next months.

Question: some manufacturers of ancillary materials are concerned about confidentiality, when they are asked to submit proprietary information because there is a clause regarding the Access of Information act in the guidance.

Answer: There is a high threshold for releasing confidential clinical trial information and there is a lot of oversight in the matter.

Question: Is the information requested by Health Canada comparable to FDA submission documentation?

Answer: Health Canada is not sure, but there is an FDA template available online. HC has accepted a Master File in the same format as that of the FDA in the past.

Question on Ancillary reagent: Master file or CoA?

Answer: When it is a critical ingredient a Master file is requested and if it is only ancillary a CoA can be sufficient. If a full Master file is not available for early phase trials, an incomplete version might be enough to serve its purpose for a particular trial.

Conclusion: New Master File guideline can be found here: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/mf-guide-ld-fm-eng.pdf

7.0 Roundtable

a) Would the stakeholder group be open to add other members to this group, in light of recent recommendations from the CCA Report on Regenerative Medicine that RMAC be the focal point for the regenerative medicine community?

Yes, the group is open. In the past other stakeholders have already been invited such as CCRM. The important thing is to keep it open and keep the interest in line with the original purpose of the stakeholder group to represent academic stakeholders since cell therapies are currently in the investigational stages. As cell therapies evolve so too will stakeholder interests. Identify challenges and get informed.

A comment was made from a representative from a similar group in the US that meets with the FDA: the person cautioned that their group has so many members that they were unable to arrange meetings for 4 years and eventually chose to split the group into subgroups.

An update of the Terms of Reference update will be on the agenda of the next meeting.

b) ISCT 2018 will be a good showcase for Canadian Cell Therapy and Regenerative Medicine.

c) The meetings are appreciated and allow Health Canada to identify issues.

Meeting was adjourned at 4:00pm.