Health Canada – Cell Therapy Stakeholder Group (CTSG) Meeting on Dec 1, 2016 in Ottawa, Canada

Health Canada Participants:

Catherine Parker, Director General, BGTD (Co-Chair)
Lindsay Elmgren, CBE, BGTD
Francisca Agbanyo, CBE, BGTD
Ariel Arias, CBE, BGTD
Gina Coleman, CBE, BGTD
Anthony Ridgway, CERB, BGTD
Agnes Klein, CERB, BGTD
Georgette Roy, ORA, BGTD
Liz Anne Gillham-Eisen, OPIC, BGTD
Kyle Norrie, OPIC, BGTD
Andrea Bedard, OPIC, BGTD
Michael Rosu-Myles, RSD, CBE
Jessie Lavoie, RSD, CBE
Chad Sheehy, RORB
Paul Gustafson (by phone), RORB

Stakeholder Group Participants:

Sowmya Viswanathan, CellCAN-University Health Network, University of Toronto, ISCT NA LRA (Co-chair)
Olive Sturtevant, ISCT NA LRA (Co-chair)
Erika Kleiderman, CellCAN, Centre of Genomics and Policy, McGill University
Martin Giroux, CellCAN-Centre d'Excellence en Thérapie Cellulaire-Hôpital Maisonneuve Rosemont
Friederike Pfau, CellCAN-Laval University/LOEX
David Courtman, CellCAN- Ottawa Hospital Research Institute
Patrick Bedford, Centre for Commercialization of Regenerative Medicine
Anne-Marie Alarco, CellCAN
Michael Mendicino, ISCT
Karen Nichols, ISCT
Deborah Griffin, ISCT (via teleconference)
Tania Bubela, University of Alberta-CellCAN (via teleconference)

ITEM 1 – Welcome by Co-chairs

Catherine Parker opens the meeting and states that Cell Therapy is an exciting domain and confirms that this is an area that Health Canada wants to develop further. The domain is getting a lot of attention from a very high level in government. Key component of regulatory affairs is to give the access to medicines.

Sowmya Viswanathan confirms that the stakeholder group is very happy to have this opportunity to share concerns and progress in these biannual meetings. She offers to take care of the first draft of the minutes and to circulate the first draft to ISCT and Health Canada. Health Canada accepts the offer. Andrea Bedard accepts to provide the attendance list. Also the use of services like WebEx could be helpful to those not attending in person.

Olive Sturtevant thanks for the great opportunity to exchange with Health Canada and her colleagues from Canada.

ITEM 2 – New Substances Notification Regulation (NSNR)

Sowmya mentions that the discussion about the New Substances Notification Regulation had been dropped from this meeting and should be returned to the agenda for the spring 2017 meeting. Health Canada confirmed that this would be the case, and that the people responsible for interacting with the Canadian Environmental Protection Agency would be present.

ITEM 3 - Labeling of cellular products – Olive Sturtevant - Information (slides)

The presentation has been presented to the FDA in October.

Practice of labeling of cellular products produced by external manufacturers is that no additional confirmatory testing is done when the product returns. The process is relying solely on donor ID – ISBT-128 practices – for blood/tissue/cellular products. Everything is bar coded and scanned against patient wrist band. No patient ID is on the product label. Someone has to assume risk of re-identifying patient.

A product ID at time of collection and all through manufacturing and infusion process would allow for – bidirectional traceability. USAN terminology and NDC + ISBT 128 coding would provide good traceability.

Health Canada responds that a collaborative effort should be sought. What is the question for Health Canada that you are looking for? An agency buy- in?

What FDA responded is that it is an issue that is not 100% on their radar and they want multiple groups to come up with proposals. Some of the issues are on a basis of institutions rules. One example was given where no initials and no birth date are allowed as an identifier. A solution would be to have the information bar coded so that it is not eye readable. And additional labels could be provided to the manufacturer.

If HC has a position, then it would be useful to help implement with REBs at our local hospitals, within policy purview, given that there is lot of pushback from REBs to protect patient privacy. A statement or requirement by Health Canada would go a long way in dealing with institutions.

ITEM 4 - Appropriate Staging and Sizing of Cell Based Therapy Trials – David Courtman – Information

No slides were used for this topic.

How do we guide investigators as to appropriate size and staging of clinical trials? There are implications coming towards us in terms of having more rigorous GMP for trials identified as late stage. Many of us are coming from academic health centres and are not targeting commercialization. What are the criteria for a decision between a Phase I (early) to a very late stage trial?

How do you view the progression through the trial stages and associated GMP facilities? Is trial size a criterion (number of centers, number of patients)?

Discussion

Early and late stage phase does not rely on size. Unconventional design of studies must be included, that is the only way you can make them work. Small studies can have appropriate analytics. There have been small trials for specificity of 30 to 40 that have the sufficient outcome with appropriate analytics. Small radiopharmaceuticals trials with patient numbers of 30-50 are okay with right statistical design. There needs to be some animal data. Standard paradigm where you can use standard treatment, some cannot be blinded or randomized.

Initial safety study is not the problem. What is the next step? The investigator wants to prove efficacy and wants as many patients as possible If someone has done a safety study, it can be an expansion of the initial cohort. It can be a back and forth, come talk to the regulators when needed. Communication is important.

From the inspection side there is the GMP issue. For later stages the rigour in GMP must be higher.

How much more rigour and where do we start applying it? Development of trial design is no longer a linear process.

HC Response - Reference to Annex 13 to current GMP guidelines GUI-0036 – give some input from early to late phase trials – might be dated – 2009. Might have to more in depth discussion to see how it can be applied to cellular tx/gene tx. EU – new GMP guidelines for ATMPs – for early vs. later stage trials. ISO / USP 1046 and 1047. Will evaluate that information to refine our guideline to get more clarity on this product class.

GMP Elements that apply with CTA – some exclusions apply. There is expectation to comply with GMP – those prescribed in Annex 13 – which allows fair bit of flexibility. As a whole process we are listening and being able to work with new technologies that are being presented to us. Work in harmonized manner with international partners – we are taking same measures to ensure safety of patients using the framework we have.

ITEM 5 - Importance of Comprehensive Characterization of Stem Cell–Based Products.– Jessie Lavoie – Information (slides)

Lavoie JR et al., Stem Cells 2016 – Integrin signaling and ECM engagement was different between responder vs. non responder MScs – EMILIN-1 and ILK identified

Decrease in potency has been observed in in animal study. The presented characterization methods could be used as a potency evaluation tool. Also the initial number of MSC in bone marrow biopsies is unknown. It is also highly donor dependent. The quality of the bone marrow sample is important. It is highly heterogeneous product.

Sometimes if you make the product more homogenous you lose efficacy. Often cells are a mixed product that works best in a mixture. How do we look at the cumulative effect of those multiple trials? Registry of data from the cell therapy community. Markers depend also on manufacturing process and all those MSC trials are produced differently.

Ad Database approach is possible.

ITEM 6 - Standards Efforts for Cell and Gene Therapies Internationally – Sowmya Viswanathan – Information (slides)

Standards are voluntary and consensus driven. Multiple standard organizations (ISO, ASTM). There are also Reference materials such as calibrators and comparators, and Reference data (defines a set of permissible data) such as country codes, calendars, fixed conversion rates.

Examples:
CD34+ is used as a control. For example in Flow Cytometry. Dependable calibrator.
CD4 FITC cell control. Distributed by NIBS. Benchmark in house assays.
Recombinant adeno-associated virus 2 (AAV2) is a reference material.
Reference data for pluripotency, a database online Pluritest (Scripps Institute), based on statistics analysis, the database the gives you a pluripotency score. Could possibly be used as a reference to prove the non-pluripotency of cells. Open access standard database.
Discussions about terminology that can evolve into guidelines or standards.
Biological activity = potency

CSA in Canada, (ISO committee's participant) ISO TC 276
Working group Biotechnology (the presenter is a participant). Was formed in 2013.
Examples: characterization of cells, requirements for biobanks.

The Standard coordinating body (SCB) is presented by Mike Mendicino.
The SCB is a non-profit organization that serves four sectors: i) cell therapy, ii) gene therapy, iiii) tissue engineering, and iv) cell-based drug discovery This work is going to be funded by different sources such as grants, etc. The SCB has an MOU with NIST. This public-private partnership will officially launch in January, 2017.

Discussion
Health Canada is a big standards supporter. They have standards referenced through food and drug regulations. Health Canada is ISO 9000 accredited too. Health Canada requested slides from SCB be shared with them.

ITEM 7

Gene Editing Workshop Background, Goal, and Output – Erika Kleiderman – information (slides)
CISPR in social representations are represented. The Nuffield Council on bioethics 2016 on genome editing is presented. Flagging of issues in various domains: from understanding health, treating disease, avoiding genetic disease to human enhancement. Potential uncontrolled use and safety.
There is an urgent need to address human reproduction issues (prohibited in Canada).
It is all about regulation of risks and uncertainties (a publication by Knoppers, Kleiderman and Isasi will soon be available in Regenerative Medicine)
Allow Canadians to enjoy benefit from this research
Allow researchers to be engaged in this type of research: Scientific freedom.

Discussion
Health Canada has published a notice of intent to go ahead with regulations under AHRA. The large number of comments needs to be reviewed before any statement can be issued.

ITEM 8
Roundtable
No further topics are discussed under item 8.