FINAL Meeting Summary of the 12th Cell Therapy/FDA Liaison Meeting

November 19, 2012
Bethesda, MD

Host Organization:

International Society for Cellular Therapy ISCT®

Participating organizations: AABB, ASBMT, BIO, CAP, FACT, FDA/CBER/OCTGT, ICCBBA, ISCT NIH, PACT, SITC, USP

Meeting transcript prepared by Karen Nichols.

Call to Order was made by **Bill Janssen** (*see presentation #1*). Bill thanked the FDA and industry representatives for attending the meeting. He went on to list the goals for the meeting, noting that the cell therapy community was asking simple as well as complex questions of themselves, their peers and regulators. Bill specifically pointed out the globalization of cell therapies as a topic of prime time interest, referencing recent network television stories. Bill reviewed the agenda in detail and noted that, much as in the case of the recent adverse events at a compounding pharmacy, things in the cell therapy community could get out of hand in bad ways without good communication, science and regulatory oversight. Bill then had each attendee identify themselves by name and organizational affiliation.

SECTION 1 - CELLULAR THERAPIES CURRENT TOPICS

ISBT 128 Labeling and Identification of Cell-based Therapeutics

Presentation by Bill Janssen, PhD

(*See presentation #2*) – Bill provided an overview of ISBT 128 and how the format was laid out, using a blood product as an example, noting all the standard language and features. Bill made a key point that though his example was written in Chinese characters for the human readable form, the machine readable coding allowed consistent interpretation across international borders. Bill went on to identify current coding coverage and proposed new areas of coding. Bill reviewed the history of and selected metrics for ICCBBA, highlighting that the numbers of cell therapy facilities are increasing, leading to more registrations. Bill identified the supporting professional societies who require use of ISBT 128, the important features of a labeling system and raised the key discussion issue; how can use of ISBT 128 labeling be reconciled with the required labeling for FDA approved cell therapy products? Bill described two labeling processes – traditional pharmaceuticals vs HPC, Apheresis and how they differ;. He emphasized the latter is closer to a blood product paradigm than the pharmaceutical model. Bill emphasized that ISBT 128 is increasingly being adopted now, worldwide.

FDA Comments – The Agency acknowledged that there is a mechanism in place to use ISBT128 labeling for licensed HPC, Cord Blood and peripheral blood stem cells. However, at this time FDA regulations require that all other marketed products use the NDC coding system. There is no requirement to use the

NDC coding system prior to licensure; ISBT 128 labeling may be used pre-licensure. FDA stated that they were open to further discussion and input from the cell therapy community regarding the use of ISBT 128 on licensed cell therapies. It was mentioned that NDC bar codes were originally implemented to manage medication errors, and were then expanded to meet other needs. In response to a question about the feasibility of using both ISBT 128 and NDC on product labels the agency stated that this may be difficult due to limited space available on small container labels.

Industry Comments – When an MD is ordering a cell therapy product, they are seeking a match between product and patient, as opposed to who made the product (the name brand), as they might for a drug. It is important to distinguish between commercial vs noncommercial products –(latter case example, unrelated allogeneic HPCs). The ICCBBA has concerns that what will become licensed will not reflect what the product is. Can ISBT/ICCBA look at a harmonized label with FDA requirements? NDC can be rationalized as long as having a proprietary name doesn't exclude having another name. Unicode product descriptions – ISBT should talk to this group as well because of the use of SPL.

The Expanding Range of Cellular Therapeutics

Presentation by Adrian Gee, PhD

(*See presentation #3*)

- Ideal commercial cell therapy product is not autologous
- Autologous advantage is that donor is available, no match needed, no immunological rejection and immunosuppression not required
- There are many countries where cell therapy is "unregulated" – similar to minimal manipulation for bone marrow for homologous use (with no other combined article)
- Screening (DE) of autologous donors not needed but proper labeling requirements must be met

Adrian provided a series of product reviews as examples of cell therapy products regulated under preapproval – focus on Carticel™, Provenge™, LaViv™(see associated slides) and comments on the CellTex warning letter, highlighting what the response says about 'nonhomologous use' for MSCs

Adrian continued by noting that there is a trend for movement of MSCs from autologous to allogeneic application. He noted the following general trends:

- Allogeneic use: regenerative medicine and the treatment/prophylaxis of GvHD
- Autologous use: for regenerative medicine, but without the possibility of immunological rejection
    - Does patient administration equal practice of medicine?

Issues to watch

- Cryopreservation and the PACT Project – NK cells / fresh vs frozen study. NK cells continue to expand when shipped fresh such that recipient ends up with more cells than were shipped– key questions include the impact of cryopreservation, need for additional testing after shipping, and whether autologous cell therapies are better suited to centralized commercial processing vs. a local "manufacturing" process?
- The future is intra-operative procedures – harvest and treat in one procedure

    - Looming safety question – how long do you leave a patient waiting while you process?
    - What is the regulatory status of these types of products?
- Improvements
    - Extending access to more patients, for example, going to more partial matches and driving down GvHD response
    - Manufacturing improvements such as using plasmids and bioreactors to improve yield and purity and reduce COGS. Scientific improvements such as using a universal safety switch to allow turning off cells (drug inducible suicide genes) – reversible within 30 minutes

Adrian argued there is a shift that is driving down the importance of autologous as an extra-corporal process – instead, allogeneic off the shelf treatments will increase and autologous treatments will be confined to bedside – new process/product deliveries as part of practice of medicine.

The Agency is aware of these trends and shifts.

SECTION 2 – MESENCHYMAL STEM CELLS

Mesenchymal Stem Cells

Presentation by Ian McNiece, PhD *– Material provided is from the University of Miami*

(*See presentation #4*). Speaker (Ian McNiece) notes that stromal cells are not all the same and relate to their unique biology of origin. Bone marrow mesenchymal stem cells (MSCs) are not the same as umbilical cord blood MSCs. Nonadherent cells are different than adherent cells even if they both express the same MSC markers. IM notes the American Heart Association paper in JAMA where autologous cell therapy and allogeneic cell therapy were almost identical in safety, arguing that clinical need will/could over-ride source. He noted that when producing MSCs, some patients' MSC samples will not expand in vitro. Slides were presented to show a summary of patient numbers who grew MSCs, by their age. The older the patient, the less potential the cells have – if looking for a target cell number of 200 million, it is difficult for MSCs from older patients to achieve this threshold. Based on his data, young males are the best source. Speaker presented slides on MSC manufacture, highlighting that low passage numbers minimize the risk of loss of proliferative capacity. Cell factories improve the surface area – the more in the stack, the greater the number of cells produced. He reinforced that with an autologous sample, even low level contamination means loss of a run. In his lab/manufacturing area, split tray numbers minimize risk of run loss. He noted that for the data set he presented, virtually all were young, male donors and reminded audience that patient specific production runs are hard to replicate. Ian discussed the "chicken or egg" problem – scientists/clinicians have no idea what the mechanism of action is without doing a human study. He also noted that it is an advantage to be able to visualize MSCs by microscopy as part of their identity. Only a fibroblast looks similar to MSC and MSCs will overgrow anyway. He prefers to look at cells by microscopy and after 4 to 5 weeks of culture, if media is clear, considers the culture to be uncontaminated. For CMC, how do you express quality measures, such as potency – CFU-F to illustrate end stage utility? Flow analysis to show that 95% of the cells exhibit the same cell surface / biomarker profile? For purity, this can be demonstrated by percentage of specific cell surface markers. Coupled with adherence, this yields essentially 100% pure MSC product. Strength – dosing may only be known through doing a human study as there is lots of biology to understand. When discussing delivery of cells to the heart, a question to be answered included how to do this with minimal invasiveness but largest cell

dose possible without clumping. One approach was to add DNAse to ameliorate stickiness and clumping. During manufacturing, there are lots of areas to have cell loss, and at the end of the day, it is the physician who has to help define the decisions for the medical treatment. Manufacturing issues encountered included a process that was inconsistent because starting materials were inconsistent and whether with excess product, should cross-over studies be pursued. Moving to a heart disease application, Ian describes a CABG treatment population (6 patients), recipients of allogeneic MSCs. Ian closed by saying that there are many sources of MSCs which could ultimately be used anywhere.

Industry Comments – it was asked whether risk of tumorigenicity increased with age? Ian responded they had one donor who may have had one from a pre-leukemic cell but he has not seen any MSCs in human tumor cases and considers mice models of tumorigenicity to be irrelevant. Taking autologous cells only to P1 and allogeneic cells to P2 before transplant/infusion of them minimizes risk.

ISCT Survey on MSC Production Methods

Presentation by Knut Niss, PhD

(*See presentation #5*). Knut noted that it was possible, based on the number of publications, the term MSC might be overused. Knut reviewed the survey timeline and noted that the goal was to make the survey noncommercial and that there were two opportunities for response (57 responses, which likely comprised multiple individuals per response) – plan to publish results in Q1 2013.

Sourcing BM hMSCs section – noted that buying MSCs meant going to Lonza, (Time to Process header refers to time from bone marrow aspiration to processing in lab). Knut noted there was consistency in how labs establish identity of MSCs and that growth conditions impact MSC phenotype. Discussion ensued about establishing age of cultures by defining/naming based on passage number versus doubling time and at what point labs assess and define confluency to determine passage. He provided an example of what happens if you take 2 of the same bone marrow samples and treat them differently – there could be completely different results at the end, and this includes how passage numbers are assigned (see slides). Again, focusing on how cell age is calculated and making a case for standardizing on CPDs (cumulative population doublings) would be helpful to the industry and science alike.

Industry Comments – Knut noted the survey did not cover changes during CFU-F and that the representation of clinical versus academic respondents was broad based. Audience member noted he was pleased to see that the passage vs CPD discussion to compare products is evident from this survey. He also noted that allogeneic banks can be tested. There was a question about morphology of cells on slides – Ian noted that cells don't "sit down and spread out" and this is different from cells that are approaching senescence. (Ian) noted that cultures are very heterogeneous and have different properties within the same flask and further commented that monocytes deplete and endothelial cells will adhere but neither will passage and full characterization, based on the panel from the ISCT paper, to look at in P5/P6, for all 3 lineages. Most people check genomic stability by karyotyping. Use of DNAse as an anti-clumping additive post-thaw – if used early in the process, where there is washout – general agreement that clumping is bad and use is dependent on final cell dose, intended use of cells, etc – all factors that matter in whether DNAse can be used and that preclinical studies in an animal should be conducted for the specific indication. (Scott B) – DNAse has been used for a while but how does that impact dose? Are there other formulations that might work? ISCT messaged to all stakeholders that the organization plans to do other surveys and Agency expressed interest in ISCT performing this function.

SECTION 3 – GLOBALIZATION OF CELLULAR THERAPIES SCIENCE AND PRACTICE

Regulatory Guidances, Trends and Data Quality

Presentation by Scott Burger, MD

(*See presentation #6*). Scott noted that clinical trials are regulated nationally vs centrally and that getting good insight and feedback was challenging because of the varying experience of the regulators. Scott provided a visual of the EU Regulatory Framework and commented that the main directives look more similar to US GTPs than different, focusing on infectious disease transmission, and how they are distinct from ATMPs (the BLA equivalent in US). Scott noted a clinical trial in a single country tended to be academic only. He went on to review the Voluntary Harmonization Procedure (VHP), described as targeted towards multi-national clinical trials, permits exchange of information between countries, interested in using a common core approach (and informative even for small, local studies). Revisions to the CTD were reviewed, with a potential implementation around 2016. The goal is to bring clinical trials back to Europe by giving sponsors some assurance their study designs will be useful across national borders. Scott then provided an overview of the guideline on risk-based approach for evaluating clinical use of ATMPs. He noted that the changes seem to be reflective of how the US has moved to a more risk-based approach but don't clearly reference classic risk management tools like FMEA to accomplish this and also the guideline does not discuss risk mitigation once risk conclusions are drawn. And, in presenting a full list of EMA/EU guidance documents, he noted that the potency guideline covers similar territory to the FDA requirements. Scott noted that TGA is revising their GMPs for tissues/blood, with a key feature being focus on minimization of infectious disease transmission, and that a stop-gap measure (Biologicals Regulatory Guideline) was put in place until revisions are completed (which focuses on infectious disease transmission knowledge and containment). Scott next turned to discussing EMA Certification of Data Quality. He emphasized that a minimum data set is required but that the advantage was the opportunity to get buy in which would permit standardization in approach and results. Scott described the guideline for Quality Documentation for Biological Investigational Medicinal Products in clinical trials as being similar to an IND application. There was a brief mention of relevant pending legislation in India. (Additional information is provided in supplemental slides).

Agency Comments - OCTGT has a number of ongoing interactions with other regulatory authorities, including the ATMP cluster with EMA and Health Canada, parallel scientific advice with EMA, and the cell therapy regulators forum group (been meeting for 2 years).

Cell Therapy Medical Tourism

Presentation by Kurt Gunter, MD

(See presentation #7). Kurt noted that not all cell therapy medical tourism is bad, using as an example the first cord blood transplant in France. This session is to highlight risk to patients and the field of cell therapy and explore whether the stakeholders can work together to reduce those risks. Kurt stated that there has always been innovative medicine, taking place in hospitals and with expert caregivers who understand what they are doing with patients. The big worry are the unregulated, unproven therapies marketed as useful. What can CT stakeholders do? KG notes that there may be things industry can do that FDA can't. Kurt credited the ISSCR for taking an early stand on this area and pointed out that the ISSCR web site patient handbook is good start, but perhaps too technical and not especially patient

friendly. KG described the early ISCT publication warning about the risks of cell therapy medical tourism (link). KG admits that there are lots of ideas but resource constraints don't permit them all to go forward. KG offered his insight as a physician – he completely agrees that patients should not be harmed and also that one patient's harm is enough to set the field back for years. In looking for solutions, need to take baby steps – for example, a joint statement from trade groups, establishment of a working committee to monitor the field and perhaps join with FDA and others in finding these solutions KG suggested some ways to take on the issue:

- Space on the FDA website to document "things to be aware of"
- Space on stakeholder websites to link to FDA WLs and 483s
- Drafting a composite statement, jointly agreed to by the CTLM stakeholder group, and shared across all stakeholder websites

As one model of how a stakeholder might work with an organization representing clinics outside the U.S. regulatory framework, Marie Csete discussed the AABB and ICMS collaboration. ICMS approached AABB to help make products and patients safer in offshore clinics using autologous adipocyte-derived stem cell therapies, stressing the importance of IRB oversight. AABB is developing standards for ICMS. Once the ICMS standards are rigorous enough for AABB, AABB will assess against the standards to accredit the clinics for ICMS. (Standards will be ICMS standards, not AABB standards.) (Bill J) referenced the network news magazine stories, noting the history of Xcel in Germany, impacts on the patients and clinic and where one patient died, which led to the clinic closure http://www.telegraph.co.uk/news/worldnews/europe/germany/8500233/Europes-largest-stem-cell-clinic-shut-down-after-death-of-baby.html [transcriptionist reference].

Agency Comments - FDA acknowledged these concerns.

Action Items for CTLM:

- Prepare and issue a joint statement from CTLM stakeholders (strong yet broad)
- Explore possibility of working with Google to drive link to joint statement high in "cell therapy" or "stem cell" search engine results (work with Google to provide free or at reduced rate as charity measure)
- Provide CTLM update on industry response next year
- Reach out to patient groups to establish affirmative links and relationships – post links across ISCT website and patient groups to reciprocate