Meeting Summary of the 18th Cell Therapy/FDA Liaison Meeting
[Not FDA Reviewed or Approved]

November 15, 2021
Virtual Meeting

Participating organizations: **AABB, ABC, ASFA, ASH, ASTCT, CAP, CBA, FACT, FDA/CBER/OTAT/OCOD, ISCT, ICCBBA, NHLBI, NMDP, SITC, SCB, USP, WMDA**

The FDA CTLM Meeting was held on November 15, 2021, from 2:00 – 5:00 pm ET. After opening remarks from the ISCT North America Legal and Regulatory Committee Designate, Olive Sturtevant, MSc, and Director of FDA Office of Tissues and Advanced Therapies (OTAT), Dr. Wilson Bryan**,** the meeting commenced.

PRESENTATION SESSION 1: Roadmap to Address Potency for Complex Products- Steven Bauer, Ph.D.

To adequately address regulatory requirements, sponsors can interact with the FDA throughout the product development process. See slides 3-4 for "quality attribute" (QA), "critical quality attribute" (CQA), and potency definitions.

The demonstration that biological product is "safe, pure, and potent" is the basis for approval in a biologics license application (BLA) application. The potency of biological products is "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result" (21 CFR 600.3(s)). Per *Potency Tests for Cellular and Gene Therapy Products Final Guidance for Industry: January 2011),* potency tests ideally i) reflect product mechanism(s) of action ii) predict relevant *in vivo* activity iii) inform molecular attributes that may be correlated with *in vivo* activity.

Multiple assays (or a matrix approach) may be implemented if one assay is insufficient to measure different product attributes associated with quality, consistency, and stability. *In vivo* assays strive to determine the physiology can be whole animal studies, organ/tissue/cell culture systems, or a combination of studies mentioned above. *In vitro* studies to assess the molecular attributes may include flow cytometry, ELISA, enzyme assay, RT-PCR, and microarray.

The common potency issues for cell-based products stem from the complex, multimodal activity and the heterogeneity in cellular preparations/bioactivity/donor properties. As such, potency should be developed

based on a sufficient understanding of the mechanism of action, stability-indication, and sensitivity to significant changes in manufacturing.

Dr. Bauer outlined two initiatives (not FDA recommendations/requirements) that address potency challenges.

- The FDA Regulatory Science Research CBER/FDA MSC Consortium aims to identify and correlate MSC attributes with *in vivo* and *in vitro* assays of safety and efficacy (slides 8-13)
- NIH Regenerative Medicine Innovation Project (RMIP, RMIC, IDCCH) (see slide 16)

Research from the CBER/FDA MSC Consortium showed that several quantitative bioassays for MSCs can detect differences among MSCs from different donors, cultured for various lengths of time, and manufactured under different conditions. Attributes assessed included proliferation, cell size, colony-forming units, adipogenic activity, osteogenic activity, chondrogenic activity, and immunosuppressive activity (see slide 10 for references).

Dr. Bauer briefly discussed a few examples. Lo Surdo JL et al. (2013) showed adipogenic potential varies between cell lines and decreases with passaging. Klinker et al. (2017) demonstrated that the immunosuppressive capacity varies between MSC cell lines and decreases with culture duration, and the IFNγ-Stimulated MSC morphology predicted immunosuppressive activity. Dr. Bauer also briefly discussed two examples of research describing promising quality attributes for cell-based products. K. Papas, University of Minnesota Department of Surgery, showed that human islet activity by ATP per amount of DNA correlates with cure in a rodent model of diabetes. In contrast, cure does not correlate with Trypan Blue viability measurements. F.P. Luyten, K.U., Leuven Department of Rheumatology demonstrated that different gene expression of osteoprogenitor preparations predicted histology scores corresponding to stable cartilage or failure *in vivo*.

In conclusion, an iterative process is recommended to identify predictive CQAs. Ideally, potency should be based on MOA, predictive *in vitro*, and *in vivo* results related to the clinical outcomes. Sponsors are reminded that scientific consultation meetings with the FDA are opportunities to discuss questions and concerns.

Discussion:

- In the study discussed on slide 14, were there other tests such as protein/signal measurements to orthogonally assess if the cure rate accurately associates with the islets' efficacy?
  In this study, the islet preparation was measured for oxygen uptake, which discriminated islets that cured chemically-induced diabetes. This was done as a cross-check of the islet activity determined by ATP per amount of DNA. When there is a difference in observable bioactivity, as demonstrated by this study, one should consider whether other measurements are to be applied and whether alternative measures are feasible and robust. A reliable and well-established disease model can help with these questions.
- Potency assays can be multi-factorial and iterative. The Agency was asked to comment on how that can be correlated to clinical outcomes. How and when to implement to sufficiently meet the potency assays requirements?
  While it is not known which potency assay(s) for each mechanism of action would be sufficient to meet all the goals of a potency assay, it is recommended to implement and strategize potency assays early on. Furthermore, the roadmap to address potency would benefit from a multimodal approach from the beginning and the strategizing of the potency assay in different ways.

PRESENTATION SESSION 2: False Positive HIV Patient results from post receipt of Genetically Modified CT Products - Armin Ghobadi, MD

The number of cancer cell therapy trials is rapidly increasing (700 in 2018 to 2100 in 2021). FDA has approved a few retroviral or lentiviral CAR-T products. Gammaretrovirus (MLV and FLV) and Lentivirus (HIV) are subtypes of retroviruses, which contain an RNA genome with different 5' and 3' sequences. There are two types of HIV tests - immunoassays and nucleic acid amplification test (NAAT).

See slide 9 for examples of quantitative and qualitative HIV tests. RNA-based HIV tests use a single-stranded nucleic acid probe that can recognize a specific sequence of HIV genome. The precise target sequence and genes for these probes are unknown (see slide 10).

Since a fraction of the HIV genome is included in retrovirus vectors, RNA-based tests using a single-stranded nucleic acid probe(s) can recognize a specific share sequence in HIV and retrovirus genomes included in the retroviral or lentiviral vector. Patients receiving cell products transduced with these vectors can receive a false-positive HIV test result if the diagnostic probe(s) recognizes a portion of the HIV genome included in the vector used to transduce the cells. References to published cases of false-positive HIV tests post receipt of genetically modified CT products can be found on slide 12.

A recent case was presented. A 16-year-old male patient with sarcoma tested negative for HIV (serology and NAAT) at baseline. The patient received a false-positive HIV result post-TCR T trial which utilizes lentiviral vectors. The patient was screened for another clinical trial nine months after the initial TCR T trial.

- COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (quantitative) and COBAS TaqScreen MPX Test (qualitative) indicated the patient is **positive** for HIV.
- Aptima HIV-1 RNA Qualitative Assay (qualitative) and fourth-generation (HIV 1/2 Ab + p24 Ag) immunoassay indicated the patient is **negative** for HIV.

Conflicting test results caused significant emotional distress for the patient and his family and a two-week delay in enrollment in the subsequent trial. It may be beneficial to encourage the manufacturer of gene-modified cellular therapies (lentiviral or gammaretroviral vectors) to provide results of HIV tests (both NAAT and serology based) of manufactured cellular products in the investigator's brochure.

Discussion:

- Did the patient receive an antigen-antibody test in the situation with the false-positive HIV test result?
  The subject was tested 3-5 days later with the fourth-generation antigen-antibody test. However, in the acute HIV phase, one can receive a negative HIV serology test result with a positive PCR-based test. As such, it was not clear whether the patient was HIV-positive. There is also no guidance on how situations similar to the described case should be handled.
- What is the frequency of a patient receiving false-positive HIV tests after receiving cellular therapies?
  In two trials involving CAR-T therapy products, three other patients received false-positive HIV results. Because the sequences for the vectors used in cellular therapies and the probe sequences of HIV tests are not available, the determination for HIV-false positivity is challenging. Given the number of available cellular therapies with retroviral and lentiviral vectors continues to increase, cases of HIV false-positivity are likely going to increase.

PRESENTATION SESSION 3: Emerging Donor Testing Requirements –Colleen Delaney, MD, MSc and Patrick Hanley, Ph.D.

The number of cell therapy products under development increased by 48 % from 2020 to 2021. Although autologous cell therapy products outnumber allogenic cell therapy products, the number of allogenic products in preclinical, phase I, and Phase II development increased by 48%, 42%, and 48 %, respectively.

Allogenic cell therapies overcome the many limitations of autologous cell therapies but introduce GvHD and alloimmunization risks. Defined Relevant Communicable Disease Agents or Diseases (RCDADs) are well established for donor eligibility determination. However, IDM testing requirements for non-relevant communicable disease to determine source material eligibility appears to be highly variable. For example, testing for HHV family virus and EBV is not necessary for evaluation of donor eligibility but may be required for when evaluating source material. Given the prevalence of EBV and HHV6 (both > 90%) in adults, the requirement for source material to be negative for these viruses severely limits the pool of available starting material. Presenters would like the FDA's guidance on determining the IDM testing requirement for non-relevant communicable diseases and the necessity to repeat IDM testing on final drug products. Official guidance for suppliers to manage and balance the stated regulatory requirements for donor eligibility with therapeutic manufacturer requirements would be beneficial.

The current FDA guidance on the requirements for adventitious testing of cell and gene therapy products is based on the *Guidance for Industry Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications (2010).* The guidance designed for viral vaccines, including vectors with master cell banks and working cell bank models, provides limited guidance for emerging therapies (ET) that fall into different categories based on cell origin, the number of products in the bank, genetic manipulation, etc. For instance, cell banks do not always contain viral vectors, and ET cell banks derived from primary human cells have different communicable disease risks. While extensive guidance is provided for continuous cell lines, guidance is requested for non-tumorigenic primary cells and defining when cells become a bank. Clarity on testing requirements would be beneficial as testing not mentioned in the guidance has been requested in recent IND submissions.

FDA guidance on the following questions is requested:

- At what point does a lot become a cell bank?
- If required of ET, are the testing requirements the same as those listed for viral vaccines and vectors?
- Are there other communicable diseases for which an ET must be tested that are not currently in the guidance?

Discussion:

- The Agency stated they would like a copy of the slides to deliberate further on the questions raised internally. The Agency has been listening to the concerns of the stakeholder groups but is not prepared to answer or comment at this time. Following internal discussion, the Agency may address the issues by changing interactions in the IND process, drafting guidance, or addressing it at the next meeting.
- A stakeholder shared that 2 billion cells are needed for both *in vivo* and *in vitro* testing. 2 billion cells are often more than what master cell banks carry. It is assumed that if *in vivo* and *in vitro* adventitious testing is needed, it would be acceptable to expand the cells for testing. It was raised

that next-generation sequencing is a faster testing method and consumes fewer cells. It would be beneficial for NGS tests for certain requirements to be allowed.

- A stakeholder shared an example where the facility was asked to test for a virus after the cell bank was made. Of interest, these test requirements were previously not requested. The additional viral testing indicated the cells were positive for EBV, which deemed the new cell bank ineligible for use. If the testing requirements were raised and clarified with the manufacturer before the cell bank was made, manufacturers would avoid the waste of resources and time.

PRESENTATION SESSION 4: Use of Non-US Starting Materials –Challenges for developers in the US–Salmah Ahmed, BSc

The World Marrow Donor Association has 114 member organizations, 55 cord banks, and 81 adult donor registries. WMDA has a global perspective on regulatory affairs. As the cell and gene therapy field rapidly expands, developers plan to launch universal treatment options to help patients globally.

High-quality starting materials from the best-available donors should be accepted. FDA's support would facilitate enabling "global" donor acceptance criteria for non-US donor-derived allogenic starting materials. Currently, North America is the largest importer of HPC products, and Europe is the largest exporter. In 2020, the USA used 133 imported HPC cord cellular products to treat 493 patients. According to NMDP, there is no known relevant viral communicable disease transmission from donor to receipt with HPC products from 2011 to 2021. Ballen et al. (2020) found only 4 SAEs in the 2356 patients who received unlicensed UCB units. The serious adverse events did not involve any relevant communicable disease transmission. International regulatory differences exist for cellular source materials across the US, Canada, Australia, and the EU.

Regulatory and industry leaders suggest the following can assistant the innovation to develop the best treatment option for patients:

- Harmonizing donor screening and testing for CGT application to ensure the selection of the best donor.
- Clarification on donor screening and testing requirement for stored material since donors cannot be contacted for more samples or screening questions
- Guidance on US patient access to products derived from embryonic stem cells since the US does not source embryonic stem cells.

Discussion:

The Agency thanked the presenter while acknowledging the importance of discussing the challenge in using international starting material and patient access. The Agency shared that the FDA has been part of international groups, including the ICH. However, the convergence of regulation is challenging, given regulatory agencies have to reach an agreement. While workshops and liaison meetings can help raise these issues in harmonization, many discussions have to occur for the harmonization of regulations.

A stakeholder provided the perspective that it could be helpful to involve a registry in the discussion as registries have experience navigating international regulations. Another stakeholder inquired how one may facilitate the challenges described.

Depending on the desired outcome, a position paper that reviews the science can be helpful to raise the issue with the FDA.

PRESENTATION SESSION 5: Challenges with Critical Sourcing Materials – Emily Hopewell, Ph.D.

Supply shortages are caused by a combination of factors such as shortage of workers, available resources focused on COVID-19, the backlog of cargo ships in ports with products with limited shelf-life, and delays in deliveries. A specific example is the impact of supply shortages at Indiana University (the Bioprocess Development Laboratory, Cell immunotherapy, and Transduction and Vector Production Facility). Seventy-two materials have been on backorder since March 2020, plastics and gowning supplies seem to be most affected. Supplies for downstream processing have experienced the most prominent impact (average wait of 6.8months). Lentiviral production has also been delayed.

A critical supply survey was disseminated through stakeholder society networks, Google Groups, LinkedIn, and direct email to understand the extent of critical supply shortage. Most respondents expressed they have had essential supply shortages in the past 18 months. The most significant impact was tied to plastics, tubing/bags, and diluents. Supply delays did not always lead to production delays. Survey respondents demonstrated resourcefulness to mitigate delays with short-term solutions such as borrowing from other facilities. Long-term solutions implemented include process changes and process requalification.

A case study on the shortage of filtration units for vector concentration was presented. The hollow fiber units for the tangential flow filtration system were back-ordered for six months, resulting in a delay of vector products. The facility investigated the shortage and found the current vendor was unable to commit to delivery units. The risk assessment demonstrated there is no alternative equivalent vendor, and the process cannot be completed with concentration with the filter. Vendors for flat cassette filtration units made with different filter materials were responsive to supply requests. However, the process and design for fluid transfer components had to be reworked to use the flat cassette filtration unit. Ultimately, the facility created and qualified a new filtration procedure with help from the vendor. The facility now maintains two TFF procedures and associated operator competency based on supplies availability.

Guidance is needed on what is required to establish supply equivalence, qualification of supplies/vendors. For example, in the certificate of analysis/sterility/conformance of flasks, the alternative flask cannot be guaranteed free from TSE/BSE risk and was not tested for cell-culturing.

Discussion:

- The Agency acknowledged that delays could be challenging to sponsors. The Agency inquired if stakeholder(s) could elaborate on the extent of delays/critical supply shortage now (18months) in comparison to 12 months into the pandemic.
  A stakeholder described that several products had experienced periods of unavailability throughout this time. Products with plastic components have been particularly challenging to source, such as connector pieces, pipettes. Other storage issues include equipment and associated components (TFF and -80 freezers), syringes, and needles. There seemed to be at least one item that was back-ordered for two weeks to a month in order. Furthermore, the power outage in Texas affected the availability of liquid nitrogen and medical-grade oxygen. Stakeholders shared that with limited staffing, the maintenance of competency for two systems can be challenging.
- Given that the survey found 40 percent of product production was delayed, was patient care delayed?
  A stakeholder shared the production of a newly approved product has been delayed. Another

stakeholder shared that some trials have been delayed for other reasons like limited availability of personnel and the hospital permitting entry of medically necessary personnel only. As elective volunteers return to trials, sponsors expect vectors to be available as soon as the trials commence.

In the closing remarks by Dr. Wilson Bryan and Olive Sturtevant, the Agency thanked the presenters for raising important considerations and providing context for the FDA in issues presented. The Agency would like to receive the slides for further internal deliberation.