Meeting Summary of the 17th Cell Therapy/FDA Liaison Meeting
[Not FDA Reviewed or Approved]

November 23, 2020
Virtual Meeting

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

The FDA CTLM Meeting was held on November 23, 2020 from 2.00 – 5.00 pm ET. After a welcome from the ISCT North America Legal and Regulatory Committee Designate, Ms. Olive Sturtevant, and Director of FDA Office of Tissues and Advanced Therapies (OTAT), Dr. Wilson Bryan, the meeting commenced.

PRESENTATION SESSION 1: Request for an update of the RMAT program

- ***Presentation 1: Wilson W. Bryan, MD (FDA)***

Dr. Bryan outlined the organizational structure of the Center for Biologics Evaluation and Research (CBER), and reviewed the diversity of OTAT-regulated products including gene therapies, stem cells/stem cell-derived products, products for xenotransplantation, blood- and plasma-derived products, therapeutic vaccines and cellular immunotherapies, combination products, devices and tissues. Investigational New Drug Applications (INDs) and Investigational Device Exemptions (IDEs) have increased substantially over the last number of years. 453 submissions in total were received in 2019, for both expanded access and research-focused applications. Between 2016-2019, the total number of research-focused new INDs nearly doubled from 142 to 277, and new INDs with Cell Therapy Development Programs increased by 44% from 63 to 91. The RMAT designation program was developed following the 21st Century Cures Act which was enacted in December 2016. It was noted that Breakthrough Designation (BTD) has been available since 2012. Dr. Bryan outlined the RMAT program objectives and discussed the guidance for industry on the use of this designation. He referred to the guidance published by FDA in 2019 that describes the benefits of RMAT and other expedited programs, clarifies types of products eligible for RMAT, necessary preliminary clinical evidence, changes to accelerated approval pathway, and the use of Real World Evidence (RWE). The primary benefit of RMAT and BTD is additional communication support from FDA (increase in

meetings, and availability to discuss IND filings regularly throughout the year). Currently, there have been a total of 155 requests for RMAT designation (gene therapy, allogeneic cell therapy products and autologous cell therapy products account for 37%, 30%, and 20% of applications received, respectively). Dr. Bryan reviewed the RMAT designation request distribution by specialty and clinical study status. Data were presented on the status of RMAT requests that have been granted, pending, or were denied. As of November 20, 2020, 155 requests have been received of which 55 were granted, 97 denied, and 3 pending review. Dr. Bryan discussed the various reasons for denial of RMAT designation requests. Analysis of denied RMAT designation requests cite administrative reasons (inactive IND, no preliminary clinical evidence), CMC reasons (different product/lack of product comparability data or not qualified as a regenerative advanced medicine therapy), or insufficient preliminary clinical evidence (study design issues, inconsistent or insufficient data). The majority of denied RMAT designation requests are due to study design issues. Dr. Bryan discussed that gene therapy accounts for the greatest success rate for RMAT designation (47%), followed by allogeneic cell therapy products (43%). In contrast, autologous cell therapy products have a success rate of 10%. It was noted that the further along a product is in development at the time of submission, the greater success with RMAT designation. Dr. Bryan concluded his presentation by summarizing that approximately 36% of RMAT designation requests have been granted. RMAT designations requested and designations granted surpassed Breakthrough Designation (BTD) in under 3 years (55 RMAT designations granted vs 35 BTD designations granted, respectively) and the trend suggests RMAT product approvals may soon surpass OTAT BTD product approvals.

Discussion

Dr. Bryan was asked to comment on how the FDA will access additional resources and funding to support the increasing development of cell and gene therapy products. Dr. Bryan noted that resourcing is an important focus to ensure the Agency can deal with the increasing workload. Staffing has increased over the past few years and the Agency is currently hiring in their CMC, Clinical, and Pharmacology/Toxicology divisions.

Dr. Bryan was also asked to comment on reasons why a gene therapy sponsor would select to apply for RMAT vs BTD. It was noted that there is no major advantage of RMAT compared to BTD. Early after the launch of the RMAT program, sponsors would apply for both; however, this trend is decreasing. The Agency ensures equivalent attention is provided to both programs.

PRESENTATION SESSION 2: Donor Adverse Events Cellular Therapies

- ***Presentation 2: Beth Kuker (NMDP), Joseph (Yossi) Schwartz, MD, MPH (ASFA)***

Ms. Kuker began the presentation by providing a background and objectives for the presentation. The presentation would include a clinical trial case study, information on adverse events for HPC(A) donors, adverse event regulations, concerns and finally, recommendations for the agency. Ms. Kuker then handed the presentation over to Dr. Schwartz to outline the clinical trial case study. Dr. Schwartz discussed a case study of a 50-year old woman with treatment-refractory stage IIIB follicular lymphoma who was being assessed for eligibility for a CAR-T cell clinical trial. Dr. Schwartz outlined the eligibility criteria for trial entry vs the peripheral blood counts of the patient and the action taken because of these differences by the Oncology service. Dr. Schwartz advised there was no clear rational for the platelet threshold of >75,000/µL as noted. The patient received one dose of platelets with inadequate increment and a subsequent dose of ABO matched platelets with inadequate increment. The oncology service continued requesting additional platelet doses despite the lack of immediate medical necessity. Several arguments were raised relating to whether the potential benefits of qualifying for a clinical trial that may treat the patient's progressive cancer outweighed the risks of platelet transfusion. In addition, upon consenting to enroll in the trial, the patient had accepted the risks of medically 'unnecessary' procedures including transfusion, extra blood draws & imaging studies. Finally, the oncology service attending further asserted that waiting for a platelet refractoriness workup was not an option given her clinical status and stage of disease. Audit results from Columbia University Irving Medical Center show a trend of bio industry cellular therapy trials establishing arbitrary non evidence-based guidelines for transfusion. Of 86 clinical trial records for cellular therapies, only 19 had established protocols. For patients on a cellular therapy trial protocol, 67% of released platelets did not meet hospital transfusion guidelines. However, for patients not on a cellular therapy protocol, only 18% of outside-of-guidelines platelets release. Platelet transfusion thresholds for the clinical trials varied from 20,000 to 150,000/µL (median 50,000/µL), however there is no literature cited to justify these increased thresholds. Ms. Kuker outlined that there can be adverse events for HPC(A) donors; these relate to mobilization and the collection procedure. There are no specific IND or BLA regulations that encompass donor safety and donor adverse event reporting for cellular therapy products or specific guidelines for use of blood products in cellular therapy trials.

Discussion

Questions were raised regarding which elements should be included in the reporting to the FDA and should the FDA set the criteria for these adverse events in conjunction with the manufacturers. It was discussed

that depending on the protocol, AEs can vary and new adverse events may occur. Input from the sponsor collecting the cells should determine what the adverse events are.

There was discussion regarding whether AE/ADEs for pediatric allogeneic donors (i.e. siblings for HSCT) should be reported separately from other donor populations. Ms. Kuker noted that NDMP does not handle pediatric donors however for related donors, it would depend on whether there is an active IND or BLA for the product. If it is possible to report under an active IND or BLA, that would be a potential route.
It was questioned whether AEs occur more frequently in certain patient types of mobilization agents and when dealing with different mobilization agents, is there a risk of dual reporting of those AEs? It was noted that for the most part, AEs for mobilization agents are common across different approaches. Due to the mechanism in which AEs are reported, dual reporting cannot be prevented.

PRESENTATION SESSION 3: Infectious Disease Lookbacks Related to Blood Product Transfusions May Not Identify All Those At Risk

- ***Presentation 3: Olive Sturtevant, MHP, MT(ASCP)SBB,SLS, CQA(ASQ) (ISCT)***

Ms. Sturtevant began the presentation by outlining the transfusion of blood products related to apheresis. Blood products may need to be given to donors prior to apheresis. The interface between blood and plasma is critical for good cell therapy collection. Often, institutions must replace several substances in order to maintain a good blood and plasma interface. Blood banks and transfusion services have standard operating procedures in place to notify either the patient's physicians or patients who received products from a donor involved in a lookback due to positive findings on a subsequent donation. However, many transitions can occur in the process chain, e.g. contracting out collection for donor, transfusion service etc. Sophisticated algorithms exist to determine when to perform a lookback and who should be notified. Despite this, there is concern that lookbacks for a blood product may not go far back enough. With that in mind, what does the notification process look like when the recipient of the blood product involved in a "Lookback" is an HCT/P Donor? Ms. Sturtevant provided data from CIBMTR and outlined that the use of allogeneic donors has increased over the last number of years, as well as the number of older siblings being used in donation procedures. There is a risk of infection through blood transfusions, for hepatitis C approximately 1 per 2 million units screened and for hepatitis B there are less than 1 per million units screened. Where the donor may test positive for Hepatitis C, HIV, etc. the question arises as to whether the services go back far enough if you are giving a blood product to a potential allogeneic donor. In addition, Ms. Sturtevant posed the question whether there are services in place to look at patients who received HCTP products from that collection.

The lookback notification rate for recipients of blood products based on donors that subsequently tested positive for a marker is low. Data from one institution indicated that the notification rate for HIV, HCV, HBV is less than 0.03%. There are a number of different arrangements amongst blood transfusion services, HCT/P collection centers and transplant programs for notifying the HCT/P recipient's physician when the donor is part of a blood product lookback. However, some organizations may contract out collection and transfusion procedures therefore the various steps in the lookback process may involve several different organizations. The presentation concluded with questions requesting clarity on regarding how much contact information or follow up is absolutely necessary with donors, whether there are processes in place for donors from a foreign country, and who gets notified when the product is shipped to another facility either directly from the collection center or the processing lab.

Discussion

FDA noted that the 21 CFR Part 1271 requires all establishments to have procedures for receiving and sharing information. These requirements extend to both 361 and 351 products and the CGTP provides information about compliance.

PRESENTATION SESSION 4: Alternative BLA Pathway to Approved Genetically Modified Autologous HCTP products

- ***Presentation 4: Olive Sturtevant, MHP, MT(ASCP)SBB, SLS, CQA(ASQ) (ISCT)***

Ms. Sturtevant began the presentation by providing some historical context on the involvement of academic institutions in cell therapy trials. Often, many academic institutions do not want to be involved with cell therapy trials and prefer manufacturing and administering products internally to their own patients. Ms. Sturtevant outlined the various stages of manufacturing and testing of autologous genetically modified cellular products (standardized processing, quality assessment of final product and patient management). There are many standardized processes for generation of selecting and depletion of desired cells, there are more and more GMP and cytokines available on the market also. However, potency is still a challenge for a lot of sponsors. At larger academic centers, all of this can be done safely on site, especially, with use of automated, closed processing devices and standardized released assays. Ms. Sturtevant posed the question if there are any other ways of going down this pathway. Is there a pathway for multiple institutions to collaborate in a way that each could apply for a BLA separately using the same data? This could be possible if the same trial design, treatments, and care regimens for the collection of combined safety and efficacy data are used. Additionally, using the same genetic modification process or viral vector construct and standardized manufacturing process and release assays may be required. There is also the option of

outsourcing to a CMO to monitor and verify the process and data. An example of this could be for a late phase 2 trial or phase 3 trial using the same processes and same vector construct. There is a desire to provide cost effective treatments to patients with safe and effective products that can be manufactured locally at academic institutions in a standardized manner. This would reduce treatment delays and costs associated with these treatments. Academic centers can share data through CIBMTR and can share other relevant clinical data beyond current requirements. The goal would be to create a pathway for BLA based on shared data, standardized manufacturing, testing and genetic modification methods. This would require finding ways to have these genetically modified autologous products recognized as safe and effective based on shared clinical data gathered across multiple institutions during clinical trials without having only one IND sponsor.

Discussion

FDA commented that the RMAT guidance describes the ability to file under one IND however to result in separate licenses, inquired what the advantage would be for an institution to hold their own IND. Ms. Sturtevant discussed that although some academic sponsors have done this, most do not want to be responsible for another academic center across the country. If each center could attest to having a uniform manufacturing process and can demonstrate that it can generate the same type of products (i.e. same insertion sites, vector copy numbers), dual manufacturing processes can be developed to determine whether the output of products is the same and shared clinical data across the different sites can demonstrate whether the products are safe and effective. This would be a benefit to patients, especially for institutions dealing with rare diseases. It was noted that further education would be required to move down this path.

There was discussion on what comparability would look like between multiple manufacturing sites (regardless of whether it is a single IND or multiple BLAs) and the depth required to compare CMC. Ms. Sturtevant noted that the SOPs can be reviewed between the two sites however another method would be to split the product between sites to determine whether a comparable process is in place. Even with written documents, there may be nuances that affect comparability.

A potential barrier for academic centers to bringing a product to market is the expectation that each site would receive their own BLA (similar to cord blood banks). Discussion arose whether this would be appropriate for this scenario with academic centers or whether there is another pathway. It was noted that this would require further exploration and convening a panel for discussion would be warranted.

PRESENTATION SESSION 5: CMC Comparability of CGT

- ***Presentation 5: Karen Nichols, Esq. (ISCT), Michael Mendicino, PhD (ISCT)***

Ms. Nichols began the presentation by outlining the ask and desired outcome from presenting this topic to the Agency. The ask was for FDA to consider providing additional/new guidance and/or other tools for understanding and triaging requirements to demonstrate comparability. The desired outcome was to provide suggestions for said guidance and/or tools and discuss if desired. Ms. Nichols then went on to highlight potential differences between autologous and differentiated cell therapy (such as an allogeneic product that may undergo master cell bank changes). These differences can impact the clinical development process all the way to filing a BLA. Dr. Mendicino noted that the presenters had decided to focus on one gene modified autologous cell therapy for the purpose of the presentation but that there are numerous other relevant examples to consider, such as non-gene-modified autologous, gene-modified allogeneic, gene edited cell-based, cell-based combination products, and others that all apply. The presenters had chosen low throughput to high throughput facility as the example of a CMC change for the purposes of the presentation. In a low throughput to high throughput facility, development is required e.g., to add or extend GMP manufacturing capacity by introducing a second, multi suite processing facility. Comparability challenges may exist whereby this new facility could be in entirely different region or geography. There may be different definitions for risk tolerances, production manufacturing experiences, and outsourcing varying from facility to facility. Facilities must undertake an impact assessment where existing processes are mapped, and a risk assessment is conducted. Ms. Nichols outlined that a technology transfer plan with training and engineering runs and processing simulations should be undertaken. There are several comparability plan considerations to be taken into account. These include supply chain, reagents and raw materials, equipment and consumables, methods and qualifications, training and batch records and process flow. The areas of focus for the comparability plan include starting materials and access to clinical starting materials from patients. Ms. Nichols outlined the execution challenges associated with comparability plans and suggestions for consideration. These suggestions included providing Q&A guidance / road maps on applying Q9 to specific CGT examples, publishing an interaction timetable to set expectations of what types of RMAT engagements will result in senior staff involvement, and clarifying expectations on data look back for inclusion of clinical data from small patient number studies where all patient data must contribute to the pivotal efficacy results in order to satisfy statistical criteria. Additionally, providing guidance on using surrogate materials, retaining samples or other testing materials for studies in lieu of clinical product and defining pre-approval comparability as an ongoing process with guidance on when formal meeting-based interactions are required vs what is acceptable for annual reporting / routine amendments.

Discussion

Discussion arose regarding the role of standards, and the collaborations with NIST, USP, and SCB. Dr. Mendicino discussed that ISCT and other organizations have been working closely with SCB, and identifying what topics are ready for standards or which require further technical progress. A 3-part ISO Technical Specification has been developed and USP has their own chapter on ancillary materials.
A question was posed regarding developing an advanced therapies pre-approval guidance for comparability. Also, benefits with using cost efficient in vitro models such as tissue chip models for screening therapeutics were discussed. Also, that the value is the use of both human controlled cells and patient specific cells for screening therapeutics for their particular applications.

FDA commented that there has been great interest in comparability in the field and if sponsors can define with confidence what changes can be made in manufacturing without a change in safety and effectiveness, this will help move the field forward. The challenge is that there is a very small number of products that have shown safety and efficacy, resulting in insufficient knowledge and data. It was suggested that because the field is still so early, it would be helpful to have sponsors share their experiences when making changes in their analytical/in vitro studies to determine impacts on their products. FDA noted there were no quick checklists, no standard flowcharts and this topic is challenging for both FDA and sponsor. FDA acknowledged the importance of these issues and noted more knowledge sharing is needed before the Agency is able to provide a formal guidance.

PRESENTATION SESSION 6: Framework for use of research grade materials in manufacturing of cellular therapies

- ***Presentation 6: Jim Richardson, PhD (USP), Emily Hopewell, PhD (SITC)***

Dr. Richardson began the presentation by outlining material issues. In general, materials can be grouped in buckets with similar risks however evaluation requires further consideration with how/where they are used, and the processes and facilities used in production. Furthermore, 'grades' have been marketed by vendors that may not be based on established regulations. Dr. Richardson then moved on to some terms of confusion, e.g., R&D or research use only, preclinical grade, cGMP grade, clinical grade and animal protein free. Several material risks and practical challenges were outlined such as cross-contamination, traceability, qualification, variability and supply chain issues. Dr. Hopewell outlined some considerations for non-GMP 'grade' materials, possible testing requirements, and critical reagent assessment from low risk reagents to high risk reagents. Dr. Hopewell provided some examples of reagent testing (animal vs. non-animal origin) with the proposed use of the reagents and compared material vs. process risk. One of the examples

discussed was the proposed use of saline for injection in washing of a product. To assess the reagent, you must assess if sterility is guaranteed, if the reagent is chemically defined and other process risks. Dr. Hopewell provided further examples such as hAB serum, HrIL-9, Gag/Pol Plasmid and a CellSTACK chamber. The presentation was concluded by noting that although there is a wealth of information about qualification of materials for cellular therapies, there is confusion regarding material risks. This confusion can cause delays and increased costs. In order to reduce this, education around these risks should be improved.

Discussion

A question was posed regarding the testing criteria for CT products for starting materials such as hydrogels, for use on target organs (lungs, heart). Dr. Richardson noted that the field still needs to work together to define these attributes.

FDA commented that hydrogels or scaffolding materials, although may be considered as raw materials, are not considered manufacturing reagents. In those particular instances, it would be important to ensure that FDA looks at additional information such as safety aspects as it may go beyond what has been written in the COAs for those materials.

Dr. Richardson noted that a guidance on plasmid DNA manufacturing may be developed in the near future.

Closing remarks

Ms. Sturtevant thanked FDA, speakers and attendees for their participation on the topics presented. Dr. Bryan commented on the outstanding presentations and noted that discussions need to be ongoing, to enable stakeholders and FDA to engage in dialogue about current challenges and to advance the field.

Attendees

Stakeholder Groups		
Name	Institution	Stakeholder organization
Aby J Mathew	BioLife Solutions, Inc.	CBA
Audrey Le	ISCT	
Bethanie Kuker	NMDP/Be The Match	NMDP
Christina Celluzzi	AABB	AABB
Clare Guy	ISCT	
Colleen Delaney	Fred Hutchinson Cancer Research Center	ASH
Emily Hopewell	Indiana University	SITC
Geeta Paranjape	Carter BloodCare	ABC
Jay Hudgins	LAC+USC Medical Center & Keck School of Medicine	CAP
Jim Richardson	US Pharmacopeia	USP
Joanne Kurtzberg	Duke University Medical Center	CBA
Karen Moniz	ICCBBA	ICCBBA
Karen Nichols	Vertex Pharmaceuticals	ISCT
Kathy Loper	NMDP Be The Match	NMDP
Ken Ip	ISCT	
Linda Kelley	Moffitt Cancer Center	PACT
Lisbeth Welniak	NHLBI	NHLBI
Martha Lundberg	NIH-NHLBI	NIH-NHLBI
Michael Mendicino	Hybrid Concepts International	ISCT
Monica Freire	ICCBBA	ICCBBA
Olive Sturtevant	Dana-Farber Cancer Institute	ISCT
Paige McKibbon	NMDP/Be The Match	NMDP
Patrick Hanley	George Washington University	FACT
Phyllis Warkentin	University of NE Medical Center	FACT
Robert Anderson	Emmes	PACT
Shari Pilon-Thomas	Moffitt Cancer Center	SITC
Susan Lepke	AABB	AABB
Susan Rossmann	Gulf Coast Regional Blood Center	CAP
Yossi Schwartz	CUIMC	ASFA

FDA Representatives	
Name	Department
Andrew Byrnes	CBER/OTAT/DCGT
Anna Kwilas	CBER/OTAT/DCGT
Anne Rowzee	CBER/OTAT/IOD
Celia Witten	CBER IOD
Denise Gavin	CBER/OTAT/DCGT/GTB
Ilan Irony	CBER/OTAT/DCEPT
Irina Tiper	CBER/OTAT/DCGT
Iwen Wu	CBER/OTAT/DCEPT/PTB
Judith Arcidiacono	CBER/OTAT
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Larissa Lapteva	CBER/OTAT/DCEPT
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Peter Marks	CBER
Rachael Anatol	CBER/OTAT
Raj Puri	CBER/OTAT/DCGT
Safa Karandish	CBER/OTAT/DHT
Scott Brubaker	CBER/OTAT/DHT
Steven Oh	CBER/OTAT/DCGT
Tejashri Purohit-Sheth	CBER/OTAT/DCEPT
Thomas Finn	CBER/OTAT/DCGT
Wei Liang	CBER/OTAT/IOD
Wilson Bryan	CBER/OTAT