Meeting Summary of the 21st Cell Therapy/FDA Liaison Meeting
[Not FDA Reviewed or Approved]

November 19, 2024
Virtual Meeting

Host Organization:

Participating organizations: **AABB, ABC, ASH, CBA, FACT, FDA/CBER/OTP/OCTHT/OGT/OCE/OCBQ/OBPV/ORO/OCOD, ICCBBA, ISCT, NHLBI, NMDP, SITC, USP, WMDA, NIST**

The FDA CTLM Meeting was held on November 19, 2024, from 10:30 – 12:30 pm ET. After opening remarks from the ISCT North America Legal and Regulatory Committee Lead Designate, **Olive Sturtevant, MHP, MT(ASCP)SBB, SLS, CQA(ASQ)**, and Director of FDA **Center for Biologics Evaluation and Research (CBER), Peter Marks, MD, PhD,** the meeting commenced.

PRESENTATION 1: Labeling of Cellular Therapy Starting Materials for Further Processing – Huy P. Pham, MD, MPH (National Marrow and Donor Program, NMDP)

At the beginning of the presentation, Dr. Pham highlighted that as cellular therapy continues to be an emerging field with exciting potential, the use of cellular therapy products has expanded from *final therapeutic products* to *starting materials for further processing*. They are often used as starting material for further processing of final products under an IND or BLA pathway.

Dr. Pham mentioned that the current FDA guidelines[1][2][3] only specify the requirements for labeling under each pathway and do not specify the labeling requirements for the starting materials used for further processing. While these guidelines are essential, they are not necessarily tailored to the unique needs of cellular therapy products that will undergo further processing. Use of an IND label on these starting materials creates ambiguity, potentially suggesting that the product is the final therapeutic—when, in reality, it is merely a component in a larger manufacturing sequence. Additionally, the current labeling requirements may inadvertently convey incorrect information regarding the product's intended use in further processing contexts. Dr. Pham further mentioned that the increasing complexity of the manufacturing process and the

[1] 21 CFR 1271.370 (Labeling)
[2] 21 CFR Part 312.6 (Labeling of an Investigational New Drug)
[3] 21 CFR Part 201 (Labeling of Biological Products under BLA)

introduction of alternative treatment options for patients have added complications to the current labeling landscape. With these challenges in mind, tracking patient-specific treatment becomes important.

ICCBBA and ISBT 128 Standards

To help address the specific need for cellular therapy products used in further processing, Dr. Pham suggested the use of industry standards from organizations such as ICCBBA. Its ISBT 128 standards indicate that cellular therapy products for further processing should be labeled '*For Further Processing.*' The example of the ISBT 128 Split Label in ST-018 was also presented which has 128 requirements on the left and manufacturing-specific information on the right. This label not only enhances clarity but also supports the unique handling requirements in cellular manufacturing. Dr. Pham also added that both AABB and FACT require facility adherence to ISBT 128 standards for labeling cellular products.

Furthermore, Dr. Pham highlighted another component of ISBT 128 Standards, Chain of Identity (CoI). CoI ensures that the cellular material is accurately tracked throughout the entire process, from collection through to the final therapeutic use. In addition, Chain of Identity Identifier (CoI Identifier) enables clear traceability, which is critical in cellular therapy, where donor-patient matching and product tracking are vital for ensuring efficacy and safety. Dr. Pham mentioned that the Standards Coordinating Body (SCB) is working to advance the standard implementation of a COI Identifier to enable consistent and efficient tracking of cell therapy products derived from a specific donor/patient throughout the collection, production, and delivery process.

Finally, Dr. Pham concluded the presentation by highlighting recommendations and emphasizing their potential benefits.

Recommendations for the Agency

1. To consider aligning FDA Labeling Guidance with ISBT 128 Standards
    a. Use "*For Further Processing*" labeling in place of "*Caution: New Drug*" for cellular starting materials, avoiding misleading information.
2. To consider integrating requirements for a Chain of Identity (CoI) Identifier
    a. The use of CoI identifiers is essential for tracking cellular products from collection to final therapeutic application.

Benefits for the Agency and Stakeholders

1. Improved Patient Safety
    a. Clearer labeling reduces the risk of mix-ups and ensures that materials are used correctly within therapeutic pathways.
2. Enhanced Traceability and Efficiency
    a. Aligning with industry standards allows for streamlined processes, supporting efficiency and reducing the potential for error in manufacturing chains.
    b. Decreased FDA CMC reviewer resource bandwidth usage
3. Support for Future Innovations
    a. As cellular therapies evolve, updated FDA guidance would create a more flexible, adaptable regulatory environment for advanced therapeutic products.

PRESENTATION 2: GxP Compliance for Phase 1 and Phase 2 Clinical Trial Manufacturing – Joanne Kurtzberg, MD (Duke University)

Dr. Kurtzberg begins her presentation by highlighting that Immune Effector Cells (IECs) have improved the prognosis and extended survival for many patients with refractory hematologic malignancies. While a few products have been commercialized, there are challenges in patient access (timing), accessibility, and cost. She added that many academic centers are actively conducting research in this area to develop improved, streamlined, and less costly IECs through point-of-care manufacturing. However, questions remain regarding the level of regulation to be applied to manufacturing facilities and processes. In addition, clarity is needed to define the level of GxP compliance for Phase 1 and Phase 2 clinical trial manufacturing.

In her presentation, Dr Kurtzberg explored a few key areas that are challenging for academic centers such as *starting materials*, *manufacturing*, *assay development,* and *cost recovery*.

As the source for starting materials collection and processing, Dr. Kurtzberg noted that academic centers require clear guidance to validate/qualify their facility. Currently, these centers are following multiple guidelines depending on their scope of activities (*i.e. cGTP 21 CFR 1271, FACT and/or AABB accreditations standards for academic sites, and FDA licensed public CBBs*). She emphasized that many academic centers are struggling to comply with FDA regulations[4][5][6][7] due to limitations in applicability and

[4] 21 CFR part 1271 (Human Cells, Tissues, and Cellular and Tissue-Based Therapies)
[5] 21 CFR part 210 (Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General)
[6] 21 CFR part 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals)
[7] 21 CFR part 820 (Quality System Regulation)

resources. A suggestion for the Agency is to reconsider the periodic environmental monitoring requirements, especially for products manufactured in closed systems. She also suggested reducing the number of validation requirements as it is difficult to identify '*real world*' materials (*i.e. sick autologous donors materials*) but also the cost of supporting materials (*i.e. vectors, reagents, disposable kits, etc.*) to conduct the full validation is costly. In addition, she suggested substituting full validations with qualifications, especially for selected critical release assays.

While the role of IEC therapies in treating rare diseases and serving patients with unmet needs is increasing, and despite the very encouraging clinical results, Dr. Kurtzberg highlighted the likelihood of these products being commercialized is small due to various factors including small markets, medically complex patients, and complicated manufacturing. Although the cost recovery scheme may help recover manufacturing costs, many academic centers seem reluctant to pursue this option due to the limited coverage. Dr. Kurtzberg suggested extending the scope of the '*cost recovery*' scheme to include non-direct costs (*i.e. facility maintenance, environmental monitoring document control, training, or quality system unit oversight*).

Dr. Kurtzberg concluded her presentation by providing questions for Agency consideration:

- Is it possible to create guidance for HCT/P manufacturing bridging areas between 21 CFR 1271 and 21 CFR 210?
- Could the Agency create a pathway for approved POC manufacturing for Academic Centers of Excellence bridging areas between 21 CFR 1271 and full GMPs?
- Could Cost Recovery be extended to recover direct and indirect costs so that more patients' needs could be met at these centers?
- Could the Agency develop a non-BLA pathway towards limited commercialization to provide access to these therapies for more patients?

PRESENTATION 3: Manufacturing Cellular Products Using Viral Vectors – Kevin Bosse, PhD, RAC-US, CABP(H) (Nationwide Children's Hospital)

Dr. Bosse highlighted that with the field of genetically modifying cellular products increasing, the community is looking for ways to expand manufacturing capacity and maintain regulatory compliance, in particular, they would like to reevaluate facility requirements when using devices like the Prodigy that offer a closed manufacturing system, especially given that the addition of media or vector can be delivered via sterile docking.

Dr. Bosse further mentioned that although there are a number of FDA guidances related to manufacturing cell and gene therapy products, and in some cases mentioned the manufacturing environment, there is limited information provided about the appropriate manufacturing environment with only passing reference to the manufacturing flow and other information that should be included in an IND submission[8]. He also noted another guidance[9] advising that facilities must be of appropriate design with sufficient space, clean environment, appropriate construction, appropriate lighting, ventilation, and heating, etc. While this is true,

[8] Food and Drug Administration. Center for Biologics Evaluation and Research, Guidance for Industry: Chemistry, Manufacturing, and Controls (CM) Information for Human Gene Therapy Investigational New Drug Applications (INDs) January 2020

[9] Food and Drug Administration. Guidance for Industry: CGMP for Phase 1, Investigational Drugs. July 2008

it does not provide specific details and remains silent on the type of manufacturing environment and workflow that is required. Additionally, the current facility designs are largely driven by regulations intended for the manufacture of traditional bulk-produced drugs. As a result, there is a significant amount of variability in facility design.

In addition, there is confusion for early phase facilities due to the lack of specifications and current manufacturing paradigms that add a significant cost to excessive product costs. This confusion may impact the widespread adoption of cell and gene therapies.

The available guidelines[10,11,12] are helpful but clarifications from the Agency are needed on facility requirements when manufacturing cellular products that involve the use of non-replicating viral vectors, especially when using a closed manufacturing device such as the Prodigy or Cocoon.

Furthermore, Dr. Bosse explored four example scenarios to support his presentation:

- Scenario 1 – ISO-7 Laboratory with Operational Zones
- Scenario 2 – Controlled Non-Classified Laboratory
- Scenario 3 – Non-Classified Laboratory for Single Product
- Scenario 4 – Plasmids and RNA Electroporation Impact

Finally, Dr. Bosse concluded his presentation by summarizing the questions for Agency considerations.

1. With appropriate operational controls, are there scenarios (*for example, using closed systems*), where viral vectors may be used during the manufacturing process in rooms with positive air pressure?
2. Is it acceptable to manufacture as stated above in a room under positive pressure with bidirectional traffic in hallways connecting different room?
3. Is it acceptable to manufacture genetically modified HCT/P products using a functionally closed (Miltenyi Prodigy) system in an unclassified space for Phase 1 or 2 manufacturing. What about an ISO-8 space?
4. Can multiple patient products be manufactured in one room if spaces are isolated by workstations or zones to prevent any cross-contamination or mix-up?
5. Would it be acceptable to use different viral vectors in a large, campaigned space if closed system manufacturing was being used for different products in the same room?
6. Would the response be different if plasmids / RNA electroporation were being used?

Discussion:

The Agency initiated discussion by recommending Type C facilities meeting with OCBQ's Division of Manufacturing and Product Quality as the best way for the relevant stakeholders to discuss and answer questions on CGT facility design (see below for further details).

[10] ISO 9001, ISO 45001, ISO 14001, ISO 15378
[11] 21 CFR 201 (Labeling)
[12] 21 CFR 21 (Food and Drugs)

The stakeholders then clarified that although such meetings are helpful, a variety of responses were received which have led to many academic centers designing their facilities differently. Therefore, it was suggested the Agency could help develop standardized guidance or practices that they could follow to make comparable products at various institutions.

Finally, the Agency concluded the discussion session by acknowledging the feedback from stakeholders and while it was emphasized that the preference is for stakeholders to request the Type C facilities meeting, and if there is an urgent need, they will consider developing a guidance/practice.

Instructions for requesting a Type C facilities meeting (telecon) with OCBQ's Division of Manufacturing and Product Quality

Please refer to guidance document on requesting meetings with CBER[13]. Further information regarding requesting a Type C meeting can be found in the guidance document addressing the placement of a formal meeting request.

Through a memorandum issued on September 14, 2020[14], DMPQ has provided a list of a general overview of the information the Agency has found useful to make the meetings as productive as possible. In addition, DMPQ is interested in a detailed description of the planned operations intended for the GMP areas, procedural controls, and to avoid potential cross-contamination.

To be considered a complete request please include the following points in a meeting request letter:

- The product name and IND number(s), if applicable
- A brief statement of the purpose of the meeting
- A list of the specific objectives or outcomes that you expect
- A proposed agenda, including estimated times needed for each item
- A list of specific questions
- A list of planned external attendees
- A list of requested participants to be represented from CBER if known
- The approximate time that a background package for the meeting will be sent to CBER
- A list of preferred dates and times for the meeting

If the stakeholder intends to include full-size architectural plans/facility blueprints with the meeting request package, there is not a different process that is preferred for submitting those very large documents in paper form. The plans and facility blueprints can be included in the meeting package. Please note that the diagrams should be readable.

The meeting packages submitted should concentrate on the anticipated manufacturing facilities going forward.

For a meeting that exclusively addresses pre-construction facility design issues, address request to the following office:

[13] Center for Biologics Evaluation and Research. SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products. Version 14. July 17, 2024. https://www.fda.gov/media/84040/download

[14] Center for Biologics Evaluation and Research. Memorandum to Sponsors or applicants requesting a pre-facility meeting with DMPQ. September 14, 2020 (*also attached as a reference at the end of this document*).

Attn: Carolyn Renshaw

Director, Division of Manufacturing and Product Quality

OCBQ/CBER/FDA

10903 New Hampshire Ave.

WO71-G112

Silver Spring, MD 20993-0002

PRESENTATION 4: FDA's current views and strategies on the ban of plasticizer (DEHP) used in manufacturing and banking of cord blood and blood products – Wouter Van't Hof, PhD (Cleveland Cord Blood Center)

Dr. Van't Hof begins his presentation by highlighting the important role of plasticizers. He mentioned that Plasticizers are essential additives to confer flexibility and pliability to materials like plastics and rubber and have long been utilized in various industries, including medical devices[15]. Phthalates, a commonly employed type of plasticizer, are utilized in medical applications, particularly in the production of polyvinyl chloride (PVC) materials used for cord blood bags[16]. These bags are crucial for the storage and transportation of blood products. However, concerns have arisen regarding the potential health risks associated with phthalates, including their classification as endocrine-disrupting, carcinogenic, and toxic to sexual organs in the human body[17].

Dr. Van't Hof added that the REACH[18] group has imposed strict restrictions on the use of certain phthalates, including DEHP, in the most commonly available in blood and cord blood banking devices, with a sunset date for the EU of July 2030 (EC 2023/2482, issued on November 13, 2023)[19].

While there are currently no similar restrictions at the US federal level, the US Environmental Protection Agency (EPA) has determined that DEHP is a probable human carcinogen, and legislation against DEHP has been introduced in a few US states.

- **California** first state with a legislation proposal (AB-2300)[20] for a DEHP-ban in medical devices, starting for intravenous solution containers as early as **January 1, 2026**.

[15] Campanale C, Massarelli C, Savino I, Locaputo V, Uricchio VF. A Detailed Review Study on Potential Effects of Microplastics and Additives of Concern on Human Health. Int J Environ Res Public Health. 2020;17(4):1212. Available from: https://www.mdpi.com/1660-4601/17/4/1212.

[16] Giuliani A, Zuccarini M, Cichelli A, Khan H, Reale M. Critical Review on the Presence of Phthalates in Food and Evidence of Their Biological Impact. Int J Environ Res Public Health. 2020;17(16):5655.

[17] Wang Y, Qian H. Phthalates and Their Impacts on Human Health. Healthcare. 2021;9(5):603. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8157593/.

[18] REACH stands for **R**egistration, **E**valuation, **A**uthorisation, and Restriction of **Ch**emicals

[19] Commission Regulation (EU) 2023/2482. Amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council as regards the substance bis(2-ethylhexyl) phthalate (DEHP) in medical devices. 13 November 2023.

[20] California Assembly Bill 2300 (2023). AB-2300 Medical devices: Di-(2-ethylhexyl) phthalate (DEHP). CA State Legislature. Retrieved from https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=202320240AB2300

    - The bill was voted in April 2024. It was amended in assembly the following month of May providing an exception as described in Title 21 CFR, for human blood collection and storage bags.
- **Pennsylvania** General Assembly has introduced Senate Bill 1301, titled "An Act Amending Title 35 (Health and Safety) of the Pennsylvania Consolidated Statutes, providing for medical devices." This proposed legislation aims to ban the use of DEHP in IV solution containers and tubing as early as **January 1, 2026**.
    - The Pennsylvania legislature is scheduled to be in session until November 30, 2024. The proposed legislation would take effect, "90 days" after the bill's passage[21].

Dr. Van't Hof further expressed industry concerns on this matter as these regulatory changes will profoundly impact the global supply chain of medical devices routinely used for CGT manufacture in the US and globally. In addition, it raises questions on the future status of CGT products in DEHP-containing vessels. He also added that cord blood banks will face challenges transitioning to non-DEHP alternatives due to possible increased hemolysis, shortened shelf life, and the need to validate various processes thoroughly[22]. The impact extends to the quality and safety of cord blood units, as studies suggest that phthalates may leach from cord blood bags, potentially affecting the viability and function of hematopoietic progenitor cells[23].

Finally, Dr. Van't Hof concluded his presentation by providing questions for and desired outcomes from the FDA.

Questions

1. What is the Agency perspective on the legislation in California and does FDA anticipate phasing out DEHP in (cord) blood banking devices at the Federal level in the US?
2. What is the Agency position on future acceptability in US of frozen CGT product inventories historically manufactured with DEHP containing devises?
3. How and when does the Agency foresee providing guidance on selection, testing and transition to alternative collection devices acceptable for future use in US and beyond?

Desired Outcome

For the CGT field to gain understanding of the Agency current views and strategies in addressing new legislation initiatives in the EU and the United States on phasing out plasticizers routinely used in manufacturing and banking of cord blood and blood products.

[21] Pennsylvania General Assembly Senate Bill #1301, August 2024.
[22] McKenna D, Sheth J. Umbilical Cord blood: Current Status & Promise for the Future. Indian J Med Res. 2019;134(3):261-9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3193706/.
[23] Nguyen PH, Nguyen VT, Chu TT, Truong LH, Do TTH, Nguyen TD, et al. Factors Affecting Human Umbilical Cord Blood Quality before Cryopreservation: The Importance of Birth Weight and Gestational Age. Biopreserv Biobank. 2020;18(1):18-24. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31841643

Discussion:

The Agency started the discussion by thanking the stakeholders for raising their awareness, especially on the Pennsylvania Senate Bill 1301. The Agency indicated that they wanted to learn more and understand the issues and difficulties stakeholders are facing.

Dr. Van't Hof clarified that two issues need to be addressed: first, the status of products currently in the inventory and are still using the DEHP-contained materials (would they become ineligible?), and second the switch to new materials/suppliers without harming the supply chain.

For the first issue, the Agency clarified that stakeholders should not anticipate that these products become ineligible because there should be some flexibility, especially for life-saving products. Stakeholders should keep in mind, in some cases, state-specific legislation could be more restrictive than federal legislation, in which case the Agency cannot do or provide something that pre-empts such legislation. However, it does not appear that the legislation in California and Pennsylvania are more restrictive than federal legislation.

For the second issue, the stakeholders further added that given the market size is relatively small, a slight change would impact the supply chain greatly. Products such as blood bags and IV solution bags are two products that will be impacted but as the stakeholders learn more about this issue, the scope is getting broader as there are more products including the ones for the manufacturing process contain DEHP. In addition, currently, there is only one supplier who can provide alternative materials which is not a sustainable solution in the long run.

To conclude, the Agency acknowledged the issues and mentioned that they would appreciate the information from stakeholders as to which products are currently impacted and suggested the stakeholders continue to apprise the Agency of the latest updates on this issue.

PRESENTATION 5: Cord Blood as Starting Material for Adoptive Immunotherapies – Rob Tressler, PhD (Excellos)

Dr. Tressler highlighted there is an increasing demand for cord blood starting material for use in the production of clinical and commercial-grade cell therapies. In addition, recently multiple trials using cord blood cells as starting material, including HSCs, NK and T cell fractions have been initiated with promising clinical results and are progressing to approvals for various oncology and immune therapies. As this field progresses, however, the limited number of licensed cord blood banks will not support the growing demands that this field is already experiencing. The majority of FACT and AABB-accredited US public cord blood banks do not have BLA status but have supplied banked cord blood units (CBUs) to support allogeneic transplants under the IND held by NMDP for over 3 decades, with an extensive database clearly supporting the efficacy and safety of these non-licensed products as transplant therapies.

Dr. Tressler further highlighted other factors that contribute to this issue:

1. Recent clinical trial results indicate that rapid cryoprocessing within 24 hours of collection are necessary to assure the potency of some cell therapies derived from CBUs, while other R&D clinical groups require fresh CBUs as starting material. These requirements pose significant logistical challenges in terms of starting material access, time constraints, geography and cost on

the ability of research and development entities to readily access CBU starting material for clinical studies.

2. Currently R&D clinical studies are focusing requests for CBU starting material to licensed cord blood banks, and the abovementioned issues cannot be addressed easily due to the current shortage and national distribution of licensed cord blood banks in the US.

For this reason, Dr. Tressler suggested that allowing CBU starting materials to be obtained from non-licensed accredited banks is an appropriate and practical solution that will readily ameliorate the starting material supply demands that are becoming issues for moving this field forward. Currently, there are over 20 FACT and AABB-accredited public cord blood banks participating under the NMDP IND for allogeneic transplants that do not hold licensure but have a strong record of safety and efficacy in the BMT setting.

Finally, Dr. Tressler concluded his presentation by requesting the Agency to consider releasing a statement that when cord blood units are selected for use as starting material, sponsors should consider CBU attributes relevant to the final product such as eligibility, cell count, etc. regardless of licensure status.

PRESENTATION 6: Cell Therapy Products: Framework for Relating Mechanism of Action, Potency & Efficacy – Carl G. Simon, Jr., PhD (National Institute of Standards & Technology, NIST)

Dr. Simon begins his presentation by highlighting the confusion surrounding the concepts of *mechanism of action*, *potency*, and *efficacy*. The Draft Guidance, Potency Assurance for Cellular and Gene Therapy Products[24], provides guidance and recommendations to help assure the potency of a human cellular therapy or gene therapy product; however, there are areas in the guidance that can be improved for better understanding.

Dr. Simon suggested separating the definition of the following 6 terms: *mechanism of action*, *potency*, *potency test*, *efficacy*, *efficacy endpoint*, and *efficacy endpoint test*. The first 3 terms are used in/related to the lab setting, while the next 3 terms are used in/related to the clinical trials setting. For this reason, Dr. Simon suggested separating *potency* from *efficacy* as they are measured by different measurements, one by lab tests and the other by clinical trials. He also suggested replacing the term "*therapeutic effect*" in the Draft Guidance with "*mechanism of action*" as follows:

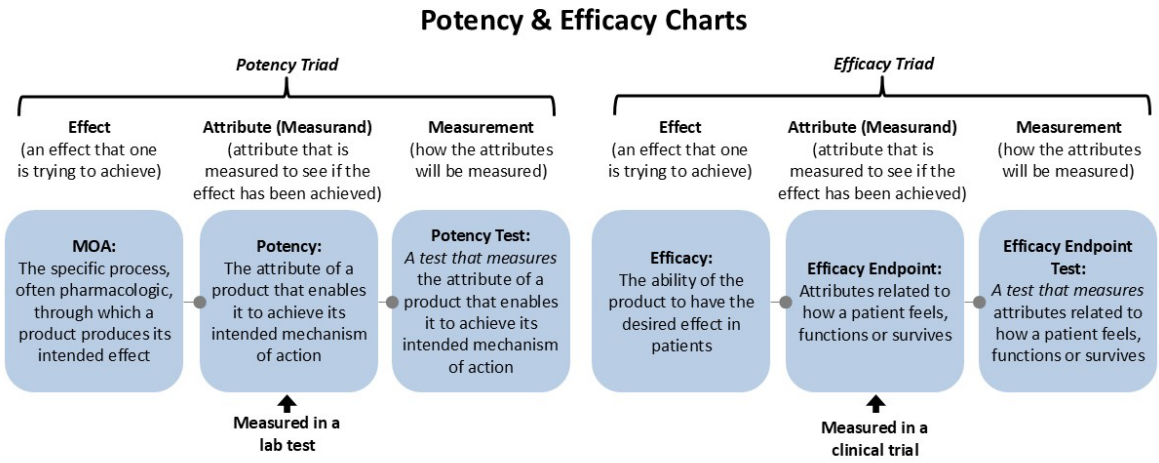
- Draft Guidance, Page 1, Lines 19-21: "*The goal of a potency assurance strategy is to ensure that every lot of a product released will have the specific ability or capacity to achieve the intended* ***therapeutic effect***."

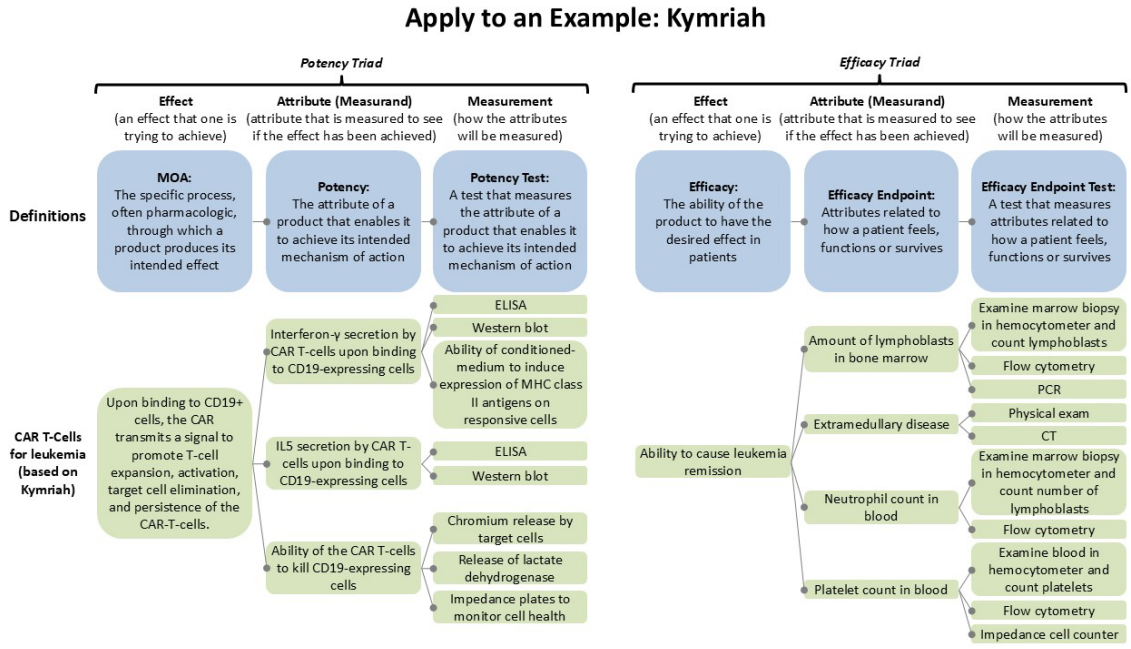
Dr. Simon also suggested separating *potency* from *potency test* because potency is the attribute being measured ("*measurand*") while the potency test is the "*measurement*". He added that according to the International Vocabulary of Metrology, "*measurand*" and "*measurement*" are defined independently:

- Measurand: "the quantity or property intended to be measured"
- Measurement: "process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity"

[24] Potency Assurance for Cellular and Gene Therapy Products; Draft Guidance for Industry, December 2023.

Additionally, Dr. Simon included the following 2 charts in his presentation:





To further support his points, Dr. Simon explored examples where a product is *potent but not efficacious* and a product is *not potent but efficacious*.

- Product might be '*potent but not efficacious'* due to various factors including wrong patient population or incorrect hypothesis

- Product might be '*not potent but efficacious'* due to various factors including alternate MOA or false negative potency test

Finally, Dr. Simon concluded his presentation with the following proposals:

- For the Agency to consider adopting the definitions and frameworks (as an appendix to the 2023 draft potency guidance); or
- For the Agency to consider developing an alternative framework that
    - Separates potency and efficacy
    - Separates measurand and measurement
    - Separates the definition of the following terms: *mechanism of action, potency, potency test, efficacy, efficacy endpoint, and efficacy endpoint test*
    - Allows a product to be
        - Potent but not efficacious
        - Efficacious but not potent

PRESENTATION 7: Use of Research-grade Material for Manufacturing due to Source Material Constraints - Rob Tressler, PhD (Excellos)

Dr. Tressler highlighted that various new cell therapies are currently being identified and in early development using novel/rare cell types typically collected and isolated by non-cGMP research methods as there are no cGMP processes mapped for these new materials. He also added that the variety of cell-based therapies being developed for various indications at times may require access to research-grade source material that may not have fully met FDA guidelines[25]. Examples are MSC subsets, rare immune cell types, cord tissue-derived products, and other tissue-derived cellular starting materials that are not typically generated under cGMP, but more so as research-grade materials in a non-cGMP compliant manner.

However, Dr. Tressler noted that currently, the criteria for access to such materials is unclear. While the FDA has made some requirements for cellular starting material in the 2020 CMC gene therapy guidance[26] and although the 2022 OTAT town hall meeting indicated that starting material does not need to be GMP compliant (as long as consistency/control are demonstrated), further guidance on the requirements deemed necessary to allow access to research-grade materials as starting material for the manufacture of cell therapies to be used in clinical trials and for commercial production of approved cell therapies would be helpful.

The presentation by Dr. Tressler concluded with the following questions to the Agency:

1. What requirements/specifications would the Agency require as relates to identity, purity and safety of non-cGMP research grade starting materials?
2. What guidelines would the Agency require for acquisition, collection, processing and handling of research grade starting materials, including informed consent, IRB approval, transition to cGMP processing activities and traceability?
3. What items should be addressed for material that may not have been initially collected under CFR part 1271 compliance guidelines? Would post-hoc testing, eg, for CMV status be acceptable?

[25] 21 CFR 1271 (Human Cells, Tissues, and Cellular and Tissue-Based Therapies)
[26] Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), Guidance for Industry, January 2020.

Discussion:

The Agency initiated the discussion by addressing Question #3. They clarified that under 21 CFR 1271 an exemption can be granted as long as the due diligence and risk mitigation are taking place and there is sufficient and rational justification. Dr. Tressler acknowledged the Agency's input and further added that many cord blood units are collected under 21 CFR 630, if there is a way to access these and have the 21 CFR 1271 catch up for CMV, that would help release the burdens.

Additionally, the Agency thanked the presenter for bringing the issue to their attention (Question #1). They understand that although this has been addressed in the recent FDA guidance, some confusion may still exist in cases where GMP requirements cannot be met, including iPSCs cases where a lot of cell lines are already established in research setting. Overall, the Agency is aware of this gap and acknowledges that there is a need to develop a new guidance.