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November 20, 2023

Dockets Management

Food and Drug Administration

5630 Fishers Lane, Rm 1061

Rockville, MD 20852

Re: Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies; Request for Information (Docket Number: FDA-2023-N-3742)

Dear Sir or Madam:

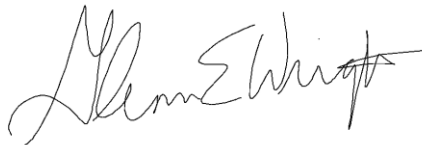
The Parenteral Drug Association (PDA) is submitting the attached responses compiled by members of the PDA Advanced Therapy Medicinal Product Advisory Board (ATMP AB) regarding FDA's request for information on Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies. The paper outlined relevant concerns around this issue and the ATMP AB has provided replies to the questions posed by the agency. In the attached comments, the team offers insight and suggestions that may assist the agency in formalizing and finalizing guidance related to cell and gene therapies.

Related to the importance of providing these groundbreaking therapies to patients, PDA sees an opportunity to collaborate with the FDA CBER on this topic in the form of a joint workshop or extended virtual meeting to promote best practices and understanding throughout the pharmaceutical industry.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. These comments have been prepared by a group of volunteers with expertise in cell and gene therapy manufacturing with the aim of aligning on best practices and policies to ensure patient safety and continuity of drug supply.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,



Glenn Wright, President and CEO

cc: Josh Eaton, Senior Director Scientific and Regulatory Affairs

A. Manufacturing

- 1) *Given the challenges to develop consistent manufacturing strategies for CGTs designed for a very small number of patients or an individual patient, how can manufacturers leverage their prior experience manufacturing one CGT to support subsequent development and approval of another related, but distinct CGT (potential areas for leveraging may include manufacturing process validation, control strategy, assay validation, and drug product stability studies)?*

PDA ATMP AB Comment:

Using established manufacturing, testing, and supply chain conditions (per ICH Q12) may aid in accelerating individualized cell and gene therapy (CGT) product development and commercialization. For example, previously approved control strategy elements (e.g., product specification setting strategies, process validation, comparability, lot release/stability testing, platform analytical procedures (PAPs) for suitable testing, raw/starting material control strategies, procedural controls, etc.) are paths that could be leveraged to support determination of product manufacturing consistency. Other examples include leveraging elements of process validation, filter validation studies, assay validation, validation of shipping and storage conditions, and container closure integrity testing. Therefore, the manufacturer can rely on their prior experience in developing the process to be robust across the range of patient variation. For example, the size range of gene insertions should be exercised when developing the process, so that anticipated patient variation will fall within that range. Guidance from the FDA would be helpful.

- 2) *When the batch size of a CGT is very small, what are some challenges and solutions regarding the volume of product (or number of vials) needed for batch release testing, stability testing, retention of reserve samples, and comparability studies?*

PDA ATMP Comment: When the batch size of a CGT product is small, one major challenge is to ensure patient supply when the volume for batch release testing is a high proportion of the lot manufactured. In these cases, clarity from the Agency would be appreciated regarding the expectation for batch release testing during product development under scenarios where CGT product batch sizes are small. Examples of areas to consider leveraging data are provided to support batch release testing are included below:

- Using a bracketed approach to minimize stability testing and the associated product sampling needs per the process control strategy,
- Bracketing of minimum/maximum critical quality attributes that are most likely to potentially impact product stability,
- Maintaining consistency with concepts outlined in ICH Q5C regarding the extrapolation of stability data for starting materials like viral vectors,

- Reference material for manufacturing and analytical testing could be manufactured as a single representative lot, then aliquoted in test-volume minimal storage unit volumes to prevent frequent replenishing (and associated qualification testing),
- Consider lessening requirement for drug product retains using a risk-based approach with consideration to patient dosing, and available drug product volume(s) manufactured.
- In cases of real-time release testing, in-process testing may be used in lieu of certain traditional release tests.

In addition, the FDA should consider allowing Sponsors to review proposed commercial sampling plans in advance of a commercial application submission to ensure an alignment of expectations for potential reduced testing of drug product (that does not compromise patient safety or product quality). Finally, FDA should consider providing additional guidance on performing comparability where patient populations are small, such as in the case for autologous cell therapies.

- 3) *What are some challenges and solutions for individualized CGTs that need to be tested and released rapidly, either because the product has a very short shelf life or because the patient's clinical status may be rapidly declining and treatment is urgently needed?*

PDA ATMP Comment:

For individualized CGTs that need to be tested and released rapidly due to short shelf life or patient's clinical status, patient identity needs to be assured throughout the process for complete tracing from patient to manufacturing and back to patient, in the case of autologous cell therapies. Comprehensive use of advanced track and trace technologies (e.g., barcoding, RFID) throughout the process may be a solution to provide this assurance. In addition, streamlining process controls (e.g., validation of aseptic processing, use of functionally closed systems, etc.) and sampling strategies (such as using rapid sterility testing) should be considered.

Patient risk should be taken into consideration at the point of care. For example, testing for CQAs (e.g., using rapid sterility testing) and allowing for physician release using a rapid submission platform between physician and Sponsor will allow for exceptional release. Aligned with this approach, is an allowance for release of product based on the Sponsor's risk assessment, potentially without FDA review. To mitigate any concern or risk from the Agency perspective, the FDA could consider pre-inspection of the Sponsor's Quality System.

From the patient supply perspective, guidance from the Agency would be appreciated regarding the phase-appropriate comparison of a Sponsor's IND data to current USP methods in order to facilitate appropriate lot release analytics (e.g., rapid sterility testing, etc.). To ensure rapid and safe patient supply, especially for autologous cell therapy products, PDA encourages sharing of lessons learned from industry regarding leading-edge technologies (e.g., automation) that can be employed to facilitate rapid lot release.

For individualized CGT products or those products with a very small patient population, it can be challenging to supply viral vector in situations where treatment is urgently needed. Leveraging the production platform would be required in order to ensure process consistency in this scenario. For this reason, PDA recommends the Agency consider providing guidance to the leveraging of vector manufacturing platform data to demonstrate phase-appropriate process consistency in scenarios where the patient status is rapidly declining, and treatment is urgently needed.

Finally, PDA recommends that Sponsors engage in a discussion with the Agency during the commercial application review process to develop a risk-based, pre-established justification and action mitigation plan which allows for rapid release of product in a way that maintains patient safety.

- 4) *For many individualized CGT products, each batch is tailored to an individual patient (e.g., autologous CAR-T cells, tumor neoantigen vaccines, certain genome editing products). For such products, what are some challenges and solutions for assuring that each batch has adequate potency to achieve the intended therapeutic effect?*

PDA ATMP Comment:

Many challenges exist in cases where each batch is tailored to an individual patient. One major challenge includes developing a robust potency assay, particularly when identifying the appropriate target and mechanism of action under conditions that mimic cells of the human body. This is true for later stages of development, however at earlier stages of development, surrogate assays can be used, but these will potentially need to be further developed. One consideration that the FDA could undertake may include aligning on approaches towards potency assay development based on the type of therapy. These assays will vary based on different applications for therapies. In parallel, clinical data should support the concept that a consistent process produces efficacious product. As such, guidance on stage-appropriate potency assay development would be beneficial.

- 5) *What are some challenges and solutions for individualized genome editing products that aim to treat monogenic diseases for which the target gene has different mutations in different patients?*

PDA ATMP Comment:

For individualized genome editing products that aim to treat monogenic diseases, demonstrating consistent manufacturing for small patient populations may be challenging. Therefore, PDA recommends consideration by the FDA regarding leveraging the use of platform manufacturing processes with clear guidance on these platform processes and associated products. Stage appropriate guidance in general would be welcome from the FDA.

B. Nonclinical Development

- 1) *What nonclinical studies could be leveraged in support of a related product using similar technologies? What nonclinical studies are important to conduct with each final clinical product?*
- 2) *What nonclinical development approaches could be considered when there are no relevant animal models or animal models are unable to replicate each individual disease/condition?*
- 3) *For patient-specific products where evaluating each individual product is infeasible or impractical, what is the role for nonclinical studies conducted with representative product(s)?*
- 4) *What are the opportunities and challenges with using computational approaches to support nonclinical development?*

C. Clinical Development

- 1) *What are challenges and strategies/opportunities with interpreting efficacy data from individual patients (including expanded access) and small groups of patients? What opportunities are there in leveraging prior and/or collective experiences?*
- 2) *What strategies can be utilized to accumulate and interpret safety data in personalized/individualized CGTs?*
- 3) *For genetic disorders with clear genotype-phenotype associations for disease manifestations or severity, what opportunities are there for tailoring treatments and study design to specific genotypes/phenotypes?*

PDA Comments:

Heavily pre-treated patients may not be representative of the commercial patient population, hence more options would be beneficial for Sponsors (e.g., doing a Ph4 study but being able to market the Drug Product). Additional guidance is needed to align clinical experience with the commercial supply population based on complexities observed with patient populations (i.e., can't do first line treatment on experimental drug). PDA requests that the FDA provides more flexibility/resilience in the approved product in terms of interpreting data with low power.

D. Additional Questions to Consider

- 1) *What additional major scientific challenges to advance the development of individualized CGTs should be considered?*
- 2) *What existing best practices or scientific approaches should be leveraged to address any of these challenges? Are there specific opportunities for collaborations to advance the development of individualized CGTs?*

PDA ATMP AB Comment:

To allow for advanced development of individualized CGTs, the Agency should consider creating a central web-based portal for the public to access published data, methods, research papers, funding opportunities, and regulatory submission examples, etc., for individual CGTs. In addition, allowing supportive *in silico* (computational) modeling and harmonization of standards and review processes that allows for mutual regulatory acceptance and reliance of submissions (including work performed within the PIC/S region) and products will enable faster development and approval of these products for rare patient populations.

3) *Are there specific areas where flexibility in regulatory approaches would improve the feasibility of developing and commercializing individualized CGTs?*

PDA ATMP AB Comment:

Flexibility in regulatory approaches would significantly allow for faster and more efficient development and subsequent commercialization of CGT products. In general, this may include leveraging Mutual Recognition Agreements (including pre-licensing inspections) for CGTs to allow for management of GMP inspections and to prevent duplicative release testing between regions/jurisdictions (which is of particular concern for low-volume, individualized products). Moreover, for cellular therapies, out-of-specification batches are often required to be filed under individual INDs. In these cases, lessons learned from individual CGTs should be leveraged as these individual INDs progress.