November 20, 2023

Dockets Management Staff
(HFA-305), Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Regarding Docket No. FDA-2023-N-3742 Request for information on *Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies*

Dear Sir or Ms.,

The Alliance for Regenerative Medicine (ARM) is pleased to have the opportunity to provide information on the scientific challenges and opportunities to advance the development of individualized cellular and gene therapies (CGTs). Our membership appreciates CBER's interest in identifying challenges and getting ahead of these issues. We applaud FDA's recognition of the need for thoughtful streamlining of processes.

The RFI provides as an example of individualized CGTs two gene therapy vector products for separate rare genetic neurological diseases, for which both products utilize the same vector backbone but contain different transgene inserts. ARM therefore views the efficiencies noted below to be applicable to rare diseases broadly, not only diseases with a very small number of patients.

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

A general recommendation to advance the development of individualized

CGTs is for the FDA to provide additional opportunities for informal discussions with sponsors to streamline rare disease development. In addition, because commercial viability for many individualized products may arise from a very small patient population dispersed across the world, we also encourage the Agency to consider areas for alignment/convergence with other regulators (e.g., through ICH guidelines and/or a Project Orbis-type approach for CGTs). Doing so will ensure that developers are provided with a streamlined pathway to reach patients globally with these transformative therapies.

Below, ARM provides information in response to CBER's questions that may be helpful in elucidating the challenges within various areas of product development for rare diseases, as well as potential solutions. We also identify some challenges that could be best addressed through further Agency guidance on its current expectations. Highlights include identification of ways to leverage prior knowledge and avoid redundancies, including the types of data that may be able to be referenced; and provision of suggestions for regulatory flexibilities to address the challenges of development for small populations, such as small batch sizes/numbers and the frequent infeasibility of randomized controlled trials.

Manufacturing and product quality

In general, it may be useful for the FDA to present examples in public forums, as able, on the management and regulatory reporting of manufacturing changes (e.g., new site, new or updated method) for CGT products, to demonstrate the specifics needed to meet FDA requirements for risk assessments, risk management, and comparability study design. Case studies or other hypothetical examples of approaches to process validation/verification for components used to treat rare diseases would also be useful for commercializing CGTs. Below are ARM recommendations in response to specific questions.

FDA question: 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 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)?

ARM answer: Our membership believes leveraging of prior knowledge to expedite CGT development is a critical regulatory concept, and we encourage FDA to continue to explore streamlining approaches for CGTs. When the same manufacturing process is used, sponsors should have greater ability to use data obtained to support one product to support (at least in part, and possibly in some cases in full) the package for a closely related product.

ARM suggests that for many CGT products, the process could be streamlined in full or in part by allowing leveraging of the following unprioritized data for a designated platform technology:

- CMC data/methods, such as upstream and downstream manufacturing methods, and manufacturing characterization and validation methods.
- Validated analytical assays (e.g., identity, titer or concentration, infectivity).
- Critical quality attributes (CQAs), critical process parameters (CPPs), and critical material attributes.
- Reference materials.
- Compatibility of shipping and storage conditions (e.g., temperature).
- Stability studies.
- Specifications (e.g., for a vector/capsid or cell line platform) in some cases and for some parameters.

More specifically regarding manufacturing process validation, studies for historic biologic products are based on commercial scale and small-scale manufacturing process studies for which the starting material is traditionally a well characterized cell line. However, analytical test panels and process validation studies are limited by the nature of the products, with many cell therapies unable to survive structure-functional studies and/or stressed stability studies. ARM would appreciate the provision in the forthcoming platform technology designation guidance on specific CMC aspects that could be leveraged for various modalities to expedite clinical development and postapproval change management.

The methods used for release, stability, characterization, comparability, and process validation for historic biologic products are well controlled, and sample matrix interference is minimized. With CGT products the suite of analytical methods is limited due to the nature of the products tested, the interference of final formulation on several drug product release methods, and the need to reduce cycle time for autologous products. For analytical validations, the validated state of compendial methods should be standardized and leveraged across CGT products, as long as matrix interference is addressed as is practical.

For individualized therapies in the rare disease space, because batch size and number may be very small, there is a need to derive more supportive information from the non-specific vendor studies of raw materials and any prior manufacturing experience from sponsors using the raw material with other CGT products. It would be helpful if FDA could use prior knowledge (e.g., raw material manufacturing master files and/or regulatory support files that contain platform raw material stability and other supportive data) to help advise sponsors on the product-specific studies needed for commercial licensure and expectations for the post-approval environment when raw material suppliers need to modernize and/or expand the original raw material manufacturing processes.

For some products, ARM would welcome review and confirmation during product development of the suitability of procedures to be used for product manufacture of products within a platform, e.g., obtaining suitable patient-derived cells, the sequence analysis to identify and choose neoantigen sequences present, production of neoantigen-related peptides from chosen sequences, priming target cell types with the peptides, and the associated manufacturing and testing procedures. For example, sponsors could submit this information in advance as a platform master

file that is pre-agreed upon for use for first-in-human multi-product clinical studies onward. Similarly, this could be used for the production of similar vectors to be used for genome editing or personalized autologous cell-based products. Guidance would be welcome both on the feasibility of such an approach and on the content and format to submit (e.g., using Module 3 structure).

FDA question: 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?

ARM answer: When the batch size of a CGT is very small, having sufficient volume/vials of product to meet current regulatory requirements can be extremely challenging. There are practical limitations in the use of retained samples, such as time stored, quantity available, and consent, especially for consent in the commercial space.

One example of current FDA policy that can be difficult is raised in the FDA draft guidance, *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products*. The FDA recommends that to provide the most readily interpretable data for a comparability study, sponsors should perform side-by-side testing of pre-change and post-change product attributes or analyze all samples using the same analytical method performed at the same testing facility. However, doing so may not always be possible when retained reserve samples are limited by small batch size, as ARM notes in its comments to this draft guidance document. In such cases, ARM recommends allowing sponsors to assess risk and discuss the approach with the Agency. In addition, not all tests for comparability need to be performed side by side, such as physiochemical and impurities testing. ARM suggests the Agency clarify by only recommending side-by-side *biological* testing of product attributes, when possible.

Small batch size can be particularly challenging for autologous products. The limitations are prominent for analytical testing, and consideration and guidance would be helpful on when that testing can be reduced by process validation experience or there can be exemptions related to small volume autologous products' stability programs.

The limited availability of patient-derived material for these products challenges the ability to meet Agency recommendations to use this material in stability studies contained in its draft guidance, *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products.* Instead of conducting stability studies on all patient-derived materials, solutions would be for sponsors to be able to emphasize proper storage conditions along with the proper handling of the product during thawing and administration to the patient, and/or to include surplus product when available in stability studies. The problem of numerous vials being consumed by stability testing could be solved by allowing appropriate surrogate tests at some points. For example, the FDA should continue to support the provision of container integrity information in lieu of compendial sterility testing.

Representative material (i.e., healthy volunteer starting material or supportive source materials such as NIST or USP standards) should be allowed to be used for stability studies. There is the potential for similar modalities to leverage platform stability data and only conduct limited product-specific stability studies (i.e., limit time points and reduce stability considerations for comparability studies, unless specific CMC changes are made).

There is also the potential to establish similarity between the final drug product (DP) container closure and a small test sample container for use in analytical testing. In addition, testing of the DP should be limited to methods of critical importance, with consideration given to process control and the potential to test upstream of the final DP sampling point to preserve DP for release testing.
For cell products stored in vapor-phase liquid nitrogen, the risk of degradation during that storage (as opposed to during freezing and thawing) in common formulations is generally well understood to be very low and accordingly guidance could be provided on how stability studies could be minimized in such cases (reducing time points compared to current ICH guidelines).

Wastage when a vial/s are consumed for a single test is a challenge that could be solved through the development of guidance and best practices that facilitate multi-attribute testing (e.g., infectivity plus potency).

To solve the challenges of obtaining sufficient sample sizes in comparability studies, guidance on alternative statistical methods would be helpful, as well as an indication of when historical data may be used as a control.

FDA question: 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?

ARM answer: As the FDA question identifies, ARM's members are increasingly aware and trying to treat monogenic diseases that can be broken down into subpopulations with different mutations which will require slightly different individualized gene-edited products to treat them. Current regulations require significant redundancy in the CMC, preclinical, and clinical evaluation required for each product. In addition, separate toxicology studies and additional clinical trials are required. This is a significant time and resource-laden duplication that could be streamlined to increase patient access.

ARM suggests that a master file concept could be extended to the specific use of a manufacturing platform intended for use in first-in-human studies onward to treat different sequence variants of a monogenic disease.

Beyond manufacturing and product quality, ARM has suggestions for potential new regulatory procedures and clinical trial design for this situation. An example is for CRISPR-based technologies. For a precise correction gene therapy platform (e.g., prime and base editor) to target different mutations in the same gene that are not

proximal to each other, different guide RNAs (gRNAs) are required, but the remainder of the gene modification machinery remains constant for different targeted mutations. Given this substantial similarity in drug product composition targeting different mutations in the same gene and the frequent similarity in disease manifestations across different pathologic mutations, ARM proposes two potential policy solutions:

- Allowing study under a single IND of products (or parent/child INDs) with identical nuclease proteins and identical delivery mechanisms, but with different gRNAs targeting different mutations all within the same gene and causing the same disease. This would additionally entail:
    - A robust set of pharmacology models that are not necessarily duplicated for all mutational variants studied.
    - A rigorous genotoxicology package that examines the on- vs. off-target confirmed edits and potential structural genome modifications for individual gRNA (*in vitro* human genome), with a risk assessment; sponsors should design a biodistribution study that serves the platform.
    - A toxicology package that may include a smaller number of animals per individual therapeutic product, but that investigates multiple therapeutic products simultaneously or in sequence.
    - Streamlined CMC packages, including using identical functional and/or potency assays for the various therapeutic product subcomponents and the final drug products.
    - A clinical trial paradigm under which:
        - Multiple therapeutic products may be investigated for safety in parallel or in a staggered fashion within a single trial.
        - Clinical efficacy and safety data from multiple therapeutic products treating multiple mutational variants may be combined and submitted together as part of a single registration package.
        - For very rare variants, an n-of-1 approach may suffice, wherein data from as few as a single clinical trial subject may be adequate for approval, if the biology of the disease, the pre-clinical pharmacology, and CMC potency assays all suggest the safety and efficacy of the product would not be meaningfully different from that of a product tested and validated in a more common variant.
- Allowing label expansion after initial approval for a prevalent mutation (or set of mutations) using an abbreviated set of preclinical and clinical studies. This approach might include:
    - Leveraging drug product release and characterization assays (especially potency assays) to demonstrate comparability between

different therapeutic products targeting different mutations in the same gene.
    - N-of-1 studies, as described above, in which preclinical pharmacology, potency assays, and a thorough biological understanding of the disease, allow a very small number of subjects with ultrarare mutations to be studied in the clinic.
    - Accelerated approval for expanded mutational sets, based on surrogate biomarkers rather than a comprehensive clinical data set.

FDA question: 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?

ARM answer: Dealing with live cells and very sick patients requires clear pathways to get treatments to patients as soon as possible. For example, as stated in the guidance document, *Chemistry, Manufacturing, and Controls (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*, rapid sterility tests may be acceptable for *ex vivo* genetically modified cells administered fresh or with limited hold time between final formulation and patient administration.

In the case of urgent clinical need, the Agency could provide a route to waive or defer release testing for potency, as well. The potency strategy is a key deliverable of the DP release panel and clarification on the final potency assay and/or potency matrix is needed well before BLA review, in order for the analytical labs to optimize and transfer technology for these vital methods. Late development requests from FDA during BLA review can lead to less robust methods, impacting timely release of product to patients.

Real-time release might also be preferable for some products, permitting the absence of some test results (which are available after administration), with the exception of identity, a measure of quantity, and a surrogate indication of potency. Guidance on how to fulfill the requirement for drug product testing stated in 21 CFR 610 would be welcome, such as an agreed upon protocol on the evidence (data to generate from development and validation studies) to show the predictable variability of critical quality attributes within an acceptable range, and therefore low risk that acceptance criteria will not be met.

Also, guidance would be beneficial for developing and validating state-of-the-art platform methods and the minimum product-specific qualification required to facilitate the use of robust methods across product types. For example, guidance could be helpful on the confirmation and quantification of edited target sequence, transgene detection and quantification, and differential expression of cell surface markers.

ARM recommends further discussion, e.g., through a workshop or listening session, in the near term on point-of-care manufacturing of products.

FDA Question: 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?

ARM answer: Potency is typically a challenge for such products and therefore guidance for practical, analytical testing strategies to confirm potency would be welcome within the upcoming draft guidance document, *Potency Assurance for Cellular and Gene Therapy Products.* For example, guidance on immunogenicity of neoantigen products for cancer treatment would be useful, as well as guidance for developing and validating state-of-the-art platform methods and minimum product-specific qualification required to facilitate the use of robust methods across product types.

Determining relative potency is highly challenging in the absence of a pertinent and qualified reference standard. ARM would welcome guidance on potency assessment that acknowledges such challenges and includes plans for analytical validation that include both pre- and post-approval studies.

Nonclinical Development

FDA question: 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?

ARM answer: We believe many of the principles that will underpin the forthcoming platform technology designation should be applicable to the development of individualized CGTs. While the specific data that may be referenced would likely vary depending on the specific product, ARM recommends that for many CGT products, the types of data a sponsor should be able to reference if appropriate, in full or in part, include the following nonclinical data:

- Biodistribution studies.
- Toxicology studies.
- Viral shedding studies.
- Insertional mutagenesis studies.
- Vertical/germline transmission studies.
- Immune response to the platform component (e.g., lipids/polyethylene glycol/capsid).
- Developmental and reproductive toxicity studies.
- Juvenile toxicity studies.

For example, if an individualized CGT product uses a vector that is shared between multiple products, the sponsor should be able to leverage safety and biodistribution data for the vector and promoter from products with the same vector. Developers can then perform specific liability assessment for the individual transgenes which comprise the product under review.

FDA question: 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)?

ARM answer: ARM welcomes the option noted in the CAR T guidance of the use of data from batches not intended for clinical use, e.g., batches manufactured in a development lab using representative processes, to understand process performance to support the IND. As noted in ARM comments to the draft guidance, *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products*, the IND should include drug product batches manufactured using the proposed manufacturing process, which may be development or engineering batches defined as representative of the batches proposed for clinical use.

FDA question: What are the opportunities and challenges with using computational approaches to support nonclinical development?

ARM answer: When using patient/disease-specific neoantigens in a product for which nonclinical studies are infeasible or impractical, developers should be able to leverage computational approaches for neoantigens to confirm that there is not off-target specificity to normally expressed human antigens/tissues.

Clinical Development

FDA question: 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?

ARM answer: Interpreting efficacy data may be challenging for small groups of patients because small sample size may diminish a study's power to detect treatment-related effects. Interpreting efficacy data based on functional endpoints for slowly progressing diseases can be especially challenging to do within a reasonable time frame for clinical trials. For these reasons, ARM suggests a totality-of-evidence approach for assessing effectiveness of CGTs for rare diseases.

While use of historical external control and real-world evidence may pose data interpretation challenges, they are often needed for CGTs for rare diseases because randomized prospective controls are often impractical and/or unethical, as ARM stated in its comments to the draft guidance on *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products*. Some of the challenges of interpreting data when using external control groups (e.g., natural history studies) can be addressed by using analytic methods (e.g., propensity scores, weighting) and/or through assignment of appropriate index dates (time zero). The Agency should consider greater acceptance of the use of single-arm data in support of new BLAs when there is no identified comparator arm that is reasonable based on the patient characteristics. The Agency should also consider greater acceptance of sponsor use of surrogate and intermediate clinical endpoints

to support registration in products which would have lengthy development timelines without the use of such endpoints.

To reduce burden on both patients and sponsors, we suggest the Agency continue to explore the ability to leverage innovative approaches to the collection of post-market efficacy data, when required, including the use of registries, remote visits, and remote data capture (e.g., through patient-reported outcome measures and digital health technologies). ARM provides additional details on this topic in its comments in response to the Agency's request for comments on *Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on Dell and Gene Therapy Products.*

ARM suggests that for many CGT products, the types of clinical data a sponsor may often be able to reference, in full or in part, to leverage prior experience and streamline development, include the following:

- Biodistribution.
- Immunogenicity.
- Viral shedding.
- Inadvertent germline integration.
- The rationale for clinical trial design elements such as patient selection (e.g., AAV neutralizing assay), study duration, dose, and endpoints.

More broadly, prior information, such as animal data, can help inform quantitative systems pharmacology (QSP) models to robustly characterize the target-organ, pathophysiology, and the cascade that the mechanism of action of the drug elicits. To elicit their therapeutic benefit, most gene therapies rely on the processes of transcription and translation, with viral vector-based gene therapies additionally relying on an initial step of transfection. Therefore, the interpretability of clinical data from small groups of patients benefits from the following:

- Developing an understanding of the critical biologic mechanisms which govern transcription and, when appropriate, translation;
- Having a bioanalytical strategy in place to assess these critical mechanisms (or their immediate products) in order to explain the observed clinical variance in a small population of clinical subjects.

An additional opportunity to leverage prior experience would be for the Agency to exercise flexibility in accepting a pan-tumor approach/tissue-agnostic study design for cellular therapy, especially in solid tumor indications, such as TCR-T cell therapy, for which patient selection is based on the intracellular antigen expression profile, and no major differences are expected based on indication type in cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). As stated in ARM comments to the draft guidance, *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products,* previous clinical experience, even for a different condition, can be used to justify the clinical starting dose for CAR T-cell therapy. Additionally, some targets such as CD19 have not shown clear dose response relationships, so independent evaluation for each cancer type or indication may not be warranted.

FDA question: 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?

ARM answer: When developing CGTs for multiple disease subtypes of the same disease that share certain clinical characteristics, data extrapolation should be possible using a platform approach, particularly in the clinical phase of development. In trials with small patient populations, developers should consider the use of synthetic controls or natural progression disease models. In addition, as suggested in ARM comments to the draft guidance, *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products*, FDA could provide guidance on the use of study designs more commonly used in oncology trials to guide study design outside of oncology.

Additionally, when a clear genotype-phenotype association is understood, developers could use gene editing tools (e.g., CRISPR-Cas9) to engineer preclinical models to optimize drug candidate selection to facilitate drug development (e.g., perform gene knockout in preclinical models to understand the performance of nucleotide-based therapies aimed at expressing proteins lost to missense mutations).

FDA question: What strategies can be utilized to accumulate and interpret safety data in personalized/individualized CGTs?

ARM Answer: Fully powered studies might not always be feasible due to the individualized nature of the dose. Because comparing active treatment arms will be difficult, a pooled analysis versus placebo may be more appropriate. It would be helpful for the Agency to provide guidance/examples on potential approaches to pool data across arms.

Data science methods such as machine learning and artificial intelligence can also leverage -omics information and natural history studies to identify responders, inform the inclusion/exclusion criteria, and to support the clinical trial design and dose selection.

A developer can accumulate bodies of data (manufacturing, non-clinical and clinical; internal and external sources of data) from related products that can be used to support new, but very similar, individualized products. It would be helpful for FDA to provide guidance on how that data can and should be collected, analyzed, presented and used for this purpose.

Additional Questions to Consider

FDA question: What additional major scientific challenges to advance the development of individualized CGTs should be considered?

ARM answer: Establishing a dose-response or, if possible, an exposure-response, is quite challenging due to the modality. For personalized therapies, there is a need to conduct clinical trials for which the exact amount of viral genome or cells will vary per participant, which makes proper dose-response evaluation even more challenging. To address this challenge, it could be beneficial to view the dose as a continuous variable, rather than a categorical fixture.

Another important part of development for these products is immunogenicity assessment and its effect on efficacy and safety, which can be a confounding factor in addition to the different doses administered. Moreover, for replication competent viral vectors (e.g., as is commonly used in oncolytic viral therapies), understanding the interplay between a growing immune response to the viral vector and the efficacy of the virus can be critical to understanding the dose-response relationship.

ARM also suggests the development of new guidance on mRNA technologies for therapeutic use, including delivery, that emerged from the vaccine experience.

FDA question: 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?

To address dose optimization for gene therapies, a fundamental concept is the administration of genetic material to a target tissue. As such, performing adequate target tissue characterization and/or understanding the pathophysiologic makeup of the target tissue (and what causes it to vary between individuals) can ease the path toward understanding the covariates which govern transgene expression and contribute to dose optimization.

FDA question: Are there specific areas where flexibility in regulatory approaches would improve the feasibility of developing and commercializing individualized CGTs?

ARM answer: Situations in which regulatory flexibility would be helpful include the following:

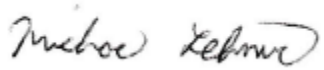
- Consider circumstances in which novel translational methods, which are targeted at optimizing the clinical representation of preclinical disease models, could support a development program.
    - For example, organ-oriented research platforms based on machine perfusion (MP) technology could do so (e.g., https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6791979/; https://pubmed.ncbi.nlm.nih.gov/28266040/).
- Given the time sensitivity of some of these products, a consideration for sponsors is that there may be unanticipated challenges due to import/export of patient starting (apheresed) material. While sponsors may leverage the import for export (IFE) exemption, this is not a streamlined process that adequately meets patient needs. We recommend the Agency consider

providing clear process considerations for sponsor import of apheresed material and potential alternatives to the IFE process.

- The development of disease progression models and/or QSP models dedicated to each disease, leveraging animal data and results from natural history studies, as well results from available studies, could help better inform the dose optimization while taking into consideration -omics information.
- Regulatory flexibility would be helpful in allowing the setting of an appropriate range (versus an exact specifications) for product release/specifications.
- For critical reagents (vectors, guide RNA, etc.) used in the manufacture of drug products for rare indications, a single batch of custom critical reagents may be sufficient to support development needs from nonclinical through commercialization phases. Therefore, flexible approaches should be considered to demonstrate process consistency (PPQ, etc.) without requiring sponsors to execute runs for validation/verification purposes without a clear clinical need for any of the material produced in those batches.
- We recommend the Agency provide considerations for leveraging expanded access data to support post-approval changes (e.g., release specification modification).
- Finally, we recommend the Agency consider how developers should approach expanding release specifications, including leveraging subsequent clinical and real-world data to inform modifications.

Thank you for your consideration of these comments. ARM appreciates your provision of this opportunity for stakeholders to provide input into potential solutions to the challenges in developing individualized cell and gene therapies.

Sincerely,



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