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

Re: FDA-2023-N-3742; Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the **Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies.**

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO applauds CBER's recognition of the many challenges in the development of individualized cellular and gene therapies. BIO values the opportunity to convey major scientific challenges faced by sponsors and to propose solutions to many of these problems. We hope these comments serve to inform FDA's considerations pertaining to town halls, workshops, discussion papers, tools, standards and guidance.

A. Manufacturing

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)?

- We commend the Friends of Cancer Research white paper entitled, "*Accelerating The Development of Engineered Cellular Therapies: A Framework for Extrapolating Data Across Related Products*". It captures well some of the challenges and solutions for supporting development of cell-based gene therapies by leveraging prior knowledge and data extrapolation.

- For development of the manufacturing process, process validation, and specifications, it is possible to leverage data from other related products manufactured in the same vector and the same serotype. For instance, early studies are often performed in academic settings whereas manufacture of late-phase material is performed at a different facility. The lack of material precludes the execution of a standard comparability study between

sites. However, it is possible to perform a risk assessment based on the new manufacturer's history in the production of other gene therapies.

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?

- Product volume is a major constraint. In some cases, more product is used in testing than is administered to the patient. For individualized cell and gene therapies, a single batch is manufactured for a single patient or limited number of patients. It is therefore desirable to minimize the volume of the batch collected for the purposes of analytical testing (including potency) to ensure sufficient material is available for patient treatment. While potency assays *per se* do not typically use large sample volumes, the potency assay strategy can impact the overall volume of product needed for analytical testing. Using a lean control strategy approach, one possible solution is to only evaluate potency at the drug product stage, and not at both drug substance and drug product. Similarly, if using a matrix approach, one might consider a single assay that can evaluate multiple critical quality attributes.

- For batch release testing, it is preferable to use non-compendial bioburden and sterility tests since the compendial tests take a long time and consume large volumes of product. While we do not yet have acceptance of newer bioburden or sterility tests that consume smaller volumes of product, it would be desirable for regulators and industry to work together to drive to acceptance. As batch testing is limited to available materials for testing, flexibility is needed for drug substance/drug product (DP/DS) release testing, especially as it pertains to bioburden testing at pre- and post-filtration. There is the potential to establish similarity between the final DP container closure and a small test sample container for use in analytical testing. In addition, testing of the DS/DP can be limited to method of critical importance, with consideration given to process control and the potential to test prefiltration DS and the final DP sampling point to preserve DS/DP for release testing.

- Stability-indicating assays should be included in the panel of assays; however, there is the potential to use up all existing patient material. The number of time points and the number and types of assays needs to be carefully considered, as they can consume large amounts of product. These products are generally cryopreserved and stored frozen. They are often fragile medicinal products that must be thawed and handled properly by health care providers prior to administration to patients to ensure they are active when administered to the patient. Therefore, in-use studies are important. If the product has a very short shelf-life, then there should be no need for further stability data beyond the shelf-life. In addition, the use of representative material (i.e., healthy volunteer starting material or supportive source materials such as ICH or USP standards) should be used when practical and/or the potential to platform stability studies for similar modalities by leveraging platform stability date and only conducting limited product-specific stability studies. Lastly, the general GMP requirement for annual stability batches is challenging to fulfil for an individualized CGT with very limited material or samples. Also, annual in-use stability data may be more useful than annual long-term stability data since the products are usually applied quickly due to the condition of patients. We suggest FDA either waive the annual stability batch, replace

long-term follow-up drug stability testing (FUST) by in-use FUST, use healthy donor batches instead of patient batches, and/or apply one FUST batch in case of several manufacturing sites.

- Retention samples also need to be minimized since the typical number might preclude some patients from being treated. This is especially an issue for Adeno-associated virus (AAV) gene therapies for rare diseases. If an individualized tumor neoantigen vaccine requires holding a large number of retention samples for a long period of time, and it is ultimately produced to treat large numbers of patients, then we would have to establish very large facilities simply to store retention samples.

- Regarding comparability studies, in cases where each batch of an individualized product (e.g., autologous CAR-T or individualized neoantigen specific immunotherapy) has unique properties tailored to each patient, this intended patient-to-patient variability needs to be distinguished from product quality differences arising from manufacturing changes. Comparability studies should be conducted using split manufacturing approaches whenever possible. This can be done for individualized tumor neoantigen vaccine products and enables head-to-head comparisons of DS and DP batches derived from a single starting material.

- For cell therapies, when there is a lack of sufficient patient material, sponsors can use healthy donors for comparability and process validation. Due to inherent difference in patient material, this approach could be facilitated by FDA adopting less rigorous statistical requirements to demonstrate "representativeness" of patient and healthy donor material.

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?

- Turnaround time (TAT) for production, testing, and release of each batch of individualized CGTs is crucial, since the manufacture of each batch can only begin once the patient samples are obtained. It is important to minimize TAT and to establish a highly consistent TAT that is always delivered so that patients and physicians can obtain the therapy in a reliable timeframe. Manufacturing failures can cause a delay in patient treatment.

- Minimizing TAT of individualized products is critical for maximizing patient benefit. Batch release testing often takes a large fraction of the total TAT, especially for high volume products. Novel control system approaches may be necessary, especially for release testing as opposed to routine monitoring. For example, certain critical quality attributes (CQAs) should be tested for every batch to ensure safety and efficacy. However, it may be reasonable to test other CQAs on a less frequent basis to ensure that the process is performing as expected. This would enable a reduction in the total number of tests being run, which could enable shorter TATs. A per-product risk assessment would be needed to enable this.

- With individualized products, it is not possible to generate a reference material or reference standard that is representative of patient-specific batches; however, there is

still a need for an analytical standard to ensure assays are performing correctly (representative batches or representative sequences). The unique properties of each batch preclude the establishment of a traditional reference standard. Instead, other types of references need to be established, such as analytical standards to ensure that test methods are performing properly. Assay controls and analytical standards need to be created or obtained and assessed for their suitability. The appropriate control or analytical standard needs to be managed to reduce the risk of assay drift and increased imprecision as a result of lot-to-lot variability in the control or analytical standard. There should be a program that manages suitable standards throughout the lifecycle of the product.

- For mRNA-based individualized tumor neoantigen vaccine products, it is necessary to establish reference sequences of DNA templates that cover the range of template length and GC (guanosine cytosine) content. These serve as references during comparability assessments when changes are made in the RNA drug substance or RNA-lipoplex drug product manufacturing processes. They may also be used in the stability program.

- For cell therapies, there are no recognized reference standards particularly given the donor-to-donor characteristics of the cells, the primary nature of the cells (not immortal) and the limited availability of donor material. For each material (reference material, analytical standards, assay controls), a program is required for assessing the suitability and stability of the material for its intended purpose. All materials used as assay controls need to be assured of long-term supply and performance that minimizes drift or compromises result reporting. Characterization of the controls should be performed to support the assessment of suitability.

- For gene-edited autologous T-cell products, there should be an allowance to address the risk of gross chromosomal abnormalities in preclinical studies or non-release testing for patients with rapidly declining health. For example, few options exist for performing karyotyping at a lab with Good Manufacturing Practice (GMP) controls suitable for release testing. The TAT for this single test can add 6-8 weeks post-manufacture, while most other analytical methods can be completed within 2 weeks.

- For autologous cell therapies, a partial release of the product is preferable when enough safeguards have been implemented in the clinical trial design for adverse event monitoring. Some safety quality attributes have tests with TATs ranging from weeks to months, significantly increasing the TAT for returning cells to patients. The TAT increase could result in a significant disease worsening or death when patients are in late-stage life-threatening conditions. Partial release could be achieved by understanding the safety complications to patients and building safeguards proactively in the clinical trial design.

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?

- Individualized CGTs pose unique control system challenges, especially when measuring potency, since each batch of product is custom-made for each patient. It is a requirement that CGTs, including individualized or made-to-order products, have a

potency assay that reflects the mechanism of action. However, *in vitro* potency assays may or may not be indicative or sufficient to reflect the *in vivo* activity. Because these products can have multiple mechanisms of action, multiple potency assays may be needed to adequately assess activity. The uniqueness of each batch of an individualized product can limit the types of potency assay formats that are technically feasible and can leave the sponsor with functional assays that measure a more limited aspect of the product's function. Nevertheless, it is an expectation that the potency method reflects the full mechanism of action and, if this is not possible, that the chosen method be bridged to the full mechanism of action.

- The classical approach for evaluating potency uses a cell-based functional assay. These assays typically take several days or weeks to execute, which significantly impacts the release time and overall turnaround time for the batch. Therefore, it is advisable to consider alternative assay formats such as qPCR, ddPCR, FACS, ELISA and SPR. Considering the complexities described above for individualized products, these alternative assay types may be better suited to the matrix approach then the more classical assay formats. Potency assay developers could consider including several assays with different TATs in the matrix, subsequently focusing on those assays that give more information about product quality in the least amount of time.

- Potency assays need not necessarily capture every mechanism of action (MoA). The matrix approach involves capturing two or more mechanisms of action and compiling the data to draw a collective conclusion. Such an approach is the combination of complementary assays based on product-specific attributes covering biological or non-biological methods. Potency methods should be MoA-reflective; however, it is important to be aware that potency may not directly correlate with *in vivo* efficacy and clinical outcome.

- The *in vivo* fate of a cellular therapy product may be complex and correlating potency assay(s) with the mechanism of action may be very challenging. Once administered, a cellular product may undergo migration from the site of administration, cellular differentiation into the desired cell type, and cellular replication. A potential potency assay matrix could include assays to determine several characteristics including viable cell number; in vitro differentiation; target-specific cytotoxicity and/or cytokine release; surrogate functional biomarker (e.g., phenotype expression or factor release that correlates with function); and biological activity (e.g., antigen presentation). The selection of biomarkers needs to have a sound scientific justification with supportive data.

- A potency assay for the drug substance of a tumor neoantigen vaccine may be a functional assay that qualitatively shows the encoded polypeptide can be translated to form the mRNA (active substance), since translation is dependent on structural features, such as a specific 5' cap structure and a poly(A)-tail at the 3' end. Thus, detection of a translation product demonstrates that these and all other structural features required for translation are correctly present on the RNA. While it would be ideal to develop a potency assay that is capable of measuring and identifying the translated polypeptide for each batch, this is not possible due to the unique set of neoepitopes for each patient. In addition, these neoepitopes are not known *a priori*. The neoepitopes are identified and prioritized during the manufacturing process and the RNA and RNA-lipoplex

nanoparticles are manufactured within day, limiting time to develop antibodies against them to serve as reagents in a potency assay.

- For individualized tumor neoantigen vaccines, the sum of the multiple assays (matrix of assays) should demonstrate the intracellular processing of the recombinant genetic information in the target cells and, in the best case, up to its functionality in the target cells. This intracellular processing can be shown experimentally *in vitro*, e.g., transduction assay of representative cell lines or *in vivo*, e.g. in adequate transgenic animal models. At least one assay of this matrix used to measure potency should be quantitative (and therefore capable as being a stability indicating functional assay) and expressed in units of activity calibrated against an appropriately qualified reference material. Where no qualified reference material exists, use of a well-characterized assay control is recommended to monitor assay performance only (not used to assign potency values for the test sample).

- In the case of a nucleic acid-based product, while each batch is patient-specific, there are components that are common across all patient batches. Therefore, the MoA consists of both "product-specific" and "patient-specific" components. Product-specific aspects of the MoA are those directly impacted by product quality parameters, while patient-specific aspects are those that are dependent on patient-intrinsic aspects. For example, for a mRNA-based Individualized neoantigen-Specific Therapy (iNeST), the product-specific aspects of the MoA include the uptake of the mRNA by antigen-presenting cells and its release into the cytoplasm where it is translated into the encoded polypeptide including both constant and patient-specific regions, and routing of the translated protein to proteasomes for degradation. The patient-specific aspect is the stimulation of T-cells with the patient-specific neoantigens. Using the concept of the matrix approach presented above, and by executing extensive characterization studies early in the development life cycle, it may be possible to justify targeting only the product-specific aspects of the MoA for product release testing. However, characterization assays (for evaluation of patient specific MoA aspects) should be maintained for other uses such as process characterization studies and comparability.

- If the product contains more than one active cell population, then multiple assays to measure potency will be needed since one assay is not likely to be sufficient to determine the activity of each active cell population. Cellular therapy products are complex and have particularly complex mechanisms of action. Multiple active ingredients (i.e., cell populations) may be present. There may be multiple cell populations combined in the final product and the potential for multiple effector functions of cells. The product may be a heterogeneous mixture of cells and peptides (from the cell culture process). Thus, there may be ambiguity regarding which components of the final drug product contribute to potency. Similarly, gene-modified cell therapy products have a multi-faceted mechanism of action. For example, a primary mechanism of action via the gene delivered with a supporting role for the cell used for delivery (e.g., via cytokine secretion).

B. Nonclinical Development

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*?

- The development of individualized CGTs would benefit from a platform designation approach. For example, where an individualized CGT product uses a vector that is shared between multiple products, the platform safety and biodistribution for the vector and promoter could be used to leverage data from products with the same vector. Developers could then perform specific assessment for the individual transgenes that compose the product under review. However, it may be challenging for individualized therapies to leverage a platform approach if the platform designation is only granted with approval of a second, follow-on product.

- The appropriate approach varies case-by-case, dependent upon how the related product relates to the 'new product'. For example, if the same CAR-binding domain is being used, tissue cross-reactivity and membrane and soluble protein arrays from previous studies could be used to support the new product. The minimum testing requirements for each final product could include pharmacology or proof of concept studies to evaluate CAR-T expansion/persistence (cellular kinetics), immune response or tumor killing (if an oncology indication). Testing could be conducted either *in vitro* or *in vivo*. For allogeneic products, the interaction of host immune cells and CAR-T cells could also be considered to assess the risk of allorejection.

- For AAV-based therapies, biodistribution studies (including potential insertional mutagenesis assessment) that are conducted with the same capsid variant, the same promoter, the same route of administration and similar dose levels, but with different transgenes could be leveraged to determine biodistribution of a final clinical product.

- Previous nonclinical studies can be leveraged in cases where there are two different versions of gene-modified cell therapies. Examples include where two therapies have the same vector construct but different manufacturing processes, or where therapies have different transgenes but the same vector backbone.

- Patient-derived primary cells or patient iPSC-derived cells representative of the target cell or tissue could be used for testing proof of mechanism of the product, and, in combination with large animal model studies, be used for determining minimal effective dose.

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?

- The appropriate approaches will vary on a case-by-case basis. In part, the approach will be dependent on the relevance of a partial animal model and the likely biodistribution of the product. A platform approach could be considered if relevant data are already available in other disease models, with read-across to a different disease setting taking disease specifics into account. The relevance of species-specific surrogate products could be considered although the ability of such approaches to identify off-target toxicities is limited.

- In the absence of suitable animal models, New Alternative Method (NAM) approaches could be strongly considered when feasible. *In silico* and *in vitro* models (including complex *in vitro* systems) of diseased and healthy tissues could be leveraged to inform both proof-of-concept of pharmacology and predictive safety assessment. These

approaches would be consistent with the 3Rs principles for ethical use of animals. Bioinformatics and literature-based assessments of target expression, specificity to the tissue being targeted, and potential for off-target effects in humans should supplement any NAM-based approaches.

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)?

- In the absence of being able to evaluate the individual clinical product, nonclinical studies conducted using representative products can serve several roles. Representative products used in nonclinical studies can help establish proof-of-concept and mechanism of action. In addition, representative products can be used to build a weight-of-evidence for the safety of the overall product and platform.

- Nonclinical studies on different batches of the representative product enable determination of the consistency of the product and identify potential risks and benefits.

- Nonclinical studies can be used to identify the minimal effective dose (especially in the case of AAV therapies where repeated dosing may not be effective) and maximum tolerated dose. Furthermore, nonclinical studies could also help to identify potential safety signals that could impact the patient's clinical management.

- For n-of-1 programs, nonclinical studies can be deployed for performing basic safety characterization, with patient and disease progression being prioritized. For autologous therapies these studies can be used to characterize any procedural safety components and inform safety when a relevant model or homolog is available.

- Representative products manufactured for nonclinical studies using the clinical process can also be used to demonstrate consistency in manufacturability across patient batches.

- When using patient/disease-specific neoantigens in your product, developers can leverage computational approaches for neoantigens to confirm that there isn’t off-target specificity to normally expressed human antigens/tissues.

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

- Computational approaches currently supplement empirical approaches during development. These approaches offer an alternative approach to designing an optimal therapy, reducing risk while increasing efficacy prior to definitive safety and efficacy studies, refining translation, and potentially accelerating timelines. For individualized therapies, where nonclinical models often do not exist, there is a unique opportunity to support development using only computational approaches.

- The potential of computational approaches both for nonclinical and clinical studies depends on there being sufficient data being available to develop and support an appropriate algorithm.

- Challenges with the use of computational approaches to predict safety assessment include lack of robust datasets of gene expression in healthy vs disease states, and the lack of racial and ethnic diversity in available genetic and proteomic databases. For CAR-T cells, there is a need for pharmacokinetic/pharmacodynamic (PK/PD) modeling approaches, especially regarding mechanistic-based modeling where there is no convergence yet. Mechanistic modeling approaches to understand and predict the heterogenous patient responses to CAR-T cell dynamics are limited due to the complexity in patient variability.

- For CAR-T therapies, computational approaches can be used to characterize the impact of target expression on CAR-T expansion or distribution and optimize the lymphodepletion regimen. They can also guide the design of next generations of CAR-T cells products or the next clinical study design.

C. Clinical Development

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?

- One challenge is that randomized clinical trials may not be feasible or ethical. Also, there may be an absence or limitation of available natural history data for some diseases. In serious or life-threatening conditions or diseases, the expected disease course may be highly variable and the published evidence or data on patients under standard of care is very limited. This makes the interpretation of efficacy data from individuals or small sample sizes very difficult. For instance, if you have a trial with only four patients, the utility of a placebo group is questionable as it may be difficult, if not impossible, to effectively balance important baseline covariates across active and placebo groups with such a small sample size. An opportunity exists to perform a concurrent comparison in patients that are matched to the treatment arm, at a stage of disease where progression is relatively predictable, acknowledging the size of this comparison is also limited by the overall number of rare disease patients.

- In contrast to traditional biologics, there is often a 1:1 correlation between a product lot and a patient for individualized therapies. For oncology indications with individualized therapies, there are a fairly large number of product batches that cumulatively yield a large dataset; however, there is, by design for individualized tumor antigen vaccines, and inherently for an autologous CAR-T, a high degree of batch-to-batch variability.

- While interpreting efficacy data from small groups of patients is a challenge, the intention-to-treat (ITT) population's efficacy data for individualized CGTs in non-rare conditions can be interpreted. If the patient group is small, registries present an opportunity to leverage the collective experience over time.

- Based on the mechanism of action of a CGT product, one may be able to form hypotheses of biomarkers that correlate to clinical efficacy. Biomarkers can serve as factors to regroup patients so that efficacy may be interpreted based on the determined new subgroups instead of individual patients.

- For CAR-T products, one can consider leveraging prior clinical data with the same target or same indication to infer the kinetics versus the efficacy the safety, or the PK/PD relationship.

- In rare progressive diseases where early stage differs from the later disease manifestation due to irreversible disease damage over time, the efficacy and safety endpoints of focus differ, and therefore ability to extrapolate between older/later stage disease patients and younger/earlier stage disease patients is challenging.

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

- When sample sizes are small and the selection of a comparator is challenging, it is crucial to have a good understanding of the expected safety profile of the study population under standard of care conditions. In addition, it may be helpful to define adverse events of special interest based on the risks of the therapy for other indications.

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?

- It may sometimes be difficult or even unethical to conduct randomized studies for genetic disorders. In such scenarios, the evidence of a large or meaningful treatment effect could be assessed using an external control or through the evaluation of the within-patient improvement that would not otherwise have occurred without the CGT intervention.

- The use of gene-editing tools to engineer preclinical models to optimize drug candidate selection can facilitate drug development. For instance, one can perform a gene knockout in preclinical models to understand the performance of nucleotide-based therapies aimed at expressing proteins.

D. Additional Questions to Consider

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

- CBER could explore a regulatory pathway similar to Project Orbis to facilitate registration review and collaboration of expertise across regulatory authorities on CGTs for rare diseases.

- Recognizing that it can take many years to demonstrate clinical benefit, CBER should consider leveraging the Accelerated Approval pathway and surrogate endpoints to the fullest extent possible for the development of individualized CGTs. Similarly, they should consider doing so for CGTs for ultra-rare diseases, since many of the challenges highlighted in this letter also impact the development of cell and gene therapies for ultra-rare diseases.

- CBER could consider harmonizing with other countries where certain exceptional release can be done on a notification basis rather than requiring individual approval for each out-of-specification product. In such a paradigm, the Agency and sponsor would align on a process for exceptional release on a notification-only basis. Such an approach would ensure that critical delays (where patient status rapidly declines) due to pending Agency approval are avoided.

- The unique nature of individualized products and the limited ability to assess the impact of process changes on the product itself calls for conceptually different approaches to lifecycle management. In some cases, the manufacturing process changes are intended to improve the product. For example, algorithms and databases used during the neoepitope selection process for tumor neoantigen vaccine production can be updated to leverage growing amounts of relevant data; such algorithm updates should be evaluated for their performance using appropriate metrics rather than an assessment at the product level.

- Given the time sensitivity 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, the process is not streamlined to meet the patient need. We recommend that the Agency consider providing clear process considerations for sponsors importing apheresed material and potential alternatives to the IFE process.

Sincerely,

/s/
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Sr. Director, Science & Regulatory Affairs
Biotechnology Innovation Organization