Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
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I. INTRODUCTION

The management of manufacturing changes presents many challenges for human cellular therapy[1] or gene therapy[2] (CGT) products due to the complexity of these products. We, FDA, are providing you, sponsors of Investigational New Drug Applications (INDs) and applicants of Biologics License Applications (BLAs) for CGT products, with recommendations regarding product comparability and the management of manufacturing changes for investigational and licensed CGT products.[3] The purpose of this guidance is to provide FDA's current thinking on 1) management and reporting of manufacturing changes for CGT products based on a lifecycle approach, and 2) comparability studies to assess the effect of manufacturing changes on product quality.[4, 5]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only

[1] For the purposes of this guidance "cellular therapy products" include certain tissue-engineered medical products (referred to in this guidance as TEMPs) that contain living cells (see section VI of this guidance) and are regulated under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262).

[2] Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids, genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells.

[3] Cellular and gene therapy products meet the definition of "biological product" in section 351(i) of the PHS Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings (see Federal Register Notice: Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 FR 53248, October 14, 1993), https://www.fda.gov/media/76647/download).

[4] This guidance does not apply to vaccines for infectious disease indications, bacteriophage products, live biotherapeutic products, fecal microbiota for transplantation (FMT) products and allergenic products.

[5] For the purposes of this guidance, the term "product quality" refers to identity, strength, quality, purity, and potency of a product, as these factors may relate to the safety or effectiveness of the product.

as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

CGT products are regulated under the existing framework for biological products. Manufacturing and control of CGT products can often be affected by unique factors, including limited knowledge of product quality attributes, limited manufacturing experience, limited and variable starting materials, limited amount of product, complex manufacturing processes, and limited product shelf life. These aspects of CGT products may make the management of manufacturing changes more challenging than for other biological products.

A CGT product manufacturer may seek to implement a manufacturing change for a variety of reasons, including improving product quality, expanding product supply, or improving manufacturing efficiency. The risk that a manufacturing change may adversely impact product quality should be prospectively assessed under the manufacturer's quality risk management processes (Refs. 1, 2). We note that while improvement of product quality is always desirable and encouraged, if the results of comparability studies indicate an improved product quality suggesting a significant benefit in effectiveness and/or safety, the pre- and post-change products may be different products and, therefore, not comparable.

Risk assessment should be performed for all types of manufacturing changes, regardless of the stage of product development. If a risk assessment indicates that a manufacturing change has the potential to adversely affect product quality, comparability studies should be performed to evaluate the impact of the proposed manufacturing change. It can be difficult to fully characterize CGT products using analytical methods, and in some cases analytical studies alone may not be sufficient to reach a conclusion regarding comparability. In such cases, additional data from nonclinical studies may help to support comparability. Otherwise, additional clinical studies may be warranted.

The extent of analytical evaluation needed to adequately evaluate a manufacturing change in comparability studies generally increases with the stage of clinical and product development and should be supported by knowledge of critical quality attributes (CQAs) (Ref. 3), accumulated manufacturing experience, and further understanding of the mechanism of action (MOA). For both licensed and investigational products, assessing the risks of manufacturing changes is essential before designing comparability studies. For licensed products, applicants are required to assess the effects of "each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s)" (Title 21 of the Code of Federal Regulations (CFR) 601.12(a)(1)-(2)).[6] Applicants must also demonstrate through appropriate validation and/or other clinical and/or

[6] For purposes of this guidance, the term "manufacturing change" in the context of a licensed product, refers to a change (other than a labeling change) that would fall within the types of changes described in 21 CFR 601.12(a)(1).

nonclinical laboratory studies that each manufacturing change does not adversely affect product quality before distributing a product manufactured using the change (21 CFR 601.12(a)(2)). For investigational products, sponsors must provide sufficient chemistry, manufacturing, and control (CMC) information to assure product safety, identity, quality, purity, and strength (including potency) of the product (21 CFR 312.23(a)(7)(i)), and some manufacturing changes without adequate comparability data may result in a clinical hold (21 CFR 312.42(b)).

The guidance entitled "Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products" dated April 1996 (Ref. 4) contains general recommendations applicable to biological products, but it does not address the specific challenges of performing comparability studies with CGT products. The guidance entitled "Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" dated June 2005 (Ref. 5) contains principles that may be useful for comparability studies of CGT products. However, its scope is limited to certain proteins and polypeptides that can be highly purified and characterized, which are typically less complex, better characterized, and manufactured to more stringent tolerances than CGT products. Other FDA guidance documents related to management of manufacturing changes and risk management for biological products generally do not address specific CGT product challenges (e.g., Refs. 1, 2, 6). The purpose of this guidance is to provide recommendations for managing manufacturing changes and assessing comparability for both investigational and licensed human CGT products while considering the unique challenges that apply to these products.

III. CONSIDERATIONS FOR THE MANAGEMENT OF MANUFACTURING CHANGES

An effective quality system maintains consistency in drug product (DP) quality throughout the product lifecycle, including by adequately managing manufacturing changes. In general, manufacturing changes should be thoroughly assessed and documented using effective change control procedures. For investigational products, maintaining product quality by control of CQAs and critical process parameters (CPPs) during manufacturing changes is important for obtaining interpretable clinical study data that can support licensure. A robust framework for managing manufacturing changes is especially valuable for CGT products because of the complexity of these products and their manufacturing processes.

A. Risk Management

Managing manufacturing changes can be challenging for CGT products due to difficulty in identifying risks to product quality and uncertainty about how to mitigate risk. Therefore, we recommend that you apply a systematic approach to quality risk management designed to identify, assess, analyze, and mitigate potential risks. Such an approach can facilitate science-based decision-making and enable a risk-based evaluation of manufacturing changes (Ref. 1).

Defining acceptable ranges for CQAs and establishing operating ranges for CPPs prior to making a manufacturing change facilitates conducting a risk assessment and evaluating the change. For example, for a cellular product that has a manual wash step, it would generally be easier to transition to an automated wash process if the acceptable operating range for the duration of the cell washes has already been established, because this parameter can impact product CQAs and process performance.

Factors such as product and process knowledge, qualification/validation of methods, and the stage of clinical development should be considered when assessing the risk of the manufacturing change. In particular, you should carefully assess risks to product quality if extensive manufacturing changes are introduced shortly before BLA submission. In such a situation, a comparability study should be comprehensive and should provide high confidence that the change does not adversely impact product quality (section V of this guidance). Additionally, introducing a manufacturing change at this late stage of development or after licensure could require additional process performance qualification studies if the existing qualification study is not representative of the intended commercial process (e.g., 21 CFR 211.22, 211.100, 211.110(a) and 211.165). For a process that has already been validated, you should also determine whether there is a need for any changes to the plans for continued process verification as a result of the manufacturing change (Ref. 7). For these reasons, we recommend that any extensive manufacturing changes be introduced prior to initiating clinical studies that are intended to provide evidence of safety and effectiveness in support of a BLA.

To facilitate manufacturing changes during rapid clinical development, CGT product manufacturers should ensure that the pace of product development is aligned with the stage of clinical development. For example, if you initiate clinical studies using product generated by a manufacturing process designed with a potential for scalability, this will help decrease the likelihood of delays later in clinical development when the manufacturing process is scaled up.

For both investigational products subject to 21 CFR part 211 and licensed products, you must evaluate data at least once a year to determine if changes in product specifications or manufacturing or control procedures are needed to maintain the quality standards of the product, even when no manufacturing changes are undertaken (21 CFR 210.2, 211.180(e) and 601.2(d)). Data trend analysis throughout product development can also be useful for verifying that manufacturing changes do not lead to shifts in manufacturing consistency over time.

B. Stability and Delivery Device Compatibility

Product stability may be adversely affected by manufacturing changes, including changes made during processing, holding steps for intermediates, and shipping or storing the drug substance (DS) or DP. CGT products are often sensitive to storage and handling conditions. DP stability should be thoroughly assessed after changes to the container closure system, formulation, product concentration, or shipping conditions.

Manufacturing changes to CGT products may also have the potential to affect compatibility of the DP with delivery devices.

When evaluating the risk of a manufacturing change, we recommend that you determine if there is a need to perform stability and/or delivery device compatibility studies to assess the effect of the change on product quality, and whether any such studies should evaluate in-process material, DS, or DP. Stability studies should focus on the evaluation of stability-indicating quality attributes. The stability testing plan should define appropriate acceptance criteria, which may be different from the acceptance criteria for release of the product.

Many CGT products are stored frozen for a significant length of time. Accelerated stability studies performed under stress conditions may be useful for identifying stability-indicating attributes, but shelf life should be based on real-time stability data obtained at the long-term storage condition. Generating real-time long-term stability data can delay product development, especially when manufacturing changes that have the potential to adversely affect stability are implemented during late stages of product development. For post-licensure manufacturing changes, there may be a need to generate real-time stability data with the post-change product to demonstrate a lack of adverse effect on product quality, and generating these data could severely delay the implementation of the manufacturing change.

C. Nonclinical studies

Nonclinical studies may be needed to support manufacturing changes for an investigational product after clinical studies have been initiated (Ref. 8), or for a licensed product (21 CFR 601.12(a)(2)). If analytical studies alone are insufficient to determine the impact of the manufacturing changes on CGT product quality, then nonclinical studies may contribute to a demonstration of comparability.

D. Clinical studies

We recommend that comparability of investigational or licensed CGT products be evaluated through analytical assessment and, if appropriate, nonclinical studies. When applicable and feasible, studies evaluating pharmacokinetic/pharmacodynamic (PK/PD) parameters may be used to contribute evidence in support of comparability between the pre- and post-change products. When comparability cannot be established through analytical, nonclinical, and/or PK/PD studies, the evidence of safety and effectiveness accumulated during clinical investigation with the pre-change product will be insufficient to support a BLA for the post-change product, and the sponsor should contact FDA to discuss plans for additional clinical investigations of the safety and/or effectiveness of the post-change product.

Investigational Products

If analytical and/or nonclinical comparability studies are insufficient to assure that a manufacturing change will not adversely affect safety, then the sponsor should discuss with the FDA (section VII of this guidance) their plans for safety evaluation of the post-change product, which may include conducting new clinical studies and/or incorporating additional safeguard measures and safety evaluations in ongoing clinical studies. For example, it may be appropriate to consider broadening the scope of the adverse events of special interest, staggering enrollment of subjects, modifying study stopping rules, and conducting additional dose-finding studies.

If comparability studies demonstrate that the manufacturing change does not adversely affect product safety but are insufficient to exclude an adverse impact on product effectiveness, then the sponsor will need to evaluate the effectiveness of the post-change product in clinical studies to support a BLA for the post-change product.

It is important to critically evaluate any manufacturing change that has the potential to affect product effectiveness when the change is proposed after initiation of studies intended to provide substantial evidence of effectiveness in support of a BLA. In addition, evidence demonstrating a prospect of direct benefit of a pre-change investigational CGT product to pediatric subjects, as required for studies conducted in accordance with 21 CFR 50.52, may not be adequate to demonstrate prospect of direct benefit with respect to the post-change product. If comparability cannot be established between the pre- and post-change product, the sponsor should discuss with the FDA (section VII of this guidance) any proposed modifications to the clinical development program for the post-change product. Such modifications could include an increase in the number of subjects exposed to the post-change product and initiation of new clinical studies with the post-change product. In the case of pediatric studies for which a prospect of direct benefit is required, nonclinical data demonstrating prospect of benefit may be sufficient during early-stage clinical development.

If you wish to pool clinical data from subjects treated with the post-change product and subjects treated with the pre-change product, you should demonstrate that the products are comparable and justify that the clinical study designs are appropriate for pooling. We also recommend that you seek FDA's advice (section VII of this guidance) on the design of the pooled data analysis, preferably before conducting late-phase studies intended to demonstrate product effectiveness in support of a BLA.

Licensed Products

If analytical and/or nonclinical comparability studies are unable to demonstrate that a manufacturing change to a licensed product has no adverse effect on product quality, FDA will not be able to approve the manufacturing change based on those studies (21 CFR 601.12). In such cases, we recommend that you discuss alternative approaches with the FDA (section VII of this guidance), which will be evaluated on a case-by-case basis. For example, you may consider initiating new clinical studies with the post-change product under an IND to obtain evidence of its safety and effectiveness.

IV. REGULATORY REPORTING OF MANUFACTURING CHANGES

IND sponsors must notify FDA of manufacturing changes through an amendment if manufacturing information previously submitted no longer accurately reflects the current state of manufacturing because essential information is missing (21 CFR 312.31(a)(1)). Applicants must notify FDA of manufacturing changes through a BLA supplement or annual report in accordance with 21 CFR 601.12 (Ref. 6). When submitting an IND amendment or a BLA supplement for a manufacturing change, your cover letter should clearly describe the purpose of the amendment and highlight proposed changes (Ref. 9). For amendments containing extensive changes, we recommend that you provide a "Reviewer's Guide" or a comprehensive summary of the changes in Common Technical Document (CTD) sections 1.2 or 1.11.1, respectively.[7] Module 3 and any other relevant sections of the IND or BLA should be modified to include the change, and the developmental history of the manufacturing process should be updated in the pharmaceutical development sections (3.2.S.2.6 and 3.2.P.2.3) of your IND or BLA. The type of submission, timing of submission, and amount of information required in the submission will vary depending on the stage of product and clinical development and the nature of the manufacturing changes, as described further below.

A. CMC Changes Requiring a New IND Submission

Some changes can fundamentally alter the design or nature of the product, resulting in a new product. Initiation of clinical studies with the new investigational product generally requires the submission of a separate IND (21 CFR 312.20). We recommend that you seek FDA advice (section VII of this guidance) regarding any manufacturing changes that could alter the product and require a new IND. Some examples of changes that may require a new IND include:

- Change in the cellular starting material of a cellular product (e.g., allogeneic vs. autologous donor; adipose-derived cells vs. umbilical cord-derived cells)
- Change to the types of cells in a cellular product (e.g., mixture of $CD4^+$ and $CD8^+$ T cells instead of solely $CD4^+$ T cells)
- Change to the scaffold or matrix component of the final construct in a TEMP (e.g., changes to chemical or physical properties) causing significant modification to the product characteristics
- Change in a viral vector capsid or envelope that changes the tropism or serotype of a viral vector used for in vivo gene therapy
- Change to the sequence of a transgene or addition of a transgene (e.g., changes to the intracellular signaling domain of a chimeric antigen receptor)
- Change in expression control elements of a viral vector (e.g., change from a tissue-specific to a ubiquitous promoter)
- Change of target gene for genome editing products, including addition of a target gene

[7] For information on electronic CTD (eCTD) submission requirements, please see the FDA website https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd.

B. Reporting Manufacturing Changes to an IND

FDA regulations require all sponsors of investigational new drug products, including investigational CGT products, to describe the CMC information for the DS (21 CFR 312.23(a)(7)(iv)(*a*)) and the DP (21 CFR 312.23(a)(7)(iv)(*b*)). The CMC information in your IND must be sufficient to assure the safety, identity, quality, purity, and strength (including potency) of the investigational product (21 CFR 312.23(a)(7)(i)). The CMC information in an IND describes a sponsor's commitment to perform manufacturing and testing of the investigational product as stated in the IND or in a cross-referenced IND or master file. If a manufacturing change could affect product quality, we consider the manufacturing change essential information that must be submitted in an information amendment to the IND (21 CFR 312.31(a)(1)). The sponsor should submit such amendments for FDA review prior to use of the changed product in clinical investigations. The FDA will review data or study reports submitted to support the change, and may provide comments (section V of this guidance). In addition, each year you must submit an annual report that provides a summary of any significant manufacturing changes made during the past year (21 CFR 312.33(b)(7)).

If a manufacturing change has the potential to adversely affect safety, and if you do not submit evidence to your IND demonstrating that the post-change product has an acceptable safety profile, then your IND may be placed on clinical hold at any phase of clinical development (21 CFR 312.42(b)(1)(i), 21 CFR 312.42(b)(1)(iv), and 21 CFR 312.42(b)(2)(i)). Evidence may be provided as an amendment to the IND in the form of analytical comparability data or other analytical data relevant to safety. If these data do not allow for a conclusive determination that the manufacturing change has no adverse effect on product quality as it relates to safety, then you should consider performing a toxicology study to evaluate whether the post-change product has an acceptable safety profile.

If you make a manufacturing change that has the potential to adversely impact the effectiveness of the product without submitting evidence to your IND demonstrating that the post-change product is comparable to the pre-change product, this may also result in a clinical hold for certain clinical studies (21 CFR 312.42(b)). FDA's review of an IND submission for a phase 2 or 3 clinical study includes assessing the likelihood that the study will yield data capable of meeting statutory standards for marketing approval (21 CFR 312.22(a)), and a phase 2 or 3 study may be placed on clinical hold if the plan or protocol for the study is clearly deficient in design to meet its stated objectives (21 CFR 312.42(b)(2)(ii)). If, for example, a phase 3 study intended to provide substantial evidence of effectiveness to support a BLA for a post-change product uses lots of both pre- and post-change product, but those products are not comparable, then the study may lack statistical power to demonstrate effectiveness of the post-change product. Such a study may be considered clearly deficient in design to meet its stated objectives and placed on clinical hold if the IND submission does not provide evidence demonstrating comparability of the pre- and post-change products.

In addition, FDA may place studies on clinical hold if subjects would be exposed to an unreasonable and significant risk of illness or injury (21 CFR 312.42(b)(1)(i) and 312.42(b)(2)(i)). If you make a manufacturing change that could adversely affect the effectiveness of the investigational product without demonstrating comparability, then the capacity of the post-change product to provide a potential benefit to subjects may be in doubt. This may lead to a conclusion that a significant risk of illness or injury involved in a clinical investigation is unreasonable, and the study may be placed on clinical hold.

C. Reporting Manufacturing Changes to a BLA

For licensed products, you must report each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application, in accordance with the requirements in 21 CFR 601.12. When reporting these changes, your supplement or annual report should include a risk assessment report and must include data from appropriate studies performed to evaluate the effect of the changes on product quality as required under 21 CFR 601.12(b)(3)(iv)-(v), 21 CFR 601.12(c)(3), or 21 CFR 601.12(d)(3)(ii) (Ref. 6).

To facilitate management of post-approval manufacturing changes, you may submit one or more comparability protocols to your BLA for FDA review, as described in 21 CFR 601.12(e). These protocols may be submitted either in the original BLA or, if the application is already approved, in a prior approval supplement (Ref. 10). Comparability protocols should be located in section 3.2.R of your BLA. Upon approval, this protocol becomes an agreed-upon plan for implementation of the manufacturing change using the reporting category specified in the approved comparability protocol submitted under 21 CFR 601.12(e), provided that there is successful completion of the plan for implementation of the change(s) as described in the comparability protocol (including achievement of all of the predefined acceptance criteria for success in the approved comparability protocol) (Ref. 10).

V. COMPARABILITY ASSESSMENT AND REPORT

Comparability between the pre-change and post-change products is generally demonstrated by evidence that the change does not adversely affect product quality for the licensed (21 CFR 601.12(a)(2)) or investigational product. However, if the change is intended to improve product quality, such that there is a significant benefit in effectiveness and/or safety, then the post-change product may be considered a different product, and therefore not comparable to the pre-change product. We recommend that you seek FDA advice (section VII of this guidance) when planning significant manufacturing changes and when designing study protocols for comparability studies. Section V of this guidance describes considerations for designing a comparability study, analyzing comparability data, and submitting a comparability study report. For information on reporting manufacturing changes to FDA, please refer to sections IV.B of this guidance for reporting changes to an IND and section IV.C of this guidance for reporting changes to a BLA.

When submitting a comparability study report to an IND or BLA, you should include a cover letter or reviewer's guide outlining the submission contents to streamline the FDA review process. In the cover letter or reviewer's guide, you should provide a description of the proposed change, rationale for the proposed change, proposed timeline for implementing the change, and justification for the design of the comparability study. Further, to aid FDA review of your study, we recommend that you provide a short summary of your current relevant manufacturing and clinical experience. When submitting a comparability study report to your IND, for example, it is helpful to describe the stage of clinical development, the number of subjects to whom the pre-change product will be administered, and the number of subjects expected to receive the post-change product. You should provide a summary of relevant previous manufacturing changes and their effect on process consistency and product quality. You should also note any previous changes made to product specifications (for DP, DS, and key intermediates) and provide a description of any CQAs for which an analytical method is still under development.

Comparability study reports should be submitted to CTD sections 3.2.S.2.6 or 3.2.P.2.3 of the BLA or IND, as appropriate. Your comparability study report should evaluate the totality of the comparability data, including historical manufacturing data, to determine if the pre- and post-change products are comparable. We recommend that you summarize the findings of the comparability study and discuss how the data and analyses support your conclusion from the study. You should also include a discussion of any potential limitations of the study. If a product quality attribute does not meet the pre-defined acceptance criterion for comparability, but you still consider the pre- and post-change products to be comparable, you should provide justification and/or additional scientific information to support your conclusion for FDA review.

A. Risk Assessment

Manufacturing changes that can present potential risk to product quality include, but are not limited to, changes to the manufacturing site, manufacturing process, materials, container closure, testing, storage, and shipping conditions. To evaluate whether the proposed manufacturing change may impact product quality, you should conduct a detailed risk assessment as recommended in International Council for Harmonisation (ICH) Q9 dated June 2006 (Ref. 1). The process of evaluating the risk of a manufacturing change for a CGT product is similar to risk evaluation for other types of drugs, and the same tools can generally be applied.

We recognize that risk assessment for changes to the manufacturing of CGT products may be more challenging than for other product types because the effects of manufacturing changes are often difficult to predict for these complex products. For example, manufacturing changes may unexpectedly alter product purity (increase process-related impurities, cellular impurities, aggregates, or particulates), reduce product stability, or change product potency.

Transferring a manufacturing process to a new manufacturing facility is generally considered a major change that may require extensive comparability evaluation in addition to technology transfer, because it may involve changes to the manufacturing

process, shipping, manufacturing equipment, testing equipment, and operators. Performing a thorough risk assessment, including consideration of method equivalence and CPPs, is essential when transferring a manufacturing process to a new facility.

Your risk assessment should consider potential impacts of the change on the manufacturing steps and in-process parameters that are downstream of the manufacturing change, as well as the impact on the product. We recommend that you take a stepwise approach to select all quality attributes and process parameters to be evaluated in a comparability study; first, you should determine which attributes might be affected by the particular change, and then you should assign a score to each attribute based on the probability, severity, and detectability of the risk. The assigned score can be used to determine the overall risk for each attribute. Manufacturing changes that are determined to have a high risk to product quality should be supported by an extensive analytical comparability study, while it may be possible to evaluate low-risk changes using a more focused approach.

You should consider whether your risk assessment is constrained by gaps in product knowledge related to the type of change being proposed. Gaps in knowledge typically raise the level of risk and may necessitate a more extensive comparability study. Please note that relying solely on established release tests and in-process controls is generally insufficient to assess the impact of manufacturing changes. Therefore, we recommend that you consider the potential impact of manufacturing changes on quality attributes that are not routinely evaluated by established release tests and process controls, and consider additional characterization studies as appropriate. Additionally, your risk assessment should evaluate whether more than one analytical method should be used to evaluate a particular attribute. Such an approach could be useful for high-risk attributes, particularly with respect to assessment of potency, as described in section V.B of this guidance. In your risk assessment, you should justify how the selected quality attributes and process parameters can be used to comprehensively evaluate the potential effect of the change on product quality.

Your risk assessment should also inform the statistical approach to comparability. Higher risk attributes typically warrant a more stringent statistical analysis than lower risk attributes. Side-by-side or graphical presentations (such as dot plot) to allow visual comparison, in lieu of statistical analysis, may be sufficient for characterization of attributes at low risk of being impacted by a manufacturing change.

It is important to note that a manufacturing change may affect product stability even if the change has no other effect on product quality or process performance. As discussed in section III.B, you should assess the potential risk to product stability and delivery device compatibility.

Finally, if multiple changes are to be implemented simultaneously, we recommend that you assess the risk of each individual change and the potential cumulative effect of the changes on product quality. It may be possible to evaluate these multiple changes under

a single comparability study. However, if you fail to demonstrate comparability in this single study, it will likely be difficult to identify which of the changes caused an adverse effect on product quality.

B. Analytical Comparability Study Design

It is essential that a comparability study be sufficiently robust to reach a definitive conclusion regarding comparability. Therefore, it is important to carefully select relevant quality attributes, analytical methods, acceptance criteria, and statistical methods. Prior to conducting a comparability study for a CGT product that is licensed or being studied under an IND, we recommend that you submit a detailed study protocol (comparability protocol) and request feedback from the FDA (section VII of this guidance) on the study design and statistical approach. As noted above, the regulations also provide for applicants to submit and seek FDA approval of a comprehensive, prospectively written plan for assessing the effect of a proposed post-approval manufacturing change(s) on product quality (21 CFR 601.12(e) and Ref. 10). These comparability protocols can be submitted in an original BLA or in a prior approval supplement (21 CFR 601.12(e)).

The extent of a comparability study should be driven by the conclusions from the risk assessment, which should inform your selection of: 1) a relevant set of quality attributes to measure the effect of the manufacturing change on product quality, 2) appropriate test methods, and 3) comparability acceptance criteria that are adequate to demonstrate a lack of adverse effect of the manufacturing change on product quality, as discussed later in this section. To adequately evaluate the impact of the manufacturing change on product quality, a comparability study will frequently need to include measurement of attributes that are not routinely used for product release.

We recommend that you consider the following factors when designing a comparability study:

Selection of product lots for the study

A comparability study should generally be performed using lots that have been manufactured at full scale. Experience with smaller scale lots can be used to identify potential risks to product quality and process controls and to aid the design of a comparability study. If it is not feasible to manufacture full-scale lots for the comparability study, you should perform data-driven risk assessment of CPPs, CQAs (including potency), and other relevant product characteristics to justify that scaling down the manufacturing process provides for an adequate evaluation of the effects of the manufacturing change on product quality.

A comparability study may be designed as a comparison of historical pre-change testing data to newer data from post-change lots. Such a study design requires that the analytical test methods are equivalent across product lots to provide interpretable data. If analytical methods have changed over time, retained samples from pre-change lots may need to be

reanalyzed using the current analytical methods. You should avoid biased selection of historical data. Ideally, the only differences between the historical pre-change lots and the post-change lots should be the manufacturing changes that are being evaluated in the comparability study. If the pre-change product was manufactured using multiple processes or facilities, comparability should be demonstrated across the pre-change lots before they are included in a comparability study evaluating a newly proposed change.

For some CGT products, the number of lots may be very small due to, for example, limited manufacturing for rare disease indications, rapid development timelines during clinical studies, or difficulty obtaining cellular starting materials from an adequate number of donors. An insufficient number of lots could compromise statistical power and be insufficient to demonstrate comparability, particularly if there is high lot-to-lot variability, as discussed later in section V.E of this guidance.

Special considerations for products derived from a variable cellular starting material

Cell-based products where each product lot is derived from a different donor often have product characteristics with very wide ranges due to the inherent variability of the cellular source materials. The number of lots that might be used for such products to perform a statistically valid comparability study could be quite large, or even unfeasible in some cases. However, there are study design considerations that may be useful for decreasing the number of lots included for the comparability study. We recommend that you use a split-source study design, whenever possible. A split-source design limits the impact of cellular variability by splitting individual cellular source materials into two equal portions. One portion of each source material is then subjected to the pre-change manufacturing conditions, and the other portion is subjected to the post-change manufacturing conditions. As described in *Comparability acceptance criteria* later in this section, the results obtained from the split runs should meet the in-process and release specifications and be representative of relevant historical data. Paired difference analysis is typically performed. If a split-source study design is not possible, and it is already known that CQAs for a specific product and clinical indication can vary within a wide range without any adverse impact on product quality, then accordingly, it may be acceptable to set wide acceptance criteria for comparability studies, which would reduce the number of lots for the study.

When manufacturing cell-based product lots for use in comparability studies, we recommend using the same type of cellular source material that would normally be used to manufacture your product. If this is not feasible due to limited source material or other justified reasons, it may be appropriate to use small-scale manufacturing runs or alternative cellular source material. For example, if patient cells are not available, using cells from healthy donors could be considered. If the number of cells from a single donor is not sufficient to manufacture a large enough lot for the comparability study, it may be possible to use cells pooled from multiple cell collections from the same or multiple donors. In your comparability study report, you should explain why the alternative cellular source material is relevant, including: 1) whether there are differences in process

parameters that might occur when using the alternative material, and 2) whether product quality can effectively be evaluated using the alternative source material. For example, for a product consisting of genetically modified cells, healthy donor cells may not be an appropriate alternative for patient cells, if transduction efficiency is different. Additionally, in the case of product intended to treat a genetic disease, the lack of the genetic defect in healthy donor cells may interfere with measurement of potency.

Special consideration for vectors used for ex vivo cell modification

GT vectors[8] used for ex vivo cell modification must be manufactured in compliance with current good manufacturing practices (cGMP) under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as appropriate for the stage of development (Ref. 11). This should include effective quality risk management and change control activities (Ref. 1). Changes to the manufacturing of GT vectors should be carefully evaluated not only for risks to the quality of the vector and the performance of the vector manufacturing process, but also for risks to the quality and manufacturing process performance for the ex vivo gene-modified cells.

Analytical comparability of the vector should typically be evaluated using the vector release assays (including an assay that measures the biological activity of the vector), as well as any relevant characterization assays, if appropriate. In addition, the effect of the vector manufacturing change on the quality of the ex vivo gene-modified cells (DS and/or DP) should be evaluated in an analytical comparability study using an adequate number of vector, DS and/or DP lots.

The number of vector lots available for comparability studies may be small in situations where each lot of vector is sufficient for the manufacture of large numbers of DP lots. In such cases, it may be appropriate for comparability studies to include vector lots that were manufactured during process development or engineering runs, if manufacture of these vector lots is similar to the manufacture of the vector lots used to manufacture DP for clinical studies. Your risk management strategy should ensure that sufficient vector lots will be available for future comparability studies because difficulties in implementing vector manufacturing changes can cause delays in clinical studies or shortages in licensed products.

Assessment of potency

The biological activity of CGT products can be highly sensitive to manufacturing changes. Therefore, we recommend that a quantitative potency assay (Ref. 12) be included when performing analytical comparability studies. You may wish to consider using several analytical methods to evaluate potency if the routinely used analytical

[8] For the purposes of this guidance, a "vector" is defined as a vehicle consisting of, or derived from, biological material that is designed to deliver genetic material. Examples include plasmids, viruses, and bacteria that have been modified to transfer genetic material. (Long Term Follow-Up After Administration of Human Gene Therapy Products; Guidance for Industry; January 2020, at 29, available at https://www.fda.gov/media/113768/download).

method is imprecise or unable to assess all aspects of the product's MOA that might be affected by the manufacturing change. For some products, animal models may be used to supplement a relevant quantitative assay(s) to demonstrate that the product has the desired biological effect and to provide supportive evidence for comparable biological activity of the pre-change and post-change product.

CGT products may have multifaceted mechanisms of action due to, for example, product complexity, the presence of multiple active ingredients, and complex PK/PD profiles. Assays that measure relevant biological activities of CGT products are challenging to develop, and these assays are often inherently variable. These difficulties can delay establishing a potency assay and release acceptance criteria until later-stage clinical studies because the relationship between the product's MOA and safety and effectiveness may not be well understood. Yet, exclusion of potency analysis from a comparability evaluation compromises the conclusions drawn from a comparability study. To avoid this situation, we recommend that samples be retained from all lots to facilitate future analysis of potency to support comparability.

When establishing an acceptance criterion for potency in comparability studies, you should consider that product quality may be adversely affected not only by a significant decrease in potency, but also if there is a significant increase in potency. A manufacturing change that significantly increases potency, even if intentional, may raise safety concerns. In such cases, if you are unable to demonstrate that the change will not adversely affect safety, the post-change product will not be considered comparable to the pre-change product.

Comparability acceptance criteria

It is not necessary for the measurements of pre- and post-change CQAs to be identical to reach a conclusion of comparability if there is evidence demonstrating that there is no adverse impact of the change on product quality. A comparability acceptance criterion should be defined prior to initiating the comparability study for each CQA determined, through risk assessment, to have a potential to be impacted by the change. For quantitative attributes, a comparability acceptance criterion may be defined as the largest acceptable difference between the pre-change and post-change attribute (an equivalence margin) or as an acceptable range for the post-change attribute (a quality range). In addition to meeting the comparability acceptance criteria, lots used in comparability studies should also meet the established in-process and release acceptance criteria, and, unless otherwise justified, the results should be representative of data (e.g., mean, standard deviations, median) from relevant pre-change historical lots.

An equivalence approach is often appropriate for evaluating comparability of CQAs when it is important to directly compare the pre- and post-change values and determine whether they are sufficiently similar. For normally distributed data, the equivalence margin should be defined as the maximum acceptable difference in population means.

Exceeding this margin would be interpreted as an adverse effect of the post-change manufacturing process on product quality.

A quality range approach evaluates whether the post-change quality results fall within a defined range. This range should often be narrower than the release acceptance criteria for those same quality attributes. The quality range approach can potentially be used for attributes with various risk levels, but higher-risk attributes should be evaluated using the more rigorous equivalence approach. The number of post-change lots sufficient for a comparability study when using the quality range approach will depend on the totality of evidence supporting the lack of adverse effect of the change on product quality. For example, if additional relevant data from other studies (such as impurity clearance studies or other process characterization studies) provide evidence that the manufacturing change does not have an adverse effect on a particular quality attribute, then this may justify the use of a smaller number of post-change lots in the comparability study. Otherwise, you should ensure that the comparability study is designed with sufficient power by calculating the number of post-change lots needed to demonstrate with high confidence that an appropriate proportion of future lots will fall within the quality range.

Regardless of the approach used, comparability acceptance criteria should ideally be based on understanding the potential effect of the attribute on the safety and effectiveness of the product, and not based solely on statistical analysis of historical data from the pre-change product. If there is clinical or manufacturing experience supporting the differences in CQAs that negatively and/or positively impact product quality, you should use this information to select appropriate quality ranges or equivalence margins for your comparability study. If instead you are using statistical analysis of historical data to define comparability acceptance criteria (e.g., based on standard deviation), you should justify how your statistical-based acceptance criteria are adequate to ensure the safety and effectiveness of the post-change product (i.e., justify how your statistical-based parameter is relevant to a biologically meaningful difference).

Please refer to section V.E of this guidance regarding statistical analysis of comparability study results.

C. Analytical Methods

Interpretation of comparability test results depends on the suitability of the analytical methods used. For example, using an imprecise, insensitive, or inconsistent method in a comparability study can invalidate the conclusions of the study. We recommend that you provide a tabular listing of the analytical methods and testing sites used in the comparability study. If method descriptions, qualification studies, or validation studies are provided elsewhere in your application, you may refer to them. For comparability studies of investigational products, all release assays used to demonstrate comparability should be qualified or validated, depending on the phase of clinical study. Assays used for extended characterization do not necessarily need to be qualified, but they should be scientifically sound and fit for their intended use, be sufficiently precise to detect

meaningful differences in product quality, and provide results that are reliable. If not described elsewhere, you should describe sample acquisition (e.g., process step, sample volume, storage temperature) and justify any differences in acquiring samples from the pre-change and post-change manufacturing processes.

FDA has issued guidance providing general guiding principles to assist applicants with assay validation (Refs. 13, 14). Some of the challenges with validation of assays for CGT products are highlighted below:

Analytical Method Precision

Small changes in an attribute can sometimes have a profound impact on the quality of CGT products. However, measuring such small changes can be challenging when the analytical methods are not precise. Therefore, it is especially important that the analytical methods used to assess the effect of manufacturing changes on product quality and process control are sufficiently precise. For example, if a 5% change in a particular cell marker represents a meaningful difference in product quality, then a flow cytometry assay with an intermediate precision of 20% coefficient of variation would not be adequate for evaluating whether there is a meaningful difference in that attribute between the pre-change and post-change products.

Consistent Method Performance

Analytical methods are often changed, added, or transferred to a new facility over the course of a CGT product lifecycle because of advancing technology and/or increasing understanding of MOA. To provide the most readily interpretable data for a comparability study, we recommend that you perform side-by-side testing[9] of pre-change and post-change product attributes or analyze all samples using the same analytical method performed at the same testing facility. Reference material should also be used, if available.

At all stages of the product lifecycle, when changing an assay or transferring an assay to a new testing facility, you should perform a risk assessment for the assay change to determine if there is a potential impact on evaluation of product quality, including evaluations conducted in comparability studies. For example, a change to an ELISA kit from a manual to an automated method could result in meaningful differences in sensitivity or precision. The equivalence of the old and new assays should be evaluated by testing identical samples with each assay. Similarly, when using multiple facilities to perform the same assay, a method transfer study should be performed to ensure reproducibility, and the assays should include identical samples or common reference materials to ensure consistent assay readouts. Additional assay qualification or validation may also be warranted after transferring an assay to a new facility (Ref. 13).

[9] In this guidance, side-by-side testing, also often referred to as "head-to-head" testing, means testing of the pre- and post-change samples in the same experiment.

D. Results

For each product attribute and process parameter assessed, we recommend that the results for each lot and the corresponding lot numbers be provided in a tabular format, together with tables that list summary statistics for the data alongside the predefined study acceptance criteria. When appropriate, we recommend that you also display data in a graphical format. We recommend that you describe and analyze any differences in the study data between the pre-change and post-change products. Any deviations from pre-established procedures should be described and justified.

E. Statistics

When designing comparability studies for CGT products, appropriate statistical methods should be used to determine if the pre- and post-change products are comparable. The statistical methods should be defined in the comparability protocol before executing the comparability study. Selection of a statistical approach to demonstrate comparability of pre- and post-change products can be challenging when there are only a limited number of samples, when quality attributes are highly variable, or when the data is not normally distributed.

We recommend that you consult with a statistician before discussing the study design and statistical approach with FDA. In general, there could be multiple appropriate statistical methods that may be used to evaluate whether data from the post-change product are within predetermined acceptable limits. To avoid errors in the design and analysis of comparability studies, a careful consideration of fundamental statistical concepts is important. For example:

- Some statistical methods may be inappropriate for a given comparison due to invalid assumptions, a need for a very large number of samples, high variability in sample data, or limited information about the population distribution. For example, parametric tests that assume a normal population distribution should not be used if the data are not normally distributed. When justified, data transformation could be useful to meet the assumption of data normality. You should describe the statistical method, justify the assumptions of the statistical approach, justify the acceptance criteria selected, and discuss limitations. Different statistical methods may be used within the same study to analyze different CQAs, if the CQAs differ in their underlying distribution (e.g., normal vs. binomial).

- The variability of a statistic is determined by the spread of its sampling distribution. Having only a small number of lots can lead to greater sampling variability, which can significantly reduce the statistical power. Therefore, the appropriate number of lots should be considered early, as the lack of sufficient numbers of samples may impede comparability analysis and implementation of

manufacturing changes, especially during late-stage development and after licensure.

- As described in section V.C of this guidance, it can be difficult to evaluate the comparability of an attribute when using an assay that has poor precision. In such situations, an alternative to improving the precision of the assay would be to reduce measurement uncertainty by performing the assay multiple times independently for each lot and reporting the mean value. Such an approach will improve the statistical power of the comparability analysis for that attribute. It is important to note that the mean of the assay results for each lot should be treated as a single data point when analyzing comparability; it is inappropriate to treat each individual assay result as an independent data point in the comparability analysis.

- For studies that compare two cellular manufacturing processes using split-donor starting material, the product data from each donor are paired. In such cases, you should select a statistical test suitable for analysis of the difference between paired data, rather than a test that assumes an independent data structure.

- The absence of a statistically significant difference between the pre- and post-change products (e.g., p-value > 0.05) does not demonstrate comparability. For example, using a two-sample t-test is not appropriate for comparability claims when the null hypothesis is that the means of CQAs of pre- and post-change products are equal, and the alternative hypothesis is that they are different. In other words, failing to reject this null hypothesis is not the same as showing equivalence.

- To evaluate equivalence, you may consider calculating an appropriate confidence interval for the difference between the pre- and post-change data, and conclude equivalence if this confidence interval is within the equivalence margin. When the CQA of interest is a mean value, you may consider using the 'Two-One-Sided Tests procedure' (TOST) or other appropriate statistical method to establish comparability. For some attributes (e.g., impurity, viability), it may be possible to demonstrate that the manufacturing change has no adverse effect on product quality using a one-sided statistical comparison, such as non-inferiority testing or other appropriate method.

- If the lots selected for the comparability study are not representative of your typical manufacturing process, the corresponding results will have limited meaningful interpretation, regardless of the particular statistical methodology applied. You should justify your selection of comparability lots and (if applicable) the cellular source material used to produce those lots.

VI. SPECIAL CONSIDERATIONS FOR TISSUE-ENGINEERED MEDICAL PRODUCTS

Tissue-engineered medical products (TEMPs)[10] commonly incorporate viable cells and scaffolds, with cells either seeded onto the scaffold's surface or embedded within the scaffold. Oftentimes, TEMPs are intended to mimic the in vivo cellular microenvironment. Although manufacturers are gaining experience with these products, there is generally still limited understanding regarding product quality, interactions between the cells and scaffolds in vitro (e.g., maturation), interactions of the DP with the host environment (e.g., remodeling), and sensitivity of TEMPs to manufacturing changes. For these reasons, manufacturing changes to TEMPs pose additional unique challenges, as changes may impact the cells, the scaffold and/or the combined cell-scaffold product in ways that are not readily anticipated or detectable based on current measurement technologies.

We recommend that you conduct a thorough risk assessment that considers the potential effects of the change on each component (e.g., cells, scaffold) and on the final cell-scaffold construct. The risk assessment should determine whether a comparability study is necessary to evaluate any potential impact of the change on product quality and whether this comparability study should evaluate the cells, scaffold, cell-scaffold intermediate(s), and/or the cell-scaffold DP.

When assessing manufacturing changes to TEMPs, you should consider scaffold characteristics, including but not limited to the scaffold source (e.g., natural or synthetic), density, shape, mechanical and physicochemical properties, interactions with cytokines and growth factors, and capacity for inducing cell signaling pathways (e.g., via mechanotransduction). Similarly, you should consider relevant cell characteristics, including but not limited to cell morphology, density, aggregation, growth, viability, and the relevant biological function(s) for the proposed specific indication. Both manufacturing changes introduced before combining the cells and scaffold and manufacturing changes introduced after combining the cells and scaffold (e.g., changes to the culture conditions, packaging, storage or shipping) may have a significant impact on the overall biological activity and/or performance of the TEMP. Therefore, comparability studies for TEMPs should often include evaluation of the effect on DP quality even when manufacturing changes are made only to the scaffold or to the cells prior to combining these two components.

Furthermore, certain changes may have a significant impact on how the DP behaves after administration in terms of safety and performance, and therefore on product quality. You should, therefore, assess the potential impact of the change on product quality post-administration (e.g., remodeling, degradation). Depending on the outcome of the risk assessment, you may need to evaluate the performance of the TEMP in a physiologically relevant environment to demonstrate comparability. This may involve additional nonclinical studies and/or clinical studies.

[10] For the purposes of this guidance, TEMPs are limited to products that consist of living cells combined with a scaffold or substrate regulated under section 351 of the PHS Act.

In general, the need to maintain the integrity and structure of TEMPs may make it difficult to acquire samples for testing and retention. In addition, products that are manufactured in a closed system, such as a bioreactor, could pose additional practical challenges to acquiring samples. Further, the seeding and growth of cells on the scaffold may not be uniform, making it difficult to obtain representative samples. Therefore, it is important to consider these unique challenges in the context of comparability study design, if relevant, surrogate[11] TEMPs could be manufactured in parallel during clinical lot production or manufactured during specific production for a comparability study. Such surrogate TEMPs could be particularly useful when destructive sampling is used for testing additional CQAs that are not routinely evaluated for lot release. An alternate approach could include sampling of the incubation media instead of the product itself, when the incubation media can be considered a representative sample of the product for the specific CQAs.

VII. COMMUNICATION WITH FDA

We recommend that sponsors and applicants of CGT products prospectively discuss proposed significant manufacturing changes with FDA's Center for Biologics Evaluation and Research (CBER), particularly when such manufacturing changes would be implemented during later stages of the product lifecycle. Communication with the FDA can be sought either by requesting FDA comment on relevant information submitted in an IND amendment or BLA product correspondence, or through a formal meeting request (Ref. 15). The type of meeting used for such discussions depends on the stage of the product lifecycle and the issues to be considered.

[11] For the purposes of this guidance, "surrogate" refers to an additional unit of the drug product that is manufactured in parallel to the clinical product for characterization purposes, which may include destructive testing.

VIII. REFERENCES

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*When finalized, this guidance will represent FDA's current thinking on this topic.