Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to sponsors interested in studying multiple versions of a cellular or gene therapy[1] product in an early-phase clinical trial[2] for a single disease. Sponsors have expressed interest in gathering preliminary evidence of safety and activity using multiple versions of a cellular or gene therapy product in a single clinical trial. Although multiple versions of a product can be studied together in a single clinical trial, each version is a distinct product that is generally submitted to FDA in a separate investigational new drug application (IND). The objective of these early-phase clinical studies is to guide which version(s) of the product to pursue for further development in later-phase studies. Thus, these studies are not intended to provide primary evidence of effectiveness to support a marketing application and generally are not adequately powered to demonstrate a statistically significant difference in efficacy between the study arms. In this guidance, we, FDA, provide recommendations for studies that evaluate multiple versions of a cellular or gene therapy product, including how to organize and structure the INDs, submit new information, and report adverse events.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations,

[1] This guidance does not apply to vaccines intended to prevent infectious diseases, bacteriophage products, live biotherapeutic products, fecal microbiota for transplantation (FMT) products and allergenic products.

[2] This guidance applies only to early-phase clinical trials of cellular or gene therapy products. Later-phase clinical trials raise different and additional considerations, including those pertaining to subject selection, safety monitoring, and effectiveness evaluation. For additional information on early-phase clinical trials of cellular and gene therapy products, see Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry, June 2015, https://www.fda.gov/media/106369/download.

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

II. BACKGROUND

Clinical trials that study multiple products in parallel for a particular disease or condition under a master protocol are commonly referred to as "umbrella" trials. In contrast to traditional trial designs where only one product is evaluated in a single clinical trial, umbrella trials use a single-trial infrastructure, design, and master protocol to simultaneously evaluate multiple products for a specific disease or condition, allowing for more efficient product development.

This guidance focuses on a certain type of umbrella trial, where the products are multiple versions of a cellular or gene therapy product being studied in a single disease, and the differences between the product versions result in individual products that are generally submitted in separate INDs that are cross-referenced among each other. For example, a sponsor investigating an autologous chimeric antigen receptor (CAR) T cell product may wish to also investigate a different version of the product (e.g., an altered CAR protein domain to increase CAR activity, or a new cell source such as an allogeneic donor). In this situation, the different product versions are considered individual investigational drugs, but they could be simultaneously evaluated within the same overall trial, as described further in this guidance. Refer to the Appendix for additional examples of versions of a cellular or gene therapy product that would be within the scope of this guidance.

The potential benefits of this type of umbrella trial include flexibility and efficiency in product development. Instead of an iterative approach to clinical studies, multiple versions of a cellular or gene therapy product can be studied in parallel, which may expedite early clinical development by expeditiously identifying alternative versions of a product that may be safer or more effective. Such comparisons can be facilitated by randomization between the study arms, if feasible. Additionally, this trial design may facilitate sharing of the control group, potentially facilitating investigator participation and subject enrollment, and may simplify study management, relative to conducting a separate clinical trial for each product version.

III. SCOPE

The scope of this guidance is limited to early-phase studies that assess the safety and the preliminary activity of multiple versions of a cellular or gene therapy product in a single disease. We recommend that sponsors contact the Center for Biologics Evaluations and Research (CBER) if they wish to apply this framework to other types of products.

This guidance addresses studies where the IND sponsor is responsible for manufacturing all versions of the cellular or gene therapy product (either directly or through a contract manufacturer) and the IND sponsor is able to provide the required chemistry, manufacturing, and controls (CMC) and pharmacology/toxicology (P/T) information for those products either in the

IND submissions or through cross-reference. Situations where the IND sponsor does not have complete access to proprietary information for those products being studied raise additional considerations beyond those described in this guidance.

This guidance does not address sponsors conducting studies that are outside the scope of this guidance (e.g., a trial designed to evaluate a single cell or gene therapy product in different populations, otherwise known as a "basket" trial). If sponsors are interested in conducting a study that is outside the scope of this guidance, we recommend the sponsor request a pre-IND meeting with the Office of Tissues and Advanced Therapies (OTAT), CBER, to discuss their proposed clinical trial design.

IV. SUBMISSION OF INFORMATION TO INDS

As noted in sections I and II of this guidance, the purpose of this guidance is to recommend a more efficient and flexible model to evaluate versions of an investigational product that would otherwise be evaluated in separate clinical studies. For a single clinical study of different versions of an investigational product where each version is submitted in a separate IND, it may be challenging to determine how to structure and organize the INDs, and how to submit changes or new information as the study progresses. The framework described here is intended to provide clarity on these topics and, as feasible, to minimize submission of the same information to multiple INDs by facilitating cross-referencing to shared information in the INDs. Sponsors may discuss their specific clinical study and planned submission approach with OTAT, CBER prior to submitting an IND (e.g., by requesting a pre-IND meeting[3]).

A. Overview

- For purposes of the framework outlined in this guidance, we refer to INDs either as "Primary" or "Secondary". The purpose of this nomenclature is to distinguish which INDs will include clinical information about the umbrella trial (Primary INDs) and which INDs will not include clinical information about the umbrella trial (Secondary INDs). For example, an IND amendment that contains only clinical information about the umbrella trial (e.g., no CMC or P/T information) would only need to be submitted to the Primary IND.

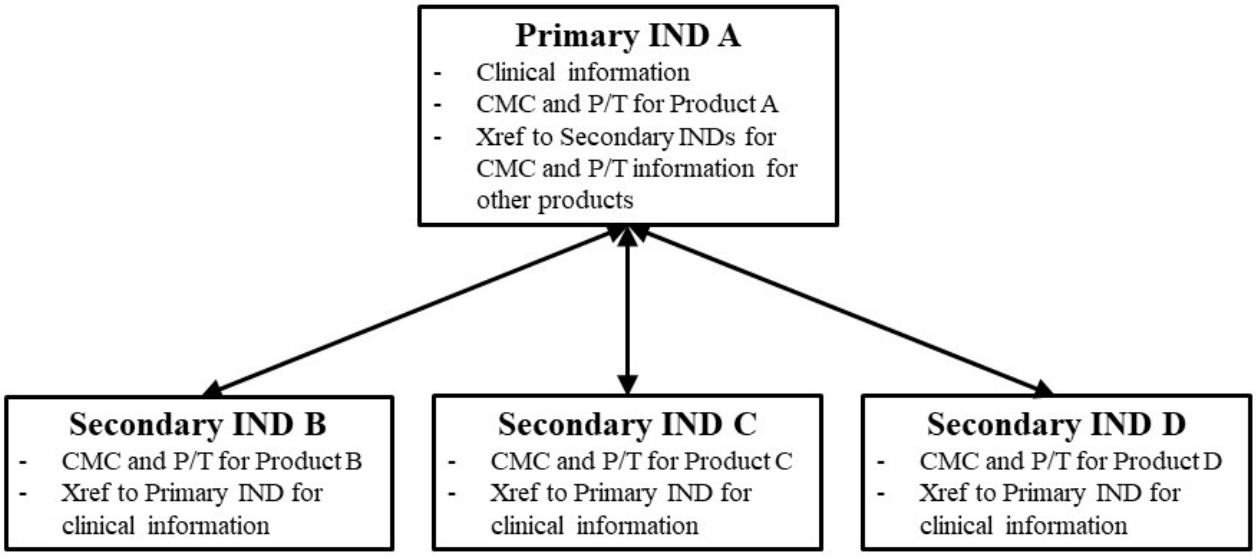
- For a clinical study with two different versions of the investigational product (Product A and Product B), we recommend that the sponsor submit two separate INDs, IND A and IND B. One of the INDs, IND A, will be considered the "Primary" IND, and should include CMC and P/T information for Product A. IND B will be considered a "Secondary" IND, and will include CMC and P/T information for Product B. Complete clinical information for the umbrella trial, including the clinical protocol and supporting documents (e.g., investigator brochure, informed consent form, Form

[3] See Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, Draft Guidance for Industry, December 2017, https://www.fda.gov/media/109951/download. When finalized, this guidance will represent FDA's current thinking on this topic.

FDA 1572), should also be submitted to the Primary IND A. This framework can be further extended to additional versions of the product; if the clinical study includes three different products (Products A, B, and C), then the CMC and P/T information for Product C should be provided in Secondary IND C.

- Sponsors should consult FDA's *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, February 2020*, for information regarding electronic common technical document (eCTD) format for IND submissions.

Figure 1: Schematic Representation of the Primary and Secondary IND Framework[4]



- For the Primary IND (including any amendments), we recommend that the cover letter clearly state that the IND is a Primary IND and specify the Secondary IND number(s). For any Secondary IND (including any amendments), we recommend that the cover letter clearly state that the IND is a Secondary IND and specify the Primary IND number. We recommend that sponsors request pre-assigned IND numbers prior to submitting the INDs, so that the cover letter and cross-references for each IND can include the IND numbers for the other INDs that support the study.

- For sponsors adopting the approach described in this guidance, the Primary IND should cross-reference the Secondary IND(s) for the CMC and P/T information contained in those INDs. The Secondary IND(s) should cross-reference the Primary IND for clinical information.

[4] In Figure 1, "Xref" is an abbreviation for cross-reference.

- In some cases, sponsors may decide to develop additional versions of a product after an IND has already been submitted. If the sponsor wishes to evaluate the original and additional versions of a product together in an umbrella trial, we recommend that sponsors submit an amendment to the existing IND specifying that it is a Primary IND and follow the steps in the section IV.B of this guidance to submit Secondary IND(s) and add arm(s) to the study.

B. Adding Arms to the Study

- If the arm to be added includes a new version of the investigational cellular or gene therapy product, (e.g., Product C), we recommend that the sponsor submit:

  - IND C with CMC and P/T information for Product C. IND C will be considered a Secondary IND. We recommend that the cover letter for a Secondary IND clearly state that the IND is a Secondary IND and specify the Primary IND number. The Secondary IND should cross-reference the Primary IND for clinical information.

  - An amendment to IND A with the updated clinical protocol, which now includes an arm for Product C. We recommend that the cover letter for IND A clearly state that the IND is a Primary IND and specify the Secondary IND number(s), including IND C. We recommend that the Primary IND also be updated to include a cross-reference to the Secondary IND for CMC and P/T information related to Product C. It should be noted that the new Secondary IND C cannot go into effect until 30 days after FDA receives the new IND (21 CFR 312.40(b)(1)), unless FDA provides earlier notification that the clinical investigations in the IND may begin (21 CFR 312.40(b)(2). Administration of Product C cannot begin until IND C goes into effect and IRB approval of the modified protocol has been granted (21 CFR 56.103).

- If the arm to be added does not include a new version of the investigational cellular or gene therapy (e.g., a new arm that will study Product B in combination with a marketed product, or a new arm that will study investigational Products A and B together), then we recommend that the sponsor submit:

  - An amendment to the Primary IND with the updated clinical protocol (i.e., with the new arm);

  - Any additional P/T information supporting the new arm, if applicable, submitted to the relevant INDs.

C. Submitting Other Types of Changes or New Information

- For revisions to the umbrella trial clinical protocol that do not add a new arm or for other types of new clinical information, the sponsor should submit the revised

protocol or new clinical information to the Primary IND. The sponsor does not need to submit any information to the Secondary INDs.

- If the sponsor would like to make changes to the CMC information for Product B, the sponsor should submit an amendment to IND B that describes the CMC changes for Product B. The sponsor does not need to submit any information to the Primary IND or other Secondary INDs.

- For new CMC or P/T information (e.g., new P/T study report): if the new information is specific to one product (e.g., Product B), then that information should be submitted to IND B only. If the new information is for multiple products (e.g., Products A and B), then the new information should be submitted to INDs A and B. For new P/T information, the updated investigator brochure should be submitted to the Primary IND.

D. Clinical Holds and Responses to Hold

- In the event FDA issues an order placing the entire study on clinical hold, then all Primary and Secondary INDs will be placed on hold (or partial hold, if appropriate). 21 CFR 312.42(a).

- If only one arm (e.g., arm studying Product B) will be placed on hold, then the Primary IND will be placed on partial hold and the relevant Secondary IND will be placed on hold (or partial hold, if appropriate).

- To respond to a clinical hold, the sponsor will need to submit a response to each IND that was placed on hold. However, detailed information responding to each hold comment does not need to be submitted to multiple INDs. For example, if the Primary IND was placed on partial hold due to CMC concerns with a product in a Secondary IND, the sponsor should submit the CMC information responding to the hold comments to the Secondary IND. The response to hold for the Primary IND can refer to the Secondary IND for detailed information.

E. Reporting

- IND safety reporting must be performed in accordance with 21 CFR 312.32.[5] The sponsor must submit safety reports for an investigational product to all of the sponsor's INDs that are relevant to that product. At a minimum, safety reports must be submitted to both the Primary IND and any Secondary IND that contains the CMC and P/T information for that product. In cases where a safety report for one product is relevant to the safety of multiple related products, the safety report must be submitted to all of the relevant INDs (21 CFR 312.32(c)).

[5] See Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012, https://www.fda.gov/media/79394/download.

- Sponsors must submit Annual Reports to each IND (21 CFR 312.33).[6] If desired, the sponsor can submit an integrated Annual Report that includes the clinical information and the CMC and P/T information for all products to the Primary IND, and submit that same Annual Report to each of the Secondary INDs.

F. Completion of Study or Arm(s)

- The Primary IND (e.g., IND A) includes CMC and P/T information for Product A along with the clinical information for the umbrella trial. If the sponsor would like to discontinue studying Product A, we do not recommend that the sponsor withdraw Primary IND A because it contains the relevant clinical information. Instead, we recommend that the sponsor submit an updated protocol to Primary IND A that no longer includes the arm with Product A.

- If the Primary IND A is withdrawn for any reason, but the sponsor intends to continue studying products other than Product A under the clinical protocol, then the sponsor would need to do the following:

  - Designate another IND (e.g., IND B or IND C) as the new Primary IND;

  - Submit complete, up-to-date clinical information to the new Primary IND; and

  - Update all cross-references so that the Secondary INDs now cross-reference the new Primary IND, and the new Primary IND cross-references the Secondary INDs. We recommend that the cover letters for each IND amendment clearly specify the new Primary IND and Secondary INDs.

- If the sponsor decides to study one of the products (e.g., Product C) in a later-phase study (e.g., a Phase 3 study), then the sponsor should submit the Phase 3 protocol to the IND that contains the CMC and P/T information for Product C (i.e., IND C).

V. ALTERNATIVE APPROACHES

There may be alternative approaches to structuring and organizing the INDs for the studies of multiple versions of an investigational product as described in this guidance. For example, sponsors may choose to submit a stand-alone IND that includes only clinical information, with CMC and P/T information from other INDs incorporated by cross-reference. In this case, the Primary IND would still include the clinical information for the umbrella trial (including the clinical protocol), but the Primary IND would cross-reference the Secondary INDs for CMC and P/T information for all the products studied under the umbrella trial protocol. We recommend

[6] See Guidance for Industry: E2F Development Safety Update Report, August 2011, https://www.fda.gov/media/71255/download.

278 that sponsors considering alternative approaches contact OTAT, CBER to discuss the proposed
279 IND organization and clinical study.
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APPENDIX: CLARIFICATION ON "VERSIONS OF A CELLULAR OR GENE THERAPY PRODUCT"

A. Changes that Result in "Versions of a Cellular or Gene Therapy Product" (i.e., within the scope of this guidance)

Examples of changes that would result in "versions of a cellular or gene therapy product," where the different versions are individual products that would generally be submitted to separate INDs, may include:

- Changing a cellular product from bulk tumor-infiltrating lymphocytes (TILs) to purified CD8+ TILs.
- Changing from dendritic cells (DCs) pulsed with a recombinant tumor antigen to DCs pulsed with immunodominant peptides from the same antigen.
- Using different types of antigen presenting cells (e.g., irradiated B-lymphoblastoid cell lines vs. DCs) to manufacture a CD4+ T cell product.
- Replacing the CAR transgene of a CAR T cell product with a new CAR transgene, as long as both CAR T cell products target the same disease.
- Modifying a CAR T cell product by adding a second transgene that expresses a costimulatory protein.
- Modifying a gene therapy vector to express the same transgene with a different promoter, enhancer or other control element.

B. Changes that Do Not Result in "Versions of a Cellular or Gene Therapy Product" (i.e., not within the scope of this guidance)

Changes to the manufacturing process may occur as product development proceeds. In many cases, these changes can be submitted as an amendment to the existing IND. These changes are often made in the course of manufacturing process improvement and optimization and/or preparation for commercial manufacturing and are generally not expected to impact product safety or effectiveness. Products with these types of manufacturing process changes are not typically studied in an umbrella trial. Examples may include:

- Changing from serum-containing media to serum-free media during cell expansion.
- Changing from adherent to suspension cell culture.
- Scaling up or scaling out the manufacturing process (e.g., increasing the capacity and/or number of cell culture containers).
- Adding a new manufacturing site.

C. Unrelated Products

Unrelated products (e.g., TILs versus CAR T cells) are not "versions of a cellular or gene therapy product," and umbrella trials that include unrelated products are not within the scope of this guidance. These trials may be considered on a case-by-case basis; we recommend that sponsors contact OTAT, CBER to discuss the appropriate regulatory path for such a proposed trial.