Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations

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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
Office of Orphan Product Development
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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance provides FDA's current thinking on determining sameness of human gene therapy[1] products under FDA's orphan drug regulations for the purpose of orphan-drug designation and orphan-drug exclusivity. This guidance is intended to assist stakeholders, including industry and academic sponsors who seek orphan-drug designation and orphan-drug exclusivity, in the development of gene therapies for rare diseases. This guidance focuses specifically on factors that FDA generally intends to consider when determining sameness for gene therapy products and does not address sameness determinations for other types of products. This guidance finalizes the draft guidance of the same title dated January 2020.

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[1] 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 (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells. Gene therapy products meet the definition of "biological product" in section 351(i) of the Public Health Service 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)), available at https://www.fda.gov/media/76647/download. For additional information regarding human gene therapies, please see, e.g., Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); Guidance for Industry, January 2020, available at https://www.fda.gov/media/113760/download.

II. BACKGROUND

As with other drugs,[2] a human gene therapy product may qualify for orphan-drug designation[3] if it is intended for the treatment of a rare disease or condition[4] and the sponsor provides sufficient scientific rationale to establish a medically plausible basis for expecting the drug to be effective in the rare disease.[5] Orphan-drug designation may provide the sponsor of a gene therapy product with financial incentives, including tax credits for qualified clinical testing and waiver of the human drug application fee for a marketing application,[6] and consideration for seven years of orphan-drug exclusivity, as long as the eligibility criteria are met.[7]

In order to be considered for orphan-drug designation, a sponsor must submit a request for designation for its drug to the Office of Orphan Products Development (OOPD) following the procedures described in 21 CFR 316.20. Sponsors can apply for orphan-drug designation at any point prior to submission of a marketing application. If sponsors have questions regarding orphan-drug designation, we recommend contacting OOPD.[8] If sponsors have questions related to specific gene therapy product development programs, we recommend contacting the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research (e.g., through an IND amendment requesting advice or through a formal meeting request).[9]

If a sponsor requests orphan-drug designation for a drug that is the same drug[10] as a drug already approved for the same use or indication, the sponsor is required to provide a plausible hypothesis that its drug is clinically superior to the previously approved drug.[11] When FDA grants marketing approval for a drug for a use or indication within the rare disease or condition for which the drug received orphan-drug designation, FDA will determine if the drug is eligible for orphan-drug exclusivity.[12] If FDA previously approved the same drug for the same use or indication, to be eligible for orphan-drug exclusivity, the sponsor of the new drug will need to demonstrate that its drug is clinically superior to all previously approved same drugs for the

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[2] For the purposes of this guidance, the term *drug* refers to both human drug and biological products.
[3] A public database of orphan-drug designations and approvals is available at https://www.accessdata.fda.gov/scripts/opdlisting/oopd/.
[4] Section 526 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 360bb, generally defines a *rare disease or condition* as any disease or condition that affects fewer than 200,000 persons in the United States.
[5] See section 526 of the FD&C Act, 21 U.S.C. 360bb; see also 21 CFR Part 316, Subpart C.
[6] For more information regarding the fee exemption, please see section V of Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products; Guidance for Industry, October 2019, available at https://www.fda.gov/media/131797/download.
[7] See section 527 of the FD&C Act, 21 U.S.C. 360cc; see also 21 CFR 316.3(b)(12) and 21 CFR Part 316, Subpart D.
[8] See Meetings with the Office of Orphan Products Development: Guidance for Industry, Researchers, Patient Groups, and Food and Drug Administration Staff, July 2015, available at https://www.fda.gov/media/111946/download.
[9] For more information regarding recommendations on formal meetings between FDA and sponsors or applicants relating to the development and review of biological products, please see Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, Draft Guidance for Industry, December 2017, available at https://www.fda.gov/media/109951/download. When finalized, this guidance will represent FDA's current thinking on this topic.
[10] 21 CFR 316.3(b)(14).
[11] 21 CFR 316.20(a).
[12] 21 CFR 316.31.

same use or indication.[13] Consideration of clinical superiority is based on greater efficacy, greater safety, or a major contribution to patient care.[14]

The orphan drug regulations define "same drug" for a drug composed of large molecules (macromolecules) as a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use or indication as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug.[15] The regulations further describe the criteria to be applied for protein drugs, polysaccharide drugs, polynucleotide drugs, and closely related, complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines.[16] However, the regulations do not elaborate on how the "same drug" definition applies specifically to gene therapy products for the purposes of orphan-drug designation and orphan-drug exclusivity. This guidance describes FDA's current interpretation of how the regulatory "sameness" criteria apply to gene therapies.

III. INTERPRETING SAMENESS OF GENE THERAPY PRODUCTS

For the purpose of granting orphan-drug designation and determining eligibility for orphan-drug exclusivity, assuming that two gene therapy products are intended for the same use or indication, FDA's determination of "sameness" will consider, per 21 CFR 316.3(b)(14)(ii), the principal molecular structural features of the gene therapy products. FDA generally intends to consider certain key features such as transgenes and vectors used in gene therapy products to be "principal molecular structural features" under this regulation.[17] For example, for two gene therapy products intended for the same use or indication:

- If the two gene therapy products express different transgenes (e.g., transgenes that encode different enzymes for treatment of the same rare disease), FDA generally intends to consider them to be different drugs for purposes of 21 CFR 316.3(b)(14)(ii) because they will not contain the same principal molecular structural features. This applies whether the products have or use the same vector or different vectors.

- If the two gene therapy products have or use different vectors, FDA generally intends to consider them to be different drugs for purposes of 21 CFR 316.3(b)(14)(ii) because they will not contain the same principal molecular structural features. This applies whether the products express the same transgene or different transgenes. For example:

    - FDA generally intends to consider vectors from a different viral group (e.g., gammaretrovirus vs. adeno-associated virus (AAV)) to be different for purposes of 21 CFR 316.3(b)(14)(ii).

[13] Section 527(c) of the FD&C Act; 21 CFR 316.34(c).
[14] 21 CFR 316.3(b)(3).
[15] 21 CFR 316.3(b)(14)(ii).
[16] 21 CFR 316.3(b)(14)(ii)(A)-(D).
[17] For the definitions of and additional information regarding transgenes and vectors, please see, e.g., Long Term Follow-Up After Administration of Human Gene Therapy Products; Guidance for Industry, January 2020, available at https://www.fda.gov/media/113768/download.

- FDA generally intends to consider vectors from the same viral group (e.g., adeno-associated virus 2 (AAV2) vs. adeno-associated virus 5 (AAV5), or gammaretrovirus vs. lentivirus) to be different for purposes of 21 CFR 316.3(b)(14)(ii), when the differences between the vectors impact factors such as tropism, immune response avoidance, or potential insertional mutagenesis.

- FDA generally intends to determine whether variants of a vector from the same viral group (e.g., AAV2 vs. a variant of AAV2) are the same or different for purposes of 21 CFR 316.3(b)(14)(ii) on a case-by-case basis.

In the scenarios described in the bullets above, FDA generally does not intend to consider these principal molecular structural features to be different for purposes of 21 CFR 316.3(b)(14)(ii) if there are only minor differences (e.g., polymorphism) in the transgenes and/or the vectors. In other words, FDA does not intend to consider two gene therapy products to be different drugs based solely on minor differences between their transgenes and/or vectors. FDA generally intends to determine whether differences between the transgenes and/or vectors are minor differences on a case-by-case basis.

If two gene therapy products express the same transgene and have or use the same vector, determining whether the gene therapy products are the same drug for purposes of 21 CFR 316.3(b)(14)(ii) may also depend on additional features of the final product that can contribute to the therapeutic effect. These additional features may include regulatory elements (e.g., promoters, enhancers, or splicing elements), or for ex vivo genetically modified cells, may include the cell type that is transduced. In these cases, FDA generally intends to determine whether the two gene therapy products are different drugs for purposes of 21 CFR 316.3(b)(14)(ii) on a case-by-case basis.