Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations

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Draft Guidance for Industry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
Office of Orphan Product Development
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This guidance provides FDA's current thinking on determining sameness of human gene therapy products[1] 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.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

As with other drugs[2], a human gene therapy product may qualify for orphan-drug designation if it is intended for the treatment of a rare disease or condition[3] and the sponsor provides sufficient scientific rationale to establish a medically plausible basis for expecting the drug to be effective

[1] 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 dated January 2020, available at https://www.fda.gov/media/113760/download.

[2] For the purposes of this guidance, the term *drug* refers to both human drug and biological products.

[3] The Federal Food, Drug, and Cosmetic Act (FD&C Act) generally defines a *rare disease or condition* as any disease or condition that affects fewer than 200,000 persons in the United States.

in the rare disease.[4] Orphan-drug designation may provide the sponsor of a gene therapy product with financial incentives, including tax credits for qualified clinical testing and an exemption from the prescription drug user fee for a marketing application,[5] and consideration for seven years of orphan-drug exclusivity, as long as the eligibility criteria are met.[6]

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. To take full advantage of the incentives provided by the Orphan Drug Act, sponsors may submit the designation request as early as possible after collecting the relevant information to adequately support the request.

If a sponsor requests orphan-drug designation for a drug that is the same drug[7] 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.[8] 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.[9] 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 same use or indication.[10] Consideration of clinical superiority is based on greater efficacy, greater safety, or a major contribution to patient care.[11]

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.[12] The regulations further describe 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.[13] However, the regulations do not elaborate on how the "same drug" definition applies specifically

[4] See section 526 of the FD&C Act, 21 U.S.C. 360bb; see also 21 CFR Part 316, Subpart C.
[5] 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 dated October 2019, available at https://www.fda.gov/media/131797/download.
[6] 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.
[7] 21 CFR 316.3(b)(14).
[8] 21 CFR 316.20(a).
[9] 21 CFR 316.31.
[10] Section 527(c) of the FD&C Act; 21 CFR 316.34(c).
[11] 21 CFR 316.3(b)(3).
[12] 21 CFR 316.3(b)(14)(ii).
[13] See 21 CFR 316.3(b)(14)(ii)(A)-(D).

to gene therapy products for the purposes of orphan-drug designation and orphan-drug exclusivity.[13] 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.[14] For example, for two gene therapy products intended for the same use or indication:

- If two gene therapy products express different transgenes (e.g., transgenes that encode different enzymes for treatment of the same rare disease), and 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.

- If two gene therapy products express different transgenes, 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, regardless of whether they have or use the same vector.

- If two gene therapy products have or use vectors from a different viral class (e.g., gammaretrovirus vs. adeno-associated virus (AAV)), 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, even if they express the same transgene (e.g., a transgene that encodes the same enzyme for treatment of the same rare disease). FDA intends to make the determination of whether two vectors from the same viral class (e.g., adeno-associated virus 2 (AAV2) vs. adeno-associated virus 5 (AAV5)) are the same or different on a case-by-case basis.

In the scenarios described in the three 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 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.

[14] 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 dated January 2020, available at https://www.fda.gov/media/113768/download.

When applicable, FDA also generally intends to consider additional features (e.g., regulatory elements, cell type that is transduced) of the final gene therapy product as described below:

- 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, or for genetically modified cells, may include the cell type that is transduced. In these cases, FDA generally intends to consider requests for designation and exclusivity of gene therapy products to evaluate whether such additional features may be considered to be "principal molecular structural features" within the meaning of 21 CFR 316.3(b)(14)(ii).