Proskauer

Orphan Drug Exclusivity for CRISPR/Cas-Based Therapeutics

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The prospect of genetic engineering using CRISPR (clustered regularly interspaced short palindromic repeats) and CRISPR-associated nucleases (Cas) has long been hailed as a "revolutionary" development in medicine.

This technology is rapidly advancing, and several CRISPR/Cas-based drugs have entered clinical trials over the past several years. One kind of product in clinical trials is CRISPR-modified cells, such as CTX001 (CRISPR-Cas9-modified autologous hematopoietic stem cells), currently under study for the treatment of b-thalassemia and severe sickle cell anemia. Another CRISPR-based product, AGN-151587, is injected into the eye with the goal of eliminating a genetic mutation in patients with Leber congenital amaurosis 10, a leading cause of childhood blindness. In parallel, others are working to harness the CRISPR/Cas system to develop drugs for rare diseases, including bespoke therapies tailored to an individual patient's needs.

Given CRISPR/Cas-based drugs' potential to treat rare diseases, issues relating to orphan drug exclusivity will arise as these products are developed. In May 2020, for example, CTX001 received an orphan drug designation for transfusion-dependent b-thalassemia.

In January 2020, the FDA provided draft guidance regarding orphan drug exclusivity for gene therapy products, which includes CRISPR/Cas gene editing ("Draft Guidance"). This guidance focuses on the analysis of whether two gene therapy products are the "same" under the Orphan Drug Act. Although informative, the limited scope of the Draft Guidance invites more questions than it answers.

"Same Drugs" Under the Orphan Drug Act

Obtaining orphan drug exclusivity involves a two-step process. First, a sponsor requests "designation" of a drug for a particular rare disease or condition. *See* 21 C.F.R. § 316.20. If this drug is the "same drug" as a drug already approved to treat the same rare disease or condition, the sponsor must provide a plausible hypothesis that the new drug is clinically superior to the previously-approved drug. *Id.* Whether two drugs are the "same" depends on consideration of structural features relevant to that type of drug. *See id.* § 316.3(b)(14).

If the new drug later obtains marketing approval for a use or indication within the rare disease or condition for which it received orphan drug designation, the FDA will determine if the drug is eligible for orphan drug exclusivity. *See* 21 C.F.R. § 316.31(a). In this situation, to receive exclusivity, the sponsor of the new drug must show that its drug is clinically superior to the "same" previously-approved drug for the same rare disease or condition. *See id.* § 316.34(c). A clinical superiority determination is based on the new drug's greater efficacy, greater safety, or a major contribution to patient care. *See id.* § 316.3(b)(3).

Highlights from Draft FDA Guidance

To determine whether one gene therapy product is the "same" as another, per § 316.3(b)(14)(ii), the FDA will evaluate the "principal molecular structural features" of the two products, particularly "transgenes" (e.g., transgenes that encode different enzymes for treatment of the same rare disease) and "vectors." For example:

- If two gene therapy products express different transgenes, the FDA "generally intends" to consider them to be different drugs even if they have or use the same vector.
- Conversely, if two gene therapy products have or use vectors from a different viral class (e.g., gammaretrovirus or adeno-associated virus), the FDA "generally intends" to consider them to be different drugs even if they express the same transgene.
- In the case of two vectors from the same class (e.g., AAV2 or AAV5), the FDA "intends" to determine their "same"-ness "on a case-by-case basis."
- However, the FDA "generally does not intend" to consider these principal molecular structural features to be different "based solely on minor differences" between the transgenes and/or the vectors.

Additionally, “[w]hen applicable,” the FDA “generally intends” to consider “additional features” of the final gene therapy product, such as regulatory elements or, in the case of genetically-modified cells, the type of cell that is transduced. It “generally intends” to consider requests for designation and exclusivity of gene therapy products to evaluate whether such additional features may also be considered to be “principal molecular structural features.”

Implications for CRISPR/Cas Therapy Exclusivity

The Draft Guidance helps answer certain high-level questions relating to whether two gene therapy products would be considered the “same” under the Orphan Drug Act. As various stakeholders have recognized, however, it is short on the details that meaningfully aid the process of drug research and development.

It is clear from the Draft Guidance that a new product can be considered “the same” as a previously-approved product even if the two products are not perfectly identical, but the guidance does not explain what would constitute a “minor” difference between such products, or what the scope of “additional features” would be.

For example, the Draft Guidance does not clarify what makes two transgenes the “same.” Nor does it cite to prior guidance or regulations that may answer this question. The question is significant because Cas nucleases and other parts of the CRISPR/Cas system may be modified in various ways. To address whether these modifications bar a finding of “same”-ness, the FDA could potentially import the kinds of considerations that govern “same”-ness of other kinds of large-molecule products, such as “polynucleotide drugs” or “closely related, complex partly definable drugs with similar therapeutic intent” (e.g., viral vaccines). *See* 21 C.F.R. §§ 316.3(b)(14)(ii)(C), (D). However, this is not clear from the Draft Guidance.

The Draft Guidance also does not explain what will factor into the "case-by-case" basis assessment of whether viral vectors from the same viral class are the "same." In the case of AAV2 and AAV5—the two viruses identified in the guidance—researchers have found that these viruses differ with respect to sequence analysis, tissue tropism, and heparin sensitivity. It is not clear from the guidance, however, whether a plausible hypothesis of clinical superiority will be required to seek orphan drug designation for a drug based on AAV2 if the previously-approved drug expresses the "same" transgene(s) but is based on AAV5.

It would be beneficial to sponsors and other stakeholders if these aspects of gene therapy drugs' "sameness" are clarified further before they invest significant resources into the design and development of these therapeutics.

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