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By Electronic SubmissionDivision of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2019-D-5392: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations

Regeneron Pharmaceuticals, Inc. (Regeneron) is submitting comments to the Food and Drug Administration (FDA or Agency) on the draft guidance for industry entitled “Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations.”

Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led for 30 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to seven FDA-approved treatments and numerous product candidates in development, all of which were homegrown in our laboratories. Our approved medicines and those in our pipeline are designed to help patients with eye disease, heart disease, muscle disease, allergic and inflammatory diseases, pain, cancer, infectious diseases, and rare diseases.

Regeneron is grateful for the Agency’s efforts to provide clarity on how it will consider “sameness” for gene therapy products. The recommendations are especially valuable for Sponsors considering orphan designations and exclusivity for innovative therapy products. Currently, some regulations define “sameness” for “small molecule” products; however, before this draft guidance, there was no regulatory definition establishing how the FDA will apply the criterion for gene therapy products. We submit the following comments to assist the Agency in enhancing the utility of the draft guidance. Consequently, we hope our proposals will contribute to bringing clear recommendations for the development of better medicines that are intended to treat patients with orphan diseases.

Specific Comments:**Section III. Interpreting Sameness of Gene Therapy Products**

1. We encourage the FDA to reconsider the last statement in the third bullet of section III., which reads:

“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.”

Regeneron requests that the Agency define two vectors from the same viral class but different serotypes, as a characteristic sufficient to classify gene therapy products as different products. Different serotypes of adeno-associated virus (AAV) are likely to exhibit differences in tissue tropism, transgene expression, and immunogenicity; important

characteristics that can significantly impact the safety and efficacy of a product. Therefore, we recommend that gene therapy products from different isotype classes should be classified as different products. Such an approach to defining a product as different will incentivize Sponsors of orphan drug products to continue to advance and develop novel gene therapies while ensuring recognition of the differentiation, nuances, and complexity of developing these innovative products. An approach that makes this determination on a case-by-case basis will lead to uncertainty, debate, and potential disputes that will impede innovation in the development of certain types of gene therapy products.

2. We encourage the FDA to elaborate on the first statements of the last paragraph of section III., which reads:

“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.”

Regeneron encourages the Agency to explicitly define “minor differences” and provide criteria that clarifies how the Agency arrives at this determination based on performance characteristics (e.g., tropism, transduction efficiency, etc.). Small variances in transgenes and vectors could have a major impact on how vectors transduce. For example, if you have two different gene therapy products for the same gene, differences in the promoter sequences should constitute a major difference because these differences will affect the level of the transgene expression as well as cell types in which it is expressed. Some promoters may result in toxic overexpression, whereas cell-type specific promoters should avoid this complication. We request that the Agency provide further clarity on how it will consider what constitutes a “minor difference.” This clarification should reduce ambiguity, minimize the number of questions received from Sponsors, and thereby reduce potential delays in gene therapy development.

Regeneron requests that the Agency consider our recommendations. We appreciate the opportunity to provide comments to the Agency that will assist the Agency in its efforts to establish and clearly define how the Agency will apply the criterion of “sameness” for gene therapy products for the purposes of the orphan drug designation. If you have any questions or additional comments, please feel free to contact me, Ned Braunstein, at 914-847-3099 or ned.braunstein@regeneron.com.

Respectfully submitted,

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