



June 23, 2020

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-D-5392: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations; Draft Guidance for Industry.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the Draft Guidance for Industry "Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations" (Draft Guidance or Guidance).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO appreciates FDA's efforts to provide drug developers with guidance pertaining to what features FDA will consider when making determinations of "sameness" for gene therapies in the context of orphan drug designation, especially as the landscape for gene therapy products continues to evolve. BIO generally finds the Draft Guidance helpful and we believe that the framework is drafted in a way that supports development of innovative gene therapy products. BIO appreciates the three bulleted "cases" provided by FDA in the Draft Guidance and believes the "cases" are sufficiently exhaustive in demonstrating under what circumstances FDA would consider two gene therapy products either the same or different. However, we do request that FDA clarify that gene editing products are out-of-scope for the guidance and will be subject to case-by-case determinations.

The Draft Guidance notes that *"If two gene therapy products express the same transgene and have or use the same vector, determining whether the gene therapy products are the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."* Similarly, FDA also indicates that *"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."*

BIO understands that regulatory discussions and certainly the science around gene therapy products are still evolving and there may not yet be sufficient information to understand all possible circumstance when gene therapies may be differentiated. Additionally, at present some factors that may ultimately result in substantially different clinical safety and efficacy



profiles cannot or have not been measured. We thus emphasize the importance of FDA updating and engaging stakeholders as additional experience is gained. To this end, BIO recommends that FDA conduct a public meeting and issue a discussion guide to collect additional input from stakeholders to be considered for incorporation prior to releasing the discussion guide as Q&A guidance in draft form, following Good Guidance Practices. The discussion guide and draft guidance should address FDA's thinking on, for example, the following questions:

1. What does FDA consider will constitute a "principal molecular structural feature" for the purpose of the gene therapy guidance?
2. What factors would FDA consider in "case-by-case" scenarios when two gene therapy products express the same transgene and use vectors in the same viral class?
3. What does FDA consider will constitute additional "regulatory elements" that may differentiate gene therapy products?
4. How will FDA consider other factors in their determination of sameness?

We think this would be a balanced approach to both update developers on FDA's thinking while also ensuring an opportunity for key stakeholders to contribute and share perspectives on FDA's approach for making determinations of sameness for gene therapy products.

BIO appreciates this opportunity to comment on FDA's Draft Guidance on Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Danielle Friend, Ph.D.
Senior Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

14 July 2020

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,

Ned Braunstein, MD
Senior Vice President, Regulatory Affairs and Pharmacovigilance
Co-head, Global Development
Regeneron Pharmaceuticals, Inc.

Cuancha-Maria Manning
Director, Regulatory Intelligence
Global Development
Regeneron Pharmaceuticals, Inc.



July 24, 2020

Dockets Management Staff (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; Draft Guidance for Industry”

Dear Sir or Madam,

CSL Behring appreciates the opportunity to submit comments on the Food and Drug Administration (FDA) Draft Guidance for Industry titled, “Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations,” and we are evaluating the Agency’s Draft Guidance through the lens of CSL Behring’s mission to save and improve the lives of people with rare and serious diseases. CSL Behring is strongly committed to bringing valuable, innovative products to market so patients can lead healthy and productive lives. Our strong R&D pipeline utilizes its expertise in plasma fractionation, recombinant technology, and cell and gene therapy to develop and deliver innovative medicines that address unmet medical needs or enhance current treatments.

CSL Behring appreciates the FDA’s efforts to develop guidance that provides the Agency’s current thinking of how the regulatory “sameness” criteria applies to human gene therapy products and the inclusion of additional features of the final gene therapy product that FDA generally intends to consider when determining sameness for gene therapy products. This is particularly helpful to sponsors who may seek orphan-drug designation and orphan-drug exclusivity in the development of gene therapies for rare diseases.

Our assessment of the Draft Guidance finds that the FDA provides clarity on the orphan drug “sameness” definition in regard to: 1) differentiating factors when two gene therapy orphan medicinal products are under development for the same target indication, and 2) that the FDA generally intends to consider certain key features, such as transgenes and/or vectors, to be “principal molecular structural features” for determining sameness of gene therapy orphan medicinal products. However, in addition to FDA’s consideration of differences in principal molecular structural features, we would ask the Agency to include the transfer system and manufacturing technology as “additional features,” which could be differentiating factors for determining sameness of gene therapy orphan medicinal products.

CSL Behring is appreciative of the concise scenarios and description for which 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. Further, we find that the guidance provides an appropriate degree of regulatory flexibility enabling sponsors to continue developmental activities towards innovative therapies in the gene therapy space.

As the science and regulatory landscape continues to evolve around gene therapy products, we suggest the Agency consider utilizing effective and timely mechanisms for updating all stakeholders as the FDA gains more experience by sharing information, metrics and generalized non-competitive criteria/rationale for making determinations of “sameness” in the context of two or more gene therapy products. CSL Behring suggests that the Agency consider utilizing the same mechanism and level of detail as currently employed in sharing information around the Center for Biologics Evaluation and Research (CBER) Regenerative Medicine Advanced Therapy (RMAT) Designation(s). FDA could also host a public meeting with prior release of a discussion guide in order to solicit input from and facilitate meaningful dialogue with stakeholders as suggested by the Biotechnology Innovation Organization (BIO) in their June 23, 2020 letter to the Agency.

Lastly, CSL Behring urges the FDA to continue engagement with other health authorities, particularly the European Medicines Agency (EMA), and discussions within international forums, such as ICH and WHO, in order to align or seek convergence in development of the regulatory frameworks applicable to gene therapy-related topics. Global harmonization to the extent possible can enhance development of these innovative products and their availability to patients globally.

CSL Behring again thanks the FDA for the opportunity to review the Draft Guidance and provide comments for the Agency’s consideration before it begins work on the final version of this document for implementation. We would be happy to discuss our points of view in more detail. Should there be any questions, please feel free to contact me at 610-878-4600 or Stephanie.Kelly@cslbehring.com to discuss further.

Sincerely,

/S/

Stephanie Sabatino Kelly
Associate Director, North America Regulatory Intelligence & Policy
Global Regulatory Affairs
CSL Behring



July 20, 2020

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations (FDA-2019-D-5392)

Submitted electronically

Dear Sir/Madam,

Biocom appreciates the opportunity to offer comments on the Food and Drug Administration (FDA) draft guidance [*Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*](#) (“draft guidance”).

Biocom is the largest, most experienced leader and advocate for California’s life science sector, which includes biotechnology, pharmaceutical, medical device, genomics and diagnostics companies of all sizes, as well as research universities and institutes, clinical research organizations, investors and service providers. With more than 1,300 members dedicated to improving health and quality of life, Biocom drives public policy initiatives to positively influence the state’s life science community in the research, development, and delivery of innovative products. California’s life sciences industry generates \$372 billion in annual economic output, boosts the state's total gross product by \$212 billion, supports over 1.4 million jobs, and increases labor income by more than \$115 billion per year¹.

We commend the agency on its ongoing efforts to develop a comprehensive gene therapy framework. With over 100 members in the cell and gene therapy sector, Biocom is committed to engaging with the Agency on developing a regulatory framework that spurs innovation and access to potentially life-saving treatments while ensuring safety and efficacy. We thank the FDA for issuing guidance to help sponsors developing gene therapies determine whether their therapy is the same as another product when aiming to apply for orphan drug designation and orphan drug exclusivity. Biocom is generally supportive of the draft guidance and offers the following comments for consideration.

¹ Biocom 2020 Economic Impact Report Databook. <https://www.biocom.org/eir/>



Although gene therapies can be eligible for orphan drug designation and orphan drug exclusivity, uncertainty can arise when trying to determine if the FDA considers two gene therapies to be the same drug for orphan purposes. FDA regulations define “same drug” for drugs composed of large molecule(s) 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 drug².

For gene therapy products, the draft guidance, states the FDA’s determination of sameness will be based on the principle molecular structural features such as transgenes and vectors. The Agency provides case examples to demonstrate scenarios where it would consider two gene therapies as the same or different. FDA will consider that two gene therapy products are different if they express different transgenes and/or use different vectors. If vectors from the same viral class are used then sameness will be determined on a case-by-case basis. When applicable, the FDA also generally intends to consider additional features (e.g., regulatory elements, cell type that is transduced) that can contribute to the therapeutic effect.

Biocom supports the FDA’s approach in determining sameness between two gene therapy products. The examples are clear and concise and help to illustrate the factors that FDA intends to consider. We recommend the Agency to include in the final guidance case examples of scenarios involving “additional features” and clarify what characterizes a “minor difference” or other factors that would lead the Agency to conduct its determination on a case-by-case basis.

Regulators must keep pace as the science and technology associated with cell and gene therapies continue to rapidly advance. With many countries establishing regulatory frameworks for cell and gene products and clinical studies being conducted in more countries to help accelerate development, Biocom applauds the Center for Biologic Evaluation and Research (CBER) on its efforts to develop a comprehensive gene therapy framework and work on global regulatory convergence. FDA predicts that by 2020 it will be receiving more than 200 investigational new drug (IND) applications per year and approving 10 to 20 cell and gene therapy products per year by 2025 based on an assessment of the current pipeline and the clinical success rates of these products³.

Biocom encourages the agency to continue its efforts as it is vital for stakeholders to fully understand how gene therapy products are regulated, and regional or national regulatory differences to enable the most efficient product development to serve patients in need. Biocom also understands that as gene therapy products continue to advance and more data is collected, the determination of “sameness” will evolve and additional examples will be available to illustrate potential cases. We ask the agency to continue to share knowledge and include industry in ongoing discussions regarding “sameness.”

² 21 CFR 316.3(b)(14)(ii)

³Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics>

Biocom comments on interpreting sameness of gene therapy 3

Thank you again for the opportunity to provide these comments. We look forward to a continued dialogue with the FDA on improving the regulatory framework for gene therapy products. If you have any questions about these comments, please contact Brittany Blocker, Manager of Regulatory Affairs at bblocker@biocom.org.

Sincerely,

A handwritten signature in black ink that reads "Joe Panetta". The signature is written in a cursive style with a large initial "J".

Joe Panetta
President and CEO
Biocom