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CLIENT ALERT

New Gene Therapy Guidances Signal Anticipated Growth of Product Submissions by FDA

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Recognizing that gene therapy products are now a "therapeutic reality" for some patients, the U.S. Food and Drug Administration ("FDA") recently unveiled six draft guidance documents intended to foster the development of safe, effective, and innovative new products. Part of the agency's broader policy framework for regenerative medicine advanced therapies, the suite of guidance documents reflects FDA's efforts to tailor its regulatory approach to the "unique challenges" raised by the development of gene therapy products, including inherent uncertainty regarding long-term safety and durability of response. FDA has also issued, for the first time, disease-specific guidance, for three categories of disease that the agency considers to be poised for "fast-paced activity" or for which there is a "significant unmet need."

The six draft guidance documents span the product lifecycle: two address pre-market considerations, three focus on a specific disease or category of disease, and one discusses long-term follow-up studies, including post-market studies for licensed gene therapy products.

Comments on the draft guidance documents are due by **October 10, 2018**. Sponsors should carefully review the guidance documents and their potential implications for product development and commercialization. In particular, sponsors may wish to evaluate the feasibility of the chemistry, manufacturing, and controls ("CMC") recommendations as they relate to investigational new drug ("IND") submissions; consider how the disease-specific recommendations align with current development plans for products in the pipeline; and assess the increased burden of extended, long-term follow-up periods.

Background

For nearly three decades, scientists have been engaged in clinical research to address disease at the molecular level through the correction of defective genes in the human

germline or tumor cell DNA. Although thousands of gene therapy trials were launched beginning in the 1990s, progress was hampered for many years by, among other challenges, the lack of a reliable and safe method to precisely deliver genes to the target location in the genome. More recently, the development of new gene delivery methods has enabled the development of new products; in the past 12 months, FDA has approved three separate gene therapy products. The new draft guidance documents are an effort by the agency to modernize its regulatory approach in light of new scientific discoveries and in anticipation of additional product developments.

Highlights of Draft Guidance Documents

Pre-Market Considerations

"Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)"

The lengthiest of the six draft guidance documents addresses the CMC information that sponsors of gene therapy products must include in applications for IND exemptions, which are a prerequisite to the clinical investigation of unapproved new drugs. When finalized, the new CMC guidance will supersede FDA's April 2008 guidance document of similar title.

The proposed CMC guidance reflects both changes in internal agency procedure and advances in gene therapy technology. In particular, the proposed guidance mirrors the Electronic Common Technical Document ("eCTD") format that is now required for new drug and biologics submissions (e.g., INDs, new drug applications ("NDAs"), and biologics license applications ("BLAs")). Sponsors should pay special attention to the information FDA expects to see as part of the CMC information, since missing or insufficient CMC information will most likely place the IND on clinical hold. Additionally, sponsors should remember that FDA does not expect all eCTD sections to be completed in the original IND submission.

The draft guidance also emphasizes and expands upon the requirement to include information about the characteristics (e.g., physical, chemical, or biological) of both the "drug substance" and the "drug product," signaling that the agency views these elements as significant in the context of reviewing IND submissions for gene therapy products. The definitions provided in the draft guidances are generally consistent with those contained in FDA regulations, although "drug substance" in the guidance is defined in terms of "biological" rather than "pharmacological" activity. The draft guidance acknowledges the potential challenge of distinguishing between the drug substance and the drug product in the gene therapy context, and recommends that sponsors explain how they are distinguishing the two as part of Module 2 of the eCTD submission.

"Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up"

The second premarket-focused draft guidance would revise previous FDA recommendations for replication competent retrovirus ("RCR") during retroviral vector-based gene therapy product manufacture and patient monitoring. Retroviruses are frequently used as a vector, or delivery mechanism, to introduce a gene into target cells. There is some risk that retroviruses capable of replicating may be created during the manufacturing process, which could result in adverse effects. The guidance provides recommendations to prevent the creation of RCR during the manufacturing process. Based on its review of new safety data, FDA has revised prior guidance to:

- eliminate RCR testing on working cell banks for retroviral producer cells;
- reduce the amount of vector that needs testing by eliminating the requirement to test based on production lot size, and instead requiring the sponsor to demonstrate that the vector contains < 1 RCR per patient dose;
- include testing of all retroviral vector transduce cell products for RCR, unless the sponsor can demonstrate that its transduced cell products are consistently RCR-negative; and
- increase post-market monitoring of patients who have received retroviral vector-based products to up to 15 years after product licensure.

Disease-Specific Guidance Documents: Hemophilia, Retinal Disorders, and Rare Diseases

Three of the draft guidances focus on preclinical and clinical study design considerations for gene therapy products targeting specific diseases or disease categories. These three disease-specific gene therapy guidances are the first of their kind to be issued by the agency.

Hemophilia

This draft guidance:

- recommends that sponsors, in general, use annualized bleeding rate ("ABR") as the primary efficacy endpoint for clinical benefit demonstration, but states that factor activity may be used as a surrogate endpoint for approval in an accelerated pathway (subject to certain limitations);
- identifies discrepancies between different assay methods used to measure factor activity and urges sponsors to evaluate and understand how these discrepancies

may affect their clinical development programs for gene therapy products for hemophilia;

- includes specific recommendations for study design, including patient population to be recruited, timing of administration of the investigational gene therapy product, length of post-administration washout period, and adverse event monitoring and response plans; and

- advises sponsors on the types of potential adverse events that should be monitored in the initial post-administration period (first two years) as well as in the long-term post-administration period (up to 15 years).

Retinal Disorders

This draft guidance:

- recognizes that certain sponsors may need to take into account the potential risks associated with intravitreal and subretinal injections in clinical study design when considering a randomized, concurrent parallel control group;

- emphasizes the importance of the endotoxin limit for intraocular delivery and of testing the vector-based final products for particulate matter; and

- provides examples for established efficacy endpoints that may be used to assess clinical benefits of gene therapies for retinal disorders, including best corrected distance visual acuity and rate of photoreceptor loss, while encouraging sponsors to develop novel endpoints.

Rare Diseases

This draft guidance:

- encourages sponsors to communicate with FDA before submitting an IND;

- highlights considerations of particular relevance to rare disease products with respect to study population, study design, dose selection, safety, and use of efficacy endpoints;

- notes the challenge of evaluating critical quality attributes ("CQA") when manufacturing fewer lots of a study drug, which may occur when developing rare disease gene therapy products, and therefore emphasizes the importance of establishing a well-controlled manufacturing process and suitable analytical assays to assess CQA as early in development as possible; and

- lists the various expedited review pathways that may be available to sponsors of rare disease drug products, including gene therapy.

Post-Market Considerations

"Long Term Follow-Up After Administration of Human Gene Therapy Products"

The last (and second-longest) draft guidance addresses whether and to what extent long-term follow-up ("LTFU") safety studies, including Phase IV post-market studies, should be considered for gene therapy products. In general, such studies will be needed where pre-clinical and clinical safety data has raised concerns about the potential for delayed adverse events.

This draft guidance would supersede FDA's 2006 guidance addressing LTFU. The 2006 guidance provided a framework for assessing the risk of gene therapy-related adverse events.

With respect to that framework, the draft guidance:

- expands the existing framework for assessing the risk of gene therapy-related adverse events to include genome-editing technology (such as CRISPR) and recommends LTFU up to 15 years for gene therapy products incorporating such technology for the in vivo modification of cells;

- recommends a 15-year LTFU period for gene therapy products that use integrating vectors, such as gammaretroviral and lentiviral vectors and transposon elements, and up to five years for adeno-associated virus ("AAV") vectors;

- notes that LTFU requirements may be modified over the course of an investigation, through IND amendment, in light of ongoing assessment of product persistence, transgene expression, and clinical findings; and

- recommends that sponsors submit a Pharmacovigilance Plan ("PVP") along with BLA submissions to help ensure that delayed adverse events are detected.

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This Client Alert was authored by **Gail Javitt** *and* **Megan Robertson.** *If you would like more information regarding response to any of these draft guidances, please contact Gail Javitt or the Epstein Becker Green attorney who regularly handles your legal matters.*

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