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FDA Issues Gene Therapy Guidances

In only a few years, gene therapy has begun to transition from concept to reality. By inserting new genetic material into a patient's cells, gene therapy (GT) products have the potential to change the way physicians treat a host of serious diseases, including neurological disorders, rare genetic conditions, and cancer. To date, FDA has approved four GT products, but more than 900 investigational new drug applications (INDs) have been filed by developers in this rapidly evolving field.

On January 28, 2020, the Food and Drug Administration (FDA) issued six final guidances on the manufacturing and clinical development of GT products and a draft guidance on the interpretation of sameness for such products.[1] While the six final guidances reflect updated versions of draft guidances released in July 2018, the draft guidance on "sameness," is entirely new. That draft guidance, titled "Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations," describes FDA's proposed approach to determining sameness of GT products for orphan drug designation and exclusivity purposes. For this reason, although the draft guidance is short – including only four pages of substance – it may have the greatest impact of the seven newly issued guidances for developers of gene therapy products.

The six final guidances address:

- the agency's expectations for the chemistry, manufacturing, and control (CMC) information that should be included in INDs;
- expectations for the testing for replication competent retroviruses during the manufacture of retroviral vector based GT products and during follow-up monitoring of patients who have received such products;
- considerations to evaluate regarding when long term follow-up studies should be conducted to monitor for long term adverse events; and
- supplemental detail regarding product development considerations in:
    - rare diseases;
    - hemophilia; and
    - retinal disorders.

While the final guidances largely track the agency's positions set out in draft versions issued in July 2018, we highlight key changes in this alert.

Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations (Draft Guidance)

Orphan drug designation and orphan drug exclusivity provide valuable incentives, such as various financial benefits and a period of marketing exclusivity, for sponsors to develop drugs for rare diseases. To qualify for orphan drug designation or orphan drug exclusivity, a sponsor must demonstrate that the new drug is not the "same drug" for the "same use or

[1] INTERPRETING SAMENESS OF GENE THERAPY PRODUCTS UNDER THE ORPHAN DRUG REGULATIONS (Draft Guidance for Industry); CHEMISTRY, MANUFACTURING AND CONTROL INFORMATION FOR HUMAN GENE THERAPY INVESTIGATIONAL NEW DRUG APPLICATIONS (Guidance for Industry); TESTING OF RETROVIRAL VECTOR-BASED HUMAN GENE THERAPY PRODUCTS FOR REPLICATION COMPETENT RETROVIRUS DURING PRODUCT MANUFACTURE AND PATIENT FOLLOW-UP (Guidance for Industry); LONG TERM FOLLOW-UP AFTER ADMINISTRATION OF HUMAN GENE THERAPY PRODUCTS (Guidance for Industry); HUMAN GENE THERAPY FOR RARE DISEASES (Guidance for Industry); HUMAN GENE THERAPY FOR HEMOPHILIA (Guidance for Industry); HUMAN GENE THERAPY FOR RETINAL DISORDERS (Guidance for Industry).

indication" as a previously approved drug. If the "same drug" has already been approved for the "same use or indication," a sponsor must, in the case of orphan drug designation, provide a plausible hypothesis that the new drug is clinically superior to the previously approved drug, or in the case or orphan drug exclusivity, demonstrate that the new drug is in fact clinically superior to the previously approved drug. While the orphan drug regulations define "same drug" for large molecules as containing the "same principal molecular structural features" and explain how this criterion is applied to different kinds of large molecules (referred to as "macromolecules"), the regulatory definition provides no guidance for how the criterion of "same principal molecular structural features" would apply to GT products. The draft guidance on sameness delivers some clarity on this question.

For GT products, FDA states that certain key features, such as transgenes (the exogenous gene introduced into the host cell) and vectors (the vehicle delivering the genetic material), will be considered the products' principal molecular structural features. Thus, under the draft guidance, if either the transgene or vector differs between two GT products, the two products would not have the same principal molecular structural features and would be considered different drugs (*i.e.*, not the "same drug" for orphan drug designation or exclusivity purposes). The draft guidance further states that FDA will determine whether two vectors from the same viral class are the same on a case-by-case basis and that two products will not be considered different drugs based solely on minor differences in the transgenes and/or vectors. FDA also may consider additional features that can contribute to the product's therapeutic effect, such as regulatory elements (*e.g.*, promoter/enhancer, introns) or cell type that is transduced, to be principal molecular structural features.

While the draft guidance is clear that GT products with different transgenes or vectors will not be considered the same drug for orphan drug designation and exclusivity purposes, it also leaves room for other product features to play significant roles in the determination of sameness. For example, the draft guidance provides transgenes, vectors, and cell types as examples of "key features" or "additional features," but also allows for the possibility that other unnamed product features could be considered "principal molecular structural features." The draft guidance also leaves unanswered or open for interpretation on a case-by-case basis several significant questions, such as what types of differences would be considered "minor differences" and when vectors from the same viral class (*e.g.*, adeno-associated virus 2 (AAV2) vs. adeno-associated virus 5 (AAV5)) would be considered the same vector.

Despite these remaining ambiguities, this draft guidance likely will be an important resource for GT product developers navigating the complex field of rare diseases. In the related news release, FDA describes the draft guidance as potentially leading to the development of multiple GT products for the same disease or indication.

The public comment period for this draft guidance closes on April 29, 2020.

CMC Information for Human Gene Therapy INDs

This final guidance outlines FDA's expectations for the chemistry, manufacturing and control (CMC) section of a GT IND. Organizationally, the guidance mirrors the structure of the Common Technical Document (CTD)—the form in which all commercial IND submissions (and all Drug Master Files beginning in May 2020) must be submitted—and offers recommendations on completing each of the CTD's three modules, with a particular focus on Module 3. The primary purpose of the guidance is to ensure that sponsors of GT products provide the information required to assure safety, identity, quality, purity and strength (including potency) of their investigational products.

With respect to Module 1, FDA makes few (mostly stylistic) changes to the July 2018 draft guidance. As in the previous guidance, FDA offers general recommendations for submitting administrative information, touching briefly on labeling, environmental analyses, and questions pertaining to previously submitted information.

FDA's Module 2 recommendations, which pertain to the summary of quality information, are similarly general. FDA provides guidance on how to identify, describe, and characterize the drug substance and drug product at issue. In

addition, it details, step by step, its recommended manufacturing process, and includes an explanation of how the critical quality attributes (CQAs) of the various components should be identified, measured, and tested throughout. Substantively, the new guidance adds significant color to certain sections of the draft by elaborating on earlier recommendations. Perhaps most significant is FDA's discussion of CQAs. The final guidance urges developers to establish CQAs as early as possible in the manufacturing process, noting that "well-established CQAs are generally necessary for demonstrating product comparability by analytical methods." New references to CQA guidance documents provide further guidance on this score.

The guidance offers far more detailed recommendations for completing Module 3 of the CTD. Over forty pages, FDA describes precisely the sort of drug substance and drug product information a sponsor should include in its application. The most substantive changes can be found in FDA's lengthy discussion of cell banks. Perhaps most notable is a new recommendation that sponsors establish a bacterial master cell bank in certain manufacturing situations.

Finally, the guidance notes that not all sections of the CTD need to be completed prior to submitting an IND. Because sponsors often have limited information in the early stages of development, FDA recognizes that sponsors may have to supplement their applications as they gain experience and information.

Long Term Follow-up After Administration of Human Gene Therapy Products

This final guidance makes recommendations regarding the design of long term follow-up studies (LTFU observations) for the collection of data on delayed adverse events following administration of a GT product. It is potentially relevant to all GT products, as its recommendations would apply to any GT product that could cause delayed adverse events. In short, the guidance describes the product characteristics, patient-related factors, and preclinical and clinical data that sponsors should consider when assessing the need to implement LTFU programs for a GT product. The guidance supersedes a 2006 guidance on the subject and finalizes a nearly identical July 2018 draft guidance.

In Q&A format, and with the help of a flowchart, the guidance establishes an analytical framework for assessing the potential for delayed risks based on preclinical data. In addition, it discusses considerations for preclinical study design to assess biodistribution and persistence of a GT product. Biodistribution studies in animals may be performed as separate studies or as a component of a pharmacology or toxicology study. The guidance makes further recommendations as to the animal study design and tissue collection. At the close of this section, FDA suggests that sponsors schedule a pre-IND meeting prior to initiating a preclinical biodistribution study, in part because interpreting such studies, especially when GT products are involved, can be uniquely challenging.

The guidance also discusses specific risks of delayed adverse events posed by technologies that modify the host genome (*e.g.*, plasmids, RNA), emphasizing the importance of conducting LTFU observations to mitigate such risks in subjects receiving GT products with integrating activity. FDA concludes the preclinical section of the guidance with general recommendations for sponsors developing genome editing products.

A long series of clinical considerations follows. Beginning with a short description of the goals of LTFU observations, FDA discusses how to select a clinical trial population for an LTFU observation, how long to run one, and how to prepare and maintain the necessary protocols and records, among other things. This section was finalized with only minor substantive revisions, its primary purpose being to structure sponsors' thinking on LTFU programs. The guidance closes with general considerations for post-marketing monitoring plans, including a recommendation that a sponsor submit a Pharmacovigilance Plan at the time it submits its BLA, and a general recommendation that sponsors with long term risks implement LTFU programs, post-licensure, to monitor delayed adverse events.

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

This highly technical final guidance supplements the two guidances discussed above. It is intended for sponsors of retroviral vector-based human GT products and makes a series of recommendations regarding product testing and patient monitoring. With the exception of the revisions discussed below, the guidance is largely identical to the July 2018 draft guidance of the same name.

With respect to testing, FDA explains the kinds and frequency of testing it will expect sponsors to conduct. Recommendations differ depending on the material at issue, whether master cell banks derived by transduction with ecotropic vector, master cell banks derived by transfection of retroviral vector plasmid, vector harvest material that includes end of production (EOP) cells, or ex vivo transduced cells. In addition, the guidance describes the various testing procedures that ensure RVRs are not created during the manufacturing process, explains how a sponsor should describe these procedures in the CMC section of an IND, and discusses the types of patient testing FDA expects sponsors to conduct. Finally, the guidance includes minor revisions to the draft guidance's recommendations regarding assays for testing, noting that "alternative methods may be appropriate for lot release testing of ex vivo transduced cells in lieu of culture based methods," particularly under time constraints.

The brief patient monitoring recommendations touch on the replication competent retrovirus (RCR) testing schedule and the recommended testing assays. In a break with the 2018 draft guidance, the final version states that collection of yearly follow-up samples may be discontinued for any individual whose post-treatment assays test negative during the first year. In such a case, the sponsor should conduct a yearly review of the patient's medical history in lieu of patient samples. As for assays, FDA recommends, as it did in 2018, two methods for detecting evidence of RCR infection in patients: 1) serologic detection of RCR-specific antibodies and 2) analysis of patient peripheral blood mononuclear cells by PCR for RCR-specific DNA sequences. The guidance notes that RCR testing should be documented in amendments to the IND file, and that negative results should be included in the IND annual report. Finally, FDA discusses a few post-licensure considerations, encouraging sponsors to account for certain risks in both their labeling and applications.

Product-Specific Guidances

Three of the new final guidances focus on narrow product classes: GT products intended to treat 1) rare diseases, 2) retinal disorders, and 3) hemophilia. Each of these guidances is substantively similar to its respective July 2018 draft, and all are more or less identical in scope, offering recommendations on all phases of the development process, from manufacturing to clinical trials.

Human Gene Therapy for Rare Diseases

The final guidance regarding human gene therapy for rare diseases, like the CMC guidance discussed above, urges developers to establish well-controlled manufacturing processes as well as analytical assays useful in assessing product CQAs for concentration, potency, identity, and purity. In addition, FDA recommends that sponsors characterize a product's CQAs prior to initiating clinical studies. In light of "CQA uncertainty" and the relatively high variability of GT products, FDA strongly encourages sponsors developing GT products for rare diseases to contact the Office of Tissues and Advanced Therapies (OTAT) early in the development process, and certainly prior to submitting an IND.

FDA briefly describes the overall objectives of the preclinical development phase and makes several specific recommendations broadly pertaining to feasibility and study design. With few exceptions, this section of the guidance is largely identical, in substance, to the draft guidance issued in July 2018. FDA made more significant revisions to certain sections of the clinical trial discussion, most notably the study design section. FDA included new language on placebo controls and intra-subject comparison. With respect to the former, FDA recommends that developers "consider

randomizing some subjects in each cohort to receive placebo" if a study has multiple dose-level cohorts. FDA also notes that intra-subject comparisons, by avoiding some of the pitfalls of inter-subject controls, "can facilitate the assessment of local therapeutic effects and are recommended for consideration when appropriate." Lastly, the guidance contains new, albeit general, recommendations on biomarker selection and concomitant medications.

Human Gene Therapy for Hemophilia

This final guidance takes up questions related to human GT products intended to treat hemophilia. Because such products generally do not entail unique CMC considerations, the rare disease guidance's CMC discussion, as well as most of that guidance's preclinical and clinical study recommendations, carry over to hemophilia products. The most significant revision from the draft version of this guidance is an updated discussion of efficacy endpoints. Whereas the draft guidance simply listed Annualized Bleeding Rate (ABR) as a primary endpoint to clinical benefit, the final guidance notes that "approval of GT products could be based on factor activity levels, if scientifically justified." Though apparently willing to consider factor levels as surrogate endpoints, in part because ABR has certain inherent limitations, FDA admits that it is "currently limited by several scientific considerations," some of which it lists in the guidance (*e.g.*, "the lack of molecular characterization of the protein translated in vivo, in contrast to recombinant factor concentrate products produced in vitro"). Ultimately, FDA recommends that sponsors use ABR as a primary endpoint, "pending the availability of [new] data and reliable calibration methods." It stops short, however, of discouraging the use of factor activity as a surrogate endpoint for primary efficacy assessment under the accelerated approval pathway.

Human Gene Therapy for Retinal Disorders

The last of the new final guidances explains FDA's current approach to the development of human GT products for retinal disorders. This guidance contains the fewest substantive changes of any discussed here. That said, a few changes bear mentioning. First, the agency describes steps a sponsor should take to reduce potential bias, and, for the first time suggests "separat[ing].. .clinical evaluators and personnel involved in [a] product administration/sham procedure" to prevent patients from distinguishing the eye which received the product from that which received the sham treatment. Another addition to the guidance is a new parenthetical that lists some of the reasons why a single administration of a GT product in each eye may not always be sufficient. The parenthetical notes, for example, that "a GT product has limited duration of effectiveness after single administration; or exposure to a GT product may be limited to a part of the target area in the eye with the initial administration and a repeat administration to the same eye may extend the treatment to additional parts of the target area for additional effect." Finally, the guidance adds to the section on "Safety Considerations" that "safety measures and post intervention follow up schedules should be incorporated into the study design based on the anticipated potential for adverse reactions for the specific disease, target population and test article attributes." Outside of these three changes, there is very little new in the finalized version of the guidance.

Conclusion

As described above, final versions of the six draft guidances issued in July 2018 clarify a few discrete areas but do not otherwise represent significant shifts in FDA policy since the guidances were issued in draft form. The new draft guidance provides initial insights on how FDA will interpret sameness for orphan designation and exclusivity purposes, clarity that is needed given that the orphan drug regulations, prior guidance, and precedents are of minimal value in the context of GT products. The comment period will be open through April 29, 2020. Ropes & Gray will continue to monitor FDA regulatory developments relevant to GT products. If you have any questions, please contact any member of our FDA regulatory practice or your usual Ropes & Gray advisor.