Cooley

April 14, 2022

On March 15, 2022, the US Food and Drug Administration issued a pair of draft guidance documents in the gene therapy space. The first, which is specific to gene therapies incorporating genome editing (GE), was aimed at helping developers of these novel therapies better understand what the FDA is looking for in Investigational New Drug (IND) submissions to control for the risks that the agency is most concerned with for these therapies. The second focused on chimeric antigen receptor (CAR) T therapies, and aimed to provide comprehensive guidance for sponsors on pre-clinical development, chemistry, manufacturing and controls (CMC), manufacturing at single versus multiple sites, and clinical study design.

What you need to know about GE and CAR T therapies

GE and CAR T therapies are regulated by the FDA as biological products. They have become the darling of biotech companies in recent years because of their unprecedented potential to address unmet medical needs. GE therapies modify DNA sequences at specified locations in the genome of human somatic cells, including correction or inactivation of deleterious mutations, introduction of therapeutic transgenes, and disruption of viral DNA. CAR T therapies can genetically modify the receptors on the T cells in the body to enable the cells to recognize specific antigens. This application of genetic modification allows sponsors to target specific diseases with known antigens.

With many clinical trials ongoing for these two types of gene therapies, and a series of recent safety-related clinical holds imposed in this space, the agency's decision to issue its first guidance documents specific to GE and CAR T therapies is not surprising.

FDA's approach to regulating GE and CAR T therapy development

As with all therapeutic products, the FDA weighs each GE product's benefits and risks, considering factors such as "the proposed indication and patient population, the extent and duration of therapeutic benefit achieved, and the availability of alternative therapeutic options." Specifically for GE products, the agency is concerned with off-target editing, as well as the unintended consequences and unknown long-term effects of on- and off-target editing.

The FDA also recognizes the idiosyncratic challenges for CAR T cell development, manufacturing, testing and clinical assessment. For example, the CAR T draft guidance points out that "CAR T cell manufacturing involves multiple biological materials and complex multi-step procedures, which are potential sources of variability among product lots."

To address these risks and challenges, the draft guidances provide detailed recommendations, such as:

- Establish case-by-case preclinical testing strategies, taking into consideration data from related products.
- Design long-term follow-ups for products with integrating vectors in preparation for the risk of delayed adverse events associated with the vectors.
- Discuss considerations for product characterization, testing, dosing and clinical study design in pre-IND meetings.
- Use cryopreservation when manufacturing CAR T therapies at a central location and shipping to different clinical sites.
- Follow a life cycle approach to CMC, taking into consideration information gathered over the course of product development. CAR T therapies and vectors should be manufactured under good manufacturing practice conditions appropriate for the stage of development.
- Include microbiological testing in vector safety testing to ensure that the final product is not compromised.
- Qualify suitability of manufacturing equipment by assessing the critical quality attributes of the product.
- Qualify and validate each assay. When changing an assay, perform a risk assessment.

- Use the same standard operating procedures, training, reagents and equipment across manufacturing facilities.

For certain topics, the FDA distinguishes between different types of products. For example:

- **Ex vivo versus in vivo genomic modification:** For ex vivo genome modification, sponsors should choose the method of delivery based on the ability of the cell type of interest to be efficiently electroporated or transduced by a vector. For in vivo genome modification, sponsors should consider the ability of the delivery vector to target the cells/tissue of interest and minimize distribution to non-targeted tissue.
- **Autologous versus allogeneic CAR T cell products:** For autologous CAR T cells, sponsors should consider using bridging therapies while subjects wait for the CAR T treatment. For allogeneic CAR T cells, sponsors should use early-phase studies to assess the risks of graft versus host disease.

As pointed out by the FDA, certain recommendations in the CAR T draft guidance may apply to other genetically modified lymphocyte products, such as CAR natural killer cells or T cell receptor-modified T cells.

The draft guidances recommend that, before submitting INDs, GE and CAR T therapy manufacturers communicate with the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research (CBER) to discuss the product-specific considerations for transitioning the products to clinical studies. The meeting types include pre-IND and INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings, which can be used in early development to obtain non-binding regulatory advice from the agency.

What to include in your IND

The FDA recommends including the following in GE product IND submissions:

- A description of, and rationale for, the design and screening processes of the GE components,[1] and the sequences of the GE components.
- The GE component optimization strategy to reduce the potential for off-target genome modification.
- A detailed description of how **each GE component** is manufactured, purified and tested, including:
  - Flow diagrams and a detailed narrative of the manufacturing process and any in-process controls.
  - Lists of the reagents used during manufacturing processes and certificates of analysis.
  - The quality control and quality assurance programs in place at each manufacturing site.
  - Procedures in place at each manufacturing site to ensure product tracking and segregation.
  - Procedures in place at each manufacturing site to prevent, detect and correct deficiencies in the manufacturing process.
  - Procedures for shipping the GE component from the component manufacturing site to the final product manufacturing site.
- Descriptions of the analytical procedures utilized for GE component testing, including the sensitivity and specificity of the procedures, as well as an outline of any in-process testing performed.
- Outlines of stability study protocols and any available stability data.
- A detailed description of how **the drug product** is manufactured, with details about any in-process controls, including:
  - Flow diagrams and a detailed narrative of the manufacturing process and any in-process controls.
  - Lists of the reagents used during manufacture and certificates of analysis.
  - Details on measures taken to ensure aseptic processing, if applicable.
- A detailed description of the testing plan for the drug product.
- Detailed descriptions of the overall clinical study design, assessment of adverse events, and subject follow-up plans.

For CAR T therapies, the agency recommends including the following in IND submissions:

- Descriptions of approaches to reduce immunogenicity (e.g., “humanization” by complementarity-determining region grafting), if applicable, and their impact on target binding and biological activity.
- A description of procedures to ensure adequate control of the CAR T cells during shipping to the clinical site.
- Information demonstrating the manufacturer’s ability to produce CAR T cells according to the proposed manufacturing

process through the production of developmental or engineering batches.

- Information to demonstrate appropriate control of test methods.
- For flow cytometry:
  - A description of the assay, including the flow cytometry antibody panel and the gating strategy used to define each cell population detected.
  - Information regarding instrument calibration and quality control to ensure accuracy of the results.
  - A list of assay controls.
- A copy of all labels and labeling to be provided to each investigator in the clinical study.
- CMC information, depending on the phase and scope of the clinical studies proposed.
- For multisite manufacturing, a description of any differences in the manufacturing process across the manufacturing sites.
- Rationale and justification for the proposed clinical study population.
- Rationale for the proposed clinical study design and analysis.

Our recommendations

The comprehensiveness and level of detail included in these draft guidances reflect that the FDA has put significant effort into designing the regulatory approach to GE and CAR T therapy development. Manufacturers should consult the draft guidances if they are developing GE and CAR T therapies, or plan to in the near future. Sponsors would be well served to verify that they have considered all applicable factors mentioned in the draft guidances.

To ensure a smooth transition of product candidates to clinical studies, GE and CAR T therapy manufacturers preparing IND submissions should check that all content recommended in the draft guidances is included in their INDs.

Upon review, if an interested party finds that any of the FDA's recommendations or considerations contained in these guidances lack scientific justification, or impose an unreasonable burden, the public comment submission process for GE therapies and CAR T therapies can be used to raise concerns or suggest alternative approaches to help the FDA effectively assess these products. Your Cooley team stands ready to assist with any comments to the docket, which are due by June 15, 2022.

[1] The draft guidance provides examples of "GE components": "the nuclease, DNA targeting elements (i.e., elements used to dictate the target DNA sequence, such as guide RNA) and a donor DNA template (i.e., DNA sequence provided to repair the target sequence)."

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