FDA Manufacturing Challenges for Gene and Cell Therapy Developers

By Peter Lindsay & Nathan Sheers

Hundreds of gene therapy candidates are currently in development, as evidenced by the numerous investigational new drug ("IND") applications submitted to the Food and Drug Administration (the "FDA").

As gene therapy candidates progress, companies are increasingly focused on the unique issues related to the commercial manufacture of these products. This focus is understandable, given that the FDA has scrutinized these processes carefully during its pre-license review of the Biological License Applications ("BLA") for these novel products.

To date, the FDA has approved a limited number of gene and cell therapy products, but the recent interactions between applicants and the agency provide some insight into the important issues that arise frequently during the agency’s review of the related chemistry, manufacturing, and control ("CMC") information for these BLAs.

It is critical that companies consider commercial manufacturing issues early so that they are best positioned to avoid receiving Complete Response Letters ("CRLs") related to these issues. This may be particularly important for products that represent breakthrough therapies because, even if clinical stages are condensed or accelerated, commercial manufacturing requirements remain significant. By planning and assessing CMC information early, companies can provide sufficient data and address questions effectively during the BLA review process.

Gene and cell therapies constitute a wide array of products, from gene-edited cell products to gene therapies using viral vectors. Although potential CMC issues will vary based on the product, the questions raised by FDA reviewers to date on these products is instructive. The following CMC topics represent examples of questions that have arisen in the BLA reviews for gene and cell therapies:

- **Storage Conditions**: Many gene and cell therapy products have strict storage conditions (e.g., \( \leq -65^\circ C \)), and the FDA has frequently posed questions about the length of the storage conditions, GMP status of the storage facilities, and impact of the recommended storage conditions on container components, including any leachables and extractables.

- **Shipping Validation**: The logistical challenges associated with cold-chain storage has resulted in multiple questions related to shipping validation reports, including questions about data related to the chain of custody from the manufacturer to the site of administration, worst-case
scenarios and data for such shipments, and whether the data is representative of actual or simulated conditions.

- **Drug Substance and Drug Product Specifications:** At the commercial manufacturing stage, the FDA expects more defined and narrower acceptance criteria. Thus, CMC reviews have scrutinized the production data and related justifications carefully to ensure the specifications are well supported. In some instances, companies have been pushed to narrow their limits. Applicants need to ensure that their justifications are well documented and account for all relevant production data. Developing complete justifications can be challenging in some cases as manufacturing processes may have been modified over time. Nevertheless, reviewers have focused on whether the specifications are determined using the appropriate universe of data (e.g., are the specifications based on data pre-dating the process validations? Does the implementation of later controls result in more consistent (and more representative) product data?).

- **Process Controls and Validation:** To facilitate the review process, operating ranges for key process parameters need to be linked clearly to supporting production data. In some cases limitations in product characterization can lead to uncertainties in process variables and critical parameters. Focus on these parameters is important as the operating ranges and duration of production steps and hold times are likely to receive focus during pre-license review. While process changes are not uncommon during development, process performance qualification studies should be reviewed to ensure that they reflect the intended commercial process. Any significant changes should be described with sufficient detail and risk analyses to justify and document decisions about further qualification activities and comparability studies. Questions around comparability studies have also arisen related to manufacturing scale up and scale out. Appropriate product characterization and process definition are key to help ensure robust comparability protocols and data.

- **Raw Material Qualification:** Qualification processes and data for key starting materials should be reviewed thoroughly, along with information related to animal-derived materials that have been the subject of questions related to source organism and country of origin. The quality of the starting materials remains a key focus in the review of these types of products.

- **Aseptic Qualification, Environmental Monitoring, and Contamination Control:** It is not uncommon for CMC-related questions to address issues related to clean room qualification, media fills, aseptic process risk analyses, cross-contamination concerns, and visual inspection processes and control of subvisible particles.

- **Analytical Test Methods:** In many cases, gene and cell therapy candidates develop or work with newer test methods, and FDA reviewers have scrutinized these methods carefully, particularly assays related to a product’s potency or purity. Issues have included assay variability, availability of properly characterized reference standards and controls, method changes or late-stage validation, use of “limit” tests instead of validating quantitation, data supporting the limit of quantitation, and ensuring that the drug product matrix is suitable for the intended analytical method (e.g., endotoxin).
Out of Specification ("OOS") Results and Rejected Lots: Questions have also arisen for clinical or early commercial lots with OOS results or lot release failures. It is important to have a clear description of the investigation, root causes, and how this data is used in connection with process ranges and product specifications.

Component Compatibility and Testing: FDA reviewers have focused on the compatibility of the product with all delivery device components, as well as data supporting compatibility with any diluent.

Although some of these issues may not be applicable to every gene or cell therapy product, these examples illustrate the challenges that developers face as they move into preparations for commercial manufacturing and regulatory licensing. Early focus on these issues is key to ensuring a successful CMC strategy and the development of data that will help avoid any unnecessary delays in product approval. While many developers focus on the clinical challenges of these novel products, the FDA’s recent reviews of CMC issues advise the diligent to also prepare for a rigorous review of their readiness for the commercial manufacturing of their gene or cell therapy products.

If you have any questions concerning these developing issues, please do not hesitate to contact either of the following Paul Hastings Washington, D.C. lawyers:

Peter V. Lindsay  
1.202.551.1922  
peterlindsay@paulhastings.com

Nathan Sheers  
1.202.551.1936  
nathansheers@paulhastings.com