When conducting a clinical trial, there are many aspects sponsors need to be aware of with regards to clinical safety, product efficacy, and the ability to bring treatments through the multiple milestones required for commercialization. Product sponsors for cell and gene therapies also need to understand the special requirements that these innovative treatments must adhere to before introducing them to clinical patient populations. A lack of expertise in understanding the special requirements associated with such treatment could result in delays for market approval and possibly failure of the product. In this article, we look at recent industry guidance and how this can help mitigate the potential for risks and accelerate your product to market.

FDA’s Long Term Follow-up Guidance

In January 2020, the Office of Communication, Outreach, and Development (OCOD) issued a 35-page non-binding set of recommendations for “Long Term Follow-Up After Administration of Human Gene Therapy Products Guidance for Industry”.

It is a known fact in the industry that genome editing, whether ex vivo or in vivo, introduces the risk for delayed adverse effects due to the permanent nature of change. It also creates the potential for off-target genome modification leading to aberrant gene expression, chromosomal translocation induction of malignancies, risk for insertional mutagenesis, associated risk of tumorigenicity, and the possibility of immune response. Gene therapy products are designed to make long-acting changes in the body. Some outcomes may be undesirable; therefore, studies must include a surveillance follow-up plan for delayed adverse events.

The FDA’s Long-Term Follow-Up (LTFU) guidance introduces gene product characteristics, patient related factors, and the related pre-clinical and clinical data to be considered. The guidance also provides recommendations on patient monitoring for licensed gene therapy products. This guidance has excellent tools and guidelines for establishing follow-up timeframes and provides expectations and a stepwise approach which includes a “Framework to Assess the Risk of Gene Therapy-Related Delayed Adverse Events”.

Gene therapy products require LTFU studies for appropriate human subject protection (up to 15 years) for clinical trials to evaluate the effects of the gene therapy product on clinical patients. Many of these LTFU activities will continue after the product is licensed meaning that a Pharmacovigilance Plan (PVP) should be submitted with the BLA. The process to identify gene therapy product and patient populations who require LTFU has been evaluated by the FDA since the first gene therapy product was introduced. Product sponsors should understand that the FDA reviews submissions and will place studies on hold if a study presents unreasonable risk to study subjects, per 21 CFR 312.42 (b)(1)(i).

Assessing the Risk of Delayed Adverse Events

Product sponsors also need to understand the integration activity of the gene therapy product – biological activity of retroviral vectors, and transposon elements that are imparted during integration in the genome. The risks include potential disruption on critical host genes at the integration site, activation of proto-oncogenes near the integration sites and risk of malignancies. Risk reduction is accomplished through testing, analysis, and understanding what gene therapy products impart in their biological activity, but also the off-target effects that have undesirable changes in the genome. This includes prolonged expression caused by transgenes causing unregulated cell growth or unknown pleotropic effects, such as latency, reactivation or delayed adverse events related to symptomatic infection, and persistent infections in immunocompromised patients.

This guidance provides a straightforward framework to assess the Risk of Gene Therapy-Related Delayed Adverse Events, and provides a pathway to determine when LTFU is required for clinical protocols including assay polymerase chain reaction (PCR) for gene therapy product persistence and absence of downward trend over time. The risk analysis is a living document which needs to be reassessed each time a new observation or trans mutational risk is found, and should be submitted in the IND, per CFR 312.23.

It is important to know that LTFU may not be needed when a comparator product (administered through same route, identical final formulation) risk assessment demonstrates lack of persistence of the vector sequence, but a similar gene therapy product, which differs in route of administration (directly to tumor and intravenously), does not conclude that LTFU is required. Additionally, when the risk of delayed adverse events is low following exposure to a gene therapy product, LTFU is not recommended.

Understanding Risk Mitigation

Advances in an analytical approach to investigating integration sites allow greater understanding of risk mitigation of the development of new vectors, specifically transposon elements that can insert transgenes into the host chromosome by a direct cut and paste mechanism, mediated by transposases (enzyme).

Studies should evaluate delayed toxicity, functional replacement of a host gene that has not been expressed, and whether the therapeutic protein is potentially immunogenic (data indicates product persistence even when studies did not, data collected indicates gene therapy product has increased risk for adverse events). DNA samples should be run in triplicate for each tissue. qPCR assay results should include a known spiked control to
confirm specified qPCR assay sensitivity. Assays are needed to assess the pattern of vector integration sites to determine if a dominant clone persists and assess the relative contribution of the dominant clone. Vector integration patterns may also need to be evaluated based upon replicative capacity and long-term survival.

One of the key steps is to discuss with Office of Tissues and Advanced Therapies (OTAT) the study design and end points for your innovative gene therapy product in a pre-IND meeting. Located nearby the FDA offices, ProPharma Group’s Washington, DC location allows for meeting preparation and support throughout the agency meetings.

Final Thoughts

From pre-clinical findings and the IND application, the sponsor knows if long term follow-up will be required. The sponsor needs to understand patient population and mitigating circumstances such as short life expectancy, multiple co-morbidity, and exposure to radiation or chemotherapy. Clinical patients may have greater value because of disease free state. Therefore, understanding patient population characteristics and disease should be considered when designing LTFU protocol and creation of Informed Consent documents. Informed Consent documents need to convey both the duration and content (including autopsy) of LTFU to participants per 21CFR 50.25 (a). Informed Consent forms are provided to the Institutional Review Board for approval per 21CFR 312.53 ©(1)(vi)(d).

Remember to continue annual testing until persistent vector sequences are undetectable. Do not be overly invasive – consider measuring surrogate data that may indicate vector persistence. Special considerations are needed regarding integrating vectors because of the risk of developing leukemia and premalignant conditions, due to the integration of gammaretroviral vectors and lentiviral vectors. If no evidence of oligoclonality or monoclonality is observed, a summary analysis of vector integration should be included in an IND report per 312.31 within 30 days of observation.

Sponsors should create a patient registry to systematically capture and track data from treated patients and provide routine surveillance for licensed biological products including adverse events (AE) in accordance with 21CFR 600.80. Reporting is required for both expedited and non-expedited AEs. Additionally, sponsors need to consult with OTAT if they withdraw the application after LTFU has started as participants require notification as well as plans for LTFU. You can find example annual reports in the guidance’s appendix.

If you need support with the development or clinical trials of your innovative therapies, partner with ProPharma Group. As a global provider of end-to-end Cell and Gene Therapy services, our Center of Excellence accelerates the commercialization of advanced therapeutic products for companies developing novel and life-changing cell and gene therapies. Our team of experts have led the development of multiple cell and gene therapy products from pre-clinical development through marketing authorization. We are a single-source provider of services, with more than 25 years of experience in helping clients overcome scientific, technical, and regulatory challenges within the cell and gene therapy space.