FDA/ASGCT Liaison Meeting Summary – November 18, 2019

Surrogate endpoints to accelerate gene therapy product development–Dan Levy, MD, PhD, Pfizer

A strong mechanistic rationale exists to support use of surrogate endpoints based on biomarkers related to gene replacement to support market authorization. For example, in FDA's *Draft Guidance on Human Gene Therapy for Hemophilia* (2018), the Agency states that factor activity may be used as a surrogate endpoint for primary efficacy to support accelerated approval. However, questions remain among sponsors on the level of correlative evidence required to qualify surrogate endpoints (SEs) for gene therapy.

While the draft FDA guidance on *Biomarker Qualification: Evidentiary Framework Guidance* (2018) provides information on this topic, it may not be particularly useful in the rare disease setting, in which clinical trial populations are small and the evidence base is limited. The FDA's *Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure* is a resource for traditional drug development, but the extent it may be applied to gene therapy development is unclear, especially regarding use of SEs for accelerated approval.

ASGCT requested FDA to issue guidance for industry on the use of SEs in gene therapy programs for rare/ultra-rare conditions, and provided the following recommendations:

- *Validated SEs* should be applicable to gene therapy clinical trials to support traditional approval. Examples are α1-proteinase inhibitor levels for A1AT deficiency; platelet count, spleen/liver volume for Gaucher disease; and Phe levels for PKU.
- *Reasonably likely SEs* which have been used to support accelerated approval of small molecule and biological drugs should be applicable to gene therapy products. Examples are full-length dystrophin levels for DMD, and GL3 levels for Fabry disease.
- *Candidate SEs*, which have less available correlative evidence than established reasonably likely SEs, have been identified for several investigational gene therapy products (for example gene therapies for XLMTM, beta thalassemia, sickle cell disease, and dystrophinopathies). Specific FDA guidance on the level of evidence required to support use of these SEs for accelerated approval could speed delivery of these products to patients with unmet medical needs.
- ASGCT supports the possibility of gathering required confirmatory post-market data from the same subjects studied in the pivotal trials used to support accelerated approval. The product transitions to full approval upon acquisition of confirmatory clinical outcomes in long-term follow-up of the same trial population.
- For some of the rare diseases that qualify as serious diseases with unmet need, SEs could be supported by strong natural history registries, even in cases of relatively small patient populations.

During the discussion, FDA staff recommended sponsors have early discussions about whether a surrogate endpoint will work for a development plan. In addition, FDA will be issuing a guidance on accelerated vs. traditional approval for gene therapy, though it will not be issued by the end of the year.

Pre- and post-market manufacturing changes: Categorization of major vs. minor changes and requirements for comparability assessment for gene therapy products—Mike Havert, PhD, Bluebird Bio

FDA indicated publicly earlier this year that it had planned to address the issue of when minor manufacturing changes could be made without requiring additional bridging studies for cell therapy products. This presentation addressed this issue as it relates to gene therapy products. The topic is significant because comparability studies may pose excessive development delays.

While review questions for traditional drugs are predominantly related to clinical issues, they are more often related to CMC issues for gene therapies. Better product characterization would help to resolve the inherent comparability challenges for gene therapy—complexity; variable cell inputs and outputs; incomplete understanding of the mechanism of action; and incomplete or inadequate test methods.

ASGCT made the following recommendations regarding manufacturing changes:

- Robust analytical data packages, along with robust quality systems, should allow manufacturing changes at all phases of investigational studies.
- Phase-appropriate lot release criteria, as well as identification of critical quality attributes and critical process parameters, should enable comparability demonstration.
- Whether and how to implement post-market manufacturing changes should be guided by the level of product understanding and the development of appropriate analytical methods.
- When required, clinical bridging studies after clinical benefit has been established should be allowed to be assessed with intermediate efficacy or surrogate endpoints, rather than the full pivotal clinical trial endpoints.

Dr. Havert noted that for early phase studies the FDA considers CMC information primarily to ensure that there is minimal risk to patients; however at later stage development the bar is higher, with an emphasis on ensuring the degree of control of the studies and relevance to the commercial process. This latter point leads to FDA recommendation and industry practice not to make any changes to a process once pivotal trials are underway. FDA staff at the meeting clarified that while the Agency encourages making manufacturing changes as early as possible, that its previous advice to lock down the manufacturing process prior to phase 3 has been misinterpreted. Process improvements may occur at any time, but at phase 3 or later, the clinical and product quality risk is higher, so comparability demonstration, which includes product and process characterization beyond standard lot release tests to ensure the product meets CQAs, will be required.

FDA staff also indicated the Agency encourages:

- More characterization early on, as well as solid scientific support for animal models and assay choices.
- Early engagement; however, its limited resources do not allow for consultative services.
- Use of the BLA supplement process for technology changes that necessitate process change over the biological product life cycle.
- For a BLA, CQAs, potency testing, and robust analytic assays are required. The requirements should not be for greater quantities of tests, but rather better designed analytics.

ASGCT plans to request a joint workshop with FDA addressing recommendations on CMC topics, including development of phase-appropriate CQAs and comparability requirements for different product classes—retroviral vectors, AAV vectors, CAR T/ TCR and/or genetically-modified stem cells.

Gene Therapy INDs: Deficiencies and Recommendations—Staff of FDA CBER Office of Tissues and Advanced Therapies (OTAT)

CMC—Anna Kwilas, PhD, Gene Therapy CMC Product Reviewer

Common CMC IND deficiencies were related to lack of information regarding the quality of the starting materials; process capability (i.e., no process development data); safety, quality and stability testing (e.g., inappropriate test methods, sampling); cross referenced information; and the manufacturing facility, quality oversight and shipping.

Additional deficiencies included poorly organized submissions, lack of alignment of CMC development and clinical timeline, and inadequate comparability plans.

Recommendations for improvement:

- Plan ahead, follow FDA guidance and communicate with FDA early (at INTERACT and Pre-IND meetings, and when changes are made).
- Identify CQAs and validate assays early, ideally pre-Phase 1, to enable comparability assessment as process changes occur over the development cycle.
- Provide quality information on product lots used in preclinical studies to support dosing and safety (e.g., residuals, empty: full ratio).

Pharmacology/Toxicology: Iwen Wu, PhD, Team Lead, Pharmacology and Toxicology

Study duration, animal models, and endpoints are the most common elements of inadequate preclinical study designs. Other common problems include differences between product used in preclinical studies and the clinical product and safety concerns based on toxicity profile, particularly for gene therapies with long persistence.

Recommendations for improvement:

- Use biologically relevant test systems.
- Do not initiate final toxicology studies before meeting with FDA.
- Use all available tools, including *in silico, in vitro, and in vivo,* to assess safety
- Refer to the guidance, *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (2013).

Efficient Clinical Development—Ilan Irony, MD, Deputy Division Director, Division of Clinical Evaluation and Pharmacology/Toxicology, FDA CBER OTAT

Recommendations:

- For rare diseases, collect robust natural history data as early as possible.
- Obtain early buy-in on clinical development plan from patient groups, FDA, and other regulatory agencies.
- To enable efficient clinical development of gene therapy products for rare diseases with a potential for robust clinical efficacy:
    - If possible, include concurrent control as early as Phase 1; if not possible (e.g., in children with invasive procedures) use blinded third-party evaluators.
    - Evaluate effect on clinical endpoints, in addition to safety and biomarker, as early as Phase 1.

Another issue discussed is the increasing difficulty in scheduling FDA meetings and following up afterward. Dr. Wilson Bryan acknowledged the difficulty FDA has in managing the workload with current staffing levels, and he indicated that some questions that FDA may lack the capacity to answer, could be directed to a regulatory consultant.

Development and regulatory considerations when leveraging platform technology – Same/similar vector, same/similar process, and analytical process—Gabor Veres, PhD, BioMarin Pharmaceutical

In the US, no regulatory definition exists of platform technology in the context of gene therapies, but in the EU, a platform is defined as a technology that has already been approved for another medicinal product and therefore has been characterized previously (at least partly). ASGCT proposed to build on the guidance document on *Preclinical Assessment of Investigational Cellular and Gene Therapy Products*

(2013), in which FDA provided useful guidance on toxicology studies for gene therapies. Replication-incompetent vector systems would be particularly amenable to the streamlining of requirements.

ASGCT made the following recommendations to establish a systematic and predictable approach to leveraging existing data and information about the similar platform elements of an approved product, to streamline future development:

- Preclinical studies to assess **biodistribution, shedding, germline transmission:**
  - May be **waived** if the platform product uses the same vector and regulatory elements (including the promoter, envelope/capsid, and route of administration), but a different transgene.
  - May be **streamlined** if the platform product uses the same vector, envelope/capsid, and route of administration, but different regulatory elements (including the promoter and transgene); sponsors should streamline studies to address residual uncertainty, e.g. the impact of a different promoter on biodistribution.
- Preclinical studies to assess **toxicology, safety and feasibility of the delivery system**:
  - May be **streamlined** if the platform product uses the same vector, envelope/capsid, and route of administration, but different regulatory elements (including the promoter and transgene); sponsors should streamline preclinical studies to address residual uncertainty.
- Platform elements should be **exempt** from lot-by-lot release requirements once gene therapy platform elements are deemed "well-characterized therapeutic recombinant DNA-derived," based on approval of a prior BLA.

FDA staff indicated that the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is working on a document on biodistribution, which may be useful regarding this topic. FDA staff and attendees discussed whether prior study data could inform platform elements in future trials by other sponsors, which would not generally be possible due to the competitive, proprietary nature of development programs. Maritza McIntyre noted that NCATS/TRND has a program in collaboration with industry and academic groups to develop a gene therapy platform and share information to accelerate development of gene therapies.

FDA staff indicated that it would be premature for them to advise on platform technologies in gene therapy, but it is a topic of significant internal consideration. FDA encouraged more discussions to occur on scientific topics and their implications in an open forum, such as what could constitute platform technologies in gene therapy. FDA is exploring the issue through CBER Advanced Technologies Team (CATT) meetings.

FDA staff clarified that CATT meetings are similar to a seminar provided to FDA staff, to discuss an advanced technology approach that could be used broadly in therapeutic development. Feedback at a CATT meeting is not product-specific, but related to the approach discussed. CATT meetings therefore have a different purpose than individual sponsor meetings with FDA (INTERACT and pre-IND meetings). Sponsors in clinical development could discuss broader platform applications of their technology for future applications, which would be an appropriate use of a CATT meeting.