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SUBMITTED ELECTRONICALLY

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Muscular Dystrophy Association Comments on "Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies; Request for Information" - Docket No. FDA-2023-N-3742

To whom it may concern;

In service of the neuromuscular disease (NMD) patient community, the Muscular Dystrophy Association (MDA) thanks the Food and Drug Administration (FDA or "the Agency") for the opportunity to comment on the Agency's Request for Information (RFI) entitled "Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies; Request for Information." With two gene therapies already approved for marketing by the FDA, and many more in the pipeline for genetic, neuromuscular diseases, cellular and gene therapies (CGTs) represent both the present and future of treatments for the NMD community. Consequently, MDA, and our allied partners in the research and clinical communities, take intense interest in cellular and gene therapy development.

MDA is the #1 voluntary health organization in the United States for people living with muscular dystrophy, ALS, and related neuromuscular diseases. For over 70 years, MDA has led the way in accelerating research, advancing care, and advocating for the support of our community. MDA's mission is to empower the people we serve to live longer, more independent lives.

Our statements below concern the development of AAV-based gene therapies for application in neuromuscular diseases and seek to answer the questions the FDA poses within this RFI on the development of cellular and gene therapies. In constructing our response, we consulted some of the foremost experts in gene therapy development within the neuromuscular disease space.

A. Manufacturing

Q. Given the challenges to develop consistent manufacturing strategies for CGTs designed for a very small number of patients or an individual patient, how can manufacturers leverage their prior experience manufacturing one CGT to support subsequent development and approval of another related, but distinct CGT (potential areas for leveraging may include manufacturing process validation, control strategy, assay validation, and drug product stability studies)?

This issue is very difficult to address for AAV-based gene therapies. Manufacturing and product measures pertaining to AAV-based gene therapies are highly dependent on many factors that can affect the final yield of the desired material. Minor sequence changes in the original plasmid material can have unexpected impact on the AAV packaging efficiency of the therapeutic. The scientific reasons behind why some sequences package more efficiently than others remain unknown. Prior manufacturing experience can be leveraged for downstream activities such as purification, infectivity assays, and stability studies. One can also explore the creation of masterfiles for muscle-directed capsids covering details on production, biodistribution, and immunological toxicity.

Q. When the batch size of a CGT is very small, what are some challenges and solutions regarding the volume of product (or number of vials) needed for batch release testing, stability testing, retention of reserve samples, and comparability studies?

One challenge includes the difference in quality-control (QC) testing requirements between the US and other countries. Therefore, if using a non-US based AAV manufacturer, in order for the product lot to be released, both testing requirements for US and the specific country of production need to be met. A lot of therapeutic material is wasted satisfying the jurisdiction requirements that are irrelevant to the sponsor but relevant to the contract development and manufacturing organization (CDMO) based on their location.

A solution could be for the FDA to coordinate with international regulatory bodies such as the EMA to hold sponsors and CDMOs accountable to the same regulatory guidelines for product release. International regulators need to synchronize product release criteria to avoid excess product utilization in testing such as sterility, archiving..etc. We know the Agency is no stranger to such harmonization efforts, through the International Conference on Harmonization (ICH) or otherwise, and would suggest that FDA prioritize this to facilitate gene therapy development.

A second challenge is that the excess good manufacturing process (GMP)-grade material is typically discarded once a vial is opened during sample testing. Some tests, such as empty/full capsid ratios, require 0.5ml of material, but given that each vial is preloaded with more (e.g. 1.75ml), the excess GMP-grade material is wasted. This could be addressed by setting vials aside for testing that should be loaded with smaller amounts of therapeutic material.

A third challenge is that production facilities for commercial grade vector are typically designed to maximize vector production with large bioreactors—up to 2000L in some cases, but typically not smaller than 500L. Even a 500L batch of commercial grade vector may be more than enough to treat everyone with an ultra-rare disorder and all new incident cases for many years. Much of the vector may be wasted if it is not used before the stability period. Compounding the problem is the requirement for multiple clinical grade batches to be produced to meet regulatory requirements for a biologics licensing application (BLA).

Either there need to be incentives for commercial manufacturers to produce small commercial grade batches of vector or there need to be publicly supported facilities devoted to small batch commercial vector production. For ultrarare applications that have no commercial path beyond

the investigation new drug (IND) application, the IND could be kept open and material be deposited in a federally funded repository that is responsible for ongoing stability and sterility testing, and may engage in limited production runs based on the deposited materials and cell banks to ensure ongoing supply.

Q. What are some challenges and solutions for individualized CGTs that need to be tested and released rapidly, either because the product has a very short shelf life or because the patient's clinical status may be rapidly declining and treatment is urgently needed?

AAV gene therapies are typically stored in -80C and have a long shelf life if not thawed. The biggest challenge lies in the lack of manufacturing capacity for GMP-grade plasmid and AAV. These two steps create huge bottlenecks in the expected timeline of the therapeutic generation. Moreover, some batches fail quality control tests and need to be re-manufactured. Also, not many CDMOs undertake small-scale GMP-grade manufacturing for AAV that are relevant to dosing n-of-1 trials.

Regulatory flexibility on the length of toxicology studies can aid in accelerating timelines. Most of the solutions will lie in manufacturing innovations such as the use of automated robotic systems to help reduce these bottlenecks, or subsidization of the high manufacturing costs by the government. For concerns relating to development speed, the process can be accelerated by referring to platform masterfiles and by limiting efficacy/on-target testing to relevant cell-based models rather than animals.

Q. What are some challenges and solutions for individualized genome editing products that aim to treat monogenic diseases for which the target gene has different mutations in different patients?

There are many different pathogenic mutations in a single gene that can give rise to a monogenic disease. Although gene editing tools have the capability to correct these distinct mutations, it cannot be achieved using a single therapeutic design, unlike gene replacement therapy. For example, different guide RNA sequences will be required to direct the gene editing machinery to the specific genome location of the mutation. This will in turn create a different efficacy and off-target editing profile for each drug. The generation of a different gene editing drug product for each mutation is currently not a scalable strategy.

Some monogenic diseases have founder mutations that account for a large percentage of the disease such as Limb Girdle Muscular Dystrophy Type 2I/R9. Editors that target founder mutations should be pursued first and constitute the bulk of the testing requirements, paving the way for less common target regions.

An alternative strategy to correcting individual mutations (e.g. base-editing pathogenic mutations), is to employ a more scalable strategy by triggering exon skipping that encompass multiple pathogenic mutations. Genome editors can be employed to ablate splice sites resulting in in-frame exon-skipping in hotspot regions of genes. Although exon skipping strategies will result in a truncated protein with potential impact on function, this strategy is more scalable.

In neuromuscular disease it will be important to establish some proof of principle examples addressing individual mutations using gene editing to show the potential impact. For those examples it will be important to select mutations that can at best be fully corrected such as pseudoexon skipping in the DMD gene – resulting in a wildtype transcript.

For private mutations that require a gene editing approach there might be a way to streamline regulatory approval by using a standardized vector/promotor package for the target tissue(s) (with biodistribution and manufacturing well-understood) with only the guide RNAs changing. If efficiency of editing and off-target effects can be reliably modeled in vitro this could be a faster path to approval.

B. Nonclinical Development

Q. What nonclinical studies could be leveraged in support of a related product using similar technologies? What nonclinical studies are important to conduct with each final clinical product?

For gene therapy products using similar technologies, toxicity and biodistribution data for a given AAV serotype can be leveraged across studies, particularly those that involve large animal models that are expensive and difficult to conduct. Important non-clinical studies to conduct with each final AAV-based gene therapy product include infectivity and potency studies, as well as QC-related studies on each batch.

Q. What nonclinical development approaches could be considered when there are no relevant animal models or animal models are unable to replicate each individual disease/condition?

We encourage FDA to establish drug development guidances for diseases that cannot be modeled using standard laboratory animals. A non-trivial number of neuromuscular diseases fall under this category (for example, TCAP-null for limb girdle type 2G and GNE mutant mice for GNE myopathy do not recapitulate a muscle-wasting phenotype) and are thus not very encouraging for companies and investigators to pursue therapeutic development. In lieu of animal model testing, therapies can be evaluated based on transcriptomic and proteomic read-outs on a cellular level such as using a patient-derived cell line. Read-outs can include expression of a missing gene or correction of a pathogenic mutation, as well as restoration of normal molecular pathways and reduction of disease-related biomarkers. FDA may consider permitting investigators to leverage safety and biodistribution data generated for "comparable" therapies in these instances such as using the same capsid and promoter from an approved gene therapy. The establishment of relevant cellular disease models (for muscle and nerve) as well as neuromuscular junction organoids can also serve an important role.

Q. For patient-specific products where evaluating each individual product is infeasible or impractical, what is the role for nonclinical studies conducted with representative product(s)?

Products designed for individualized therapies should be tested on cell or tissue models derived from the intended patient and genetic background, particularly as it relates to genetic therapies. A

minimal set of patient tissues including the target organ (e.g. skeletal muscle) and potential off-target organs (e.g. liver) can be collected for cell line or organoid establishment for the purposes of potency and safety testing of gene therapies. Alternatively, induced pluripotent stem cells (iPSCs) derived from a patient skin biopsy can also be used to generate multiple types of relevant cell lines for these studies.

Q. What are the opportunities and challenges with using computational approaches to support nonclinical development?

Human biology is complex, with many influencing factors that cannot be faithfully recapitulated by current computational approaches. Despite these limitations, machine learning and AI based algorithms have reached maturity and are now being applied to different areas of biology, including therapeutic design and testing.

Computational algorithms such as advanced protein folding software (e.g. Rosetta Commons) have been used to predict immunogenic regions within gene therapy constructs and are now being used to guide design decisions that reduce the chances of adverse immune reactions. Opportunities in this space include intersecting cross-disciplinary datasets (genomic) to better mimic the complexity of human biology. AI tools can also be used to predict splice modulation, guide targeting, off target effects, etc.

C. Clinical Development

Q. What are challenges and strategies/opportunities with interpreting efficacy data from individual patients (including expanded access) and small groups of patients? What opportunities are there in leveraging prior and/or collective experiences?

Individual patient trials will not have a placebo control group for comparison, and minor therapeutic benefits may not be assessable. Trials with small groups will find it difficult to achieve statistical significance on therapeutic outcomes given the large variability between patients in both therapeutic read-out and disease progression.

Multiple clinic assessments over the span of a few years can inform a disease trajectory for each patient. With the help of machine learning approaches, natural history studies performed on larger cohorts of the same or similar disease can be used as additional input to model the disease trajectory for each patient. Deviations from this trajectory post-treatment can be used to inform therapeutic benefit. Natural history studies on different but related disorders can also inform outcome measure selection. The use of wearables will be ever more important, as will be the definition of biomarkers that can span various disease groups (such a plasma NFL).

Q. What strategies can be utilized to accumulate and interpret safety data in personalized/individualized CGTs?

Small numbers are not conducive to revealing trends. Trial sponsors should be encouraged to submit safety and monitoring data of treated patients to a centralized database. The collective

data across multiple small trials may reveal potential drug class effects in capsids, promoters, and/or transgenes that may not be evident in small individual trials. FDA should work with field experts to develop guidelines on safety and monitoring protocols relevant to specific classes of therapeutics that are collected for each patient treated and stored on a centralized FDA database. Although public access to such data may not be allowable, such data will ensure that the FDA will be poised to quickly identify safety issues that have implications across multiple trials. An additional recommendation is to request for QC metrics including but not limited to empty/full capsid ratio, endotoxin levels, and titer to enable comparison across trials.

Q. For genetic disorders with clear genotype-phenotype associations for disease manifestations or severity, what opportunities are there for tailoring treatments and study design to specific genotypes/phenotypes?

For neuromuscular diseases, there can be clear subpopulations that arise within each disease subtype based on factors such as age of onset, progression, and loss of ambulation. In some cases, these is a clear genotype basis. For example, in facioscapulohumeral muscular dystrophy (FSHD), less D4Z4 repeats are linked to an earlier onset of disease with a more severe prognosis. These distinct disease subpopulations should be taken into consideration in study designs and/or when analyzing trial read-outs, as they may confound or skew interpretation if over-represented in a treatment arm of a trial. In these scenarios, study designs can attempt to categorize patients into subpopulations and balance these groups equally across the different trial arms. Alternatively, sponsors can choose to focus only on a specific subpopulation that they anticipate will have the highest probability of demonstrating therapeutic benefit. Therefore, natural history studies paired with genetic studies have the capacity to shed light on disease-specific subpopulations that can be informative for designing clinical trials. It will be of great importance to also consider host/recipient genetic variation as it relates to response to gene therapy toxicity beyond variability of the disease itself (such as MHC genotypes, complement and inflammasome variation) – therefore databasing of genomic data for all gene therapy recipients needs to be considered.

Conclusion

We are grateful for the opportunity to comment on the FDA's RFI on the development of gene therapies. For questions regarding MDA or the above comments, please contact Paul Melmeyer, Vice President, Public Policy and Advocacy, at 202-253-2980 or pmelmeyer@mdausa.org.

Sincerely,

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