Alliance for Regenerative Medicine

April 1, 2019

Dockets Management (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Specific Comments for FDA Docket No. Docket No. FDA-2015-D-2818: Rare Diseases: Common Issues in Drug Development; Draft Guidance for Industry

The Alliance for Regenerative Medicine (ARM) is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of investigational new drug (IND) applications, and Biologics License Applications (BLA) for such products to the Food and Drug Administration (FDA). Many of our member companies have products under development covering a broad range of rare diseases and conditions. ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

ARM commends the FDA for the revision of the draft guidance on common issues in rare disease drug development. We recognize that the standard for safety and efficacy for drug approval does not differ between orphan products for rare diseases in comparison to the standards for drug approval for products for common diseases. However, there is need for regulatory flexibility to support drug development for rare diseases. We request the Agency to consider how the guidance can leverage even more comprehensively the flexibility afforded by the FDA in the context of drug development in rare diseases. The draft guidance is prefaced with the general statement on the flexibility in applying regulatory standards (lines 101-104); however, the subsequent sections of the draft guidance do not represent the full potential of regulatory flexibility that can be leveraged for rare disease drug development. For example, certain sections and statements in the guidance are common to drug development in general, but do not address specific concerns and approaches for drug development for rare diseases (such statements include but are not limited to lines 625-629; 652-657; 692-713; and 763-768 of the draft guidance). It would be helpful if the Agency relayed more detail in such specific statements as to how they apply to specifically to rare disease drug development. The draft guidance also does not incorporate all the principals that the Agency has publicly communicated elsewhere with regard to innovative approaches to clinical trial design and regulatory flexibility in this space. Overall, ARM highly appreciates that the Agency recognizes the difficulties associated with the development of therapies for rare diseases. We encourage the Agency to develop recommendations that address more directly the stated understanding of the unique challenges of this therapeutic space, such as those stemming from small patient populations and lack of natural history data. ARM offers the following comments for the Agency's consideration as they finalize the revised draft guidance.

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Natural history studies

As the treatment landscape evolves, the natural history of a disease also changes over time. With the availability of new treatments, the Agency should provide guidance on how to address the challenges associated with the ever-evolving standard of care in terms of informing the understanding of the disease progression as well as utility of these data as an external control. Further, novel statistical approaches that allow for borrowing data from natural history studies are not highlighted. Also, it would be helpful to get the Agency's perspective on the possibility of using patients in the natural history studies in the future interventional trials, while maintaining the ability to use the natural history cohort as a historical control. As mentioned above, a provision for borrowing data to augment a concurrent comparator arm should be added.

Evidence of Effectiveness

The draft guidance calls for a historical comparison only in "limited and special circumstances" (line 492). More often than not, concurrent controls, especially in the ultra-rare diseases, are infeasible. We recommend that the guidance communicate a greater acceptance of historic controls than as currently stated. The draft guidance is also silent on the FDA's initiative on use of complex innovative designs (CID) in clinical trials, especially created for rare diseases. The guidance should address how CIDs can be leveraged for drug development for rare diseases.

We recommend the Agency to provide an avenue of early discussions regarding use of surrogate endpoints. The type C meetings established under PDUFA VI for early consultation on the use of new surrogate endpoints are limited in their ability to enhance efficiency of drug development because they require preliminary human clinical data.[1] Requirement of preliminary human data undermines the intent for an "early" consultation with FDA. In cases of development of advanced therapies, such as gene therapy, for rare diseases based on underlying disease pathophysiology and clear mechanism of action, proof of concept studies and other types of data may form the basis of use of a surrogate endpoint. In such cases, early consultation with FDA *before* conducting human studies and collecting preliminary human data would enhance the usefulness of such consultation. This would also be in line with and would support the recommendation in the FDA draft guidance for Human Gene Therapy for Rare Diseases (lines 247-249 of that guidance) for sponsors to design their first-in-human study to be an adequate and well-controlled investigation that has the potential, depending on the study results, to provide evidence of effectiveness to support a marketing application. Such approach would benefit from early consultation with FDA on use of a surrogate endpoint before preliminary human study data is collected. Accordingly, ARM recommends that the need for preliminary human clinical data for these early meetings is eliminated or made optional for sponsors developing rare disease products in order to maximize the usefulness of these meetings.

Biomarkers

The draft guidance makes references to the guidance for drug development tool (DDT) qualification as well as Critical Path Innovation Meetings (CPIM). Both approaches require significant amount of information and have been proven to be extraordinarily rigorous, even in the context of highly prevalent diseases. The application of this general framework for rare diseases appears untenable. We recommend that the guidance provide recommendations on how biomarkers could be leveraged as efficacy endpoints

[1] Section I, subsection I on ENHANCING REGULATORY SCIENCE AND EXPEDITING DRUG DEVELOPMENT, sub-sub-section 3 on Early Consultation on the Use of New Surrogate Endpoints on page 22 of the PDUFA VI Goals Letter.

in the context of the rare disease space, including the specifics on the extent of flexibility the Agency is prepared to exercise in applying the evidentiary standards for acceptance of biomarkers as surrogate endpoints for accelerated approval.

The draft guidance recommends clinical and analytical validity of a biomarker test (Line 282). However, there is a lack of explanation on the "clinical validity" in this section, which helps the sponsor better understand how well the biomarker(s) being analyzed is related to the presence, absence, or risk of a specific rare disease, especially if it is genetically/congenitally related. Also, there is a lack of guidance on "clinical utility". It would be beneficial that this guidance includes this topic, which may help the sponsor better design a test that can provide more useful information about diagnosis, treatment, management, or prevention of a disease (i.e. enzyme replacement therapy, gene therapy), if applicable. In general, more clear guidance on analytical validity, clinical validity and clinical utility for the development of drugs for rare diseases will be beneficial for genetic testing and establishment of endpoints.

Phenotype versus Genotype

The draft guidance suggests that the sponsors should consider "phenotype" of the disease in multiple sections as an endpoint for the full range of patient population for which therapy development may be better designed. It is known that there are disadvantages in only utilizing the definition of "phenotypes" as disease endpoints, measurement quantitative traits, etc. Further, no guidance is provided on "genotype," which may also be helpful in identifying genetic variance in certain rare diseases and sub-population. This guidance will be most beneficial when it comes to "Gene Therapy," which often targets both genotypes and phenotypes. Overall, there should be direct correlation between genotype and phenotype especially when it comes to gene medication (genotype), and the way it manifests itself in patients' expression (phenotype). In other words, if genotype-phenotype correlations are identified, that information may help establish better endpoints for the clinical studies. At present, this guidance document makes no mention of "genotyping". It would be beneficial for the Agency to provide more guidance on this.

In conclusion, ARM appreciates the opportunity to provide comments on this draft guidance to the Agency. Responding to draft guidances provide a significant opportunity to foster development of advanced therapies for rare disease with significant unmet medical need. Additionally, ARM hopes that the Agency will consider our December 7, 2018 comment letter on the draft guidance for industry "Human Gene Therapy for Rare Diseases," which addresses related concerns for rare disease drug development.

Sincerely,

Robert J. Falb
Director, U.S. Policy and Advocacy

Alliance for Regenerative Medicine

Re: Specific Comments for FDA Docket No. FDA–2018-D-2258: Human Gene Therapy for Rare Diseases; Draft Guidance for Industry

SECTION / LINES	GUIDANCE TEXT	COMMENT	PROPOSED CHANGE
I.	**INTRODUCTION**		
Lines			
II.	**BACKGROUND**		
Lines			
III.	**NATURAL HISTORY**		
140	"In special circumstances, such as when it may be impractical or unethical, a well-designed and conducted natural history study can provide an external control group for interventional trials."	Arm requests additional clarity on what may be unethical in this context. See proposed edits to further clarify.	"In special circumstances, such as when it may be impractical or unethical to randomize patients to control, a well-designed and conducted natural history study can provide an external control group for interventional trials."
A. Considerations for Natural History Studies			
Lines 161-163	"A sponsor can modify the type and extent of data collection in a natural history study based on accumulated knowledge as the study proceeds."	Recommendations on considerations for and approaches to how a sponsor can modify a natural history study based on accumulated data as the study proceeds would be helpful. Further, consider if the procedure to make such modifications can be facilitated, e.g. allowance to proceed without the need for formal protocol amendments, which are costly and typically take significant time to approve. FDA may recommend sponsors to build potential modifications into the original protocol such elements of data collection that can be removed, if for example, the measure ends up proving	Additional detail and recommendations needed.

SECTION / LINES	GUIDANCE TEXT	COMMENT	PROPOSED CHANGE
		too burdensome to complete, or if it turns out that less than originally planned number of patients are needed to complete a measure. It is understandable, and may be discussed that additions may need to be reviewed by ethics committee. But there should be considerations discussed for simply stopping collection, or halting a study, or modifying certain tests that have no impact on patients or what was defined in the protocol.	
B. Types of Natural History Studies			
Lines			
IV.	**DISEASE PATHOPHYSIOLOGY, CLINICAL MANISFESTATTIONS, AND IDENTIFICATION AND USE OF BIOMARKERS**		
Line 242	N/A	Recommendations in the 2015 draft guidance version (lines 193-199), which discussed how the length of time of the biomarker response and its reversion can help guide dosing schedule/frequency, are not included in the 2019 draft guidance version. ARM recommends adding that language to the guidance as helpful considerations for how biomarker response can help guidance dosing schedule/frequency.	Recommending adding the omitted bullet from 2015 draft guidance version to line 242: "Estimating the schedule of drug administration that will provide adequate drug exposure. The rate of pathophysiologic response to drug action on the target, both onset of action and washout, may guide the selection of drug regimen. For example, if a limited duration of drug exposure produces a long-lasting alteration in a critical pathophysiologic process, then a treatment administration schedule that does not ensure continuous exposure may be sufficient. In contrast, if the pathophysiologic process is rapidly reestablished after loss of drug exposure, more frequent drug administration may be needed."
Lines 282-283	"The use of a surrogate endpoint requires demonstration of	This section states that use of a surrogate endpoint requires demonstration of both analytical and clinical validation of the biomarker test. Then the next few lines	Provide recommendations and information on the expectations for the "clinical validation" of a biomarker.

SECTION / LINES	GUIDANCE TEXT	COMMENT	PROPOSED CHANGE
	analytical and clinical validation of the biomarker test."	(285-296) discuss considerations for "analytical validation." However, there is no guidance on what is meant by "clinical validation" and FDA's expectation regarding clinical validation. Recommendations specific to clinical validation would be helpful. In general, clinical validation often refers to demonstration of association with clinical benefit. In a rare disease setting, this is very difficult in small clinical trials. Flexibility is needed in this area. Also, the guidance should clarify whether there a link here with a possible accelerated approval pathway.	
V. NONCLICNIAL STUDIES			
Lines			
VI. EFFICACY ENDPOINTS			
Lines			
VII. EVIDENCE OF EFFECTIVENESS AND SAFETY			
Lines			
A. Effectiveness			
Lines			
B. Use of Historical Controls and Early Randomization			
Lines			
1. Historical (external) controls			
519-521	"For serious rare diseases with unmet medical need, interest is frequently expressed in using an external, *historical*, control in which all enrolled patients receive the	Please clarify and confirm the intent of the statement. See proposed edits. As currently phrased in the revised draft guidance document, the statement may only apply to established off-label use.	"For serious rare diseases with unmet medical need, interest is frequently expressed in using an external, *historical*, control in which ~~all~~ none of the enrolled patients receive the investigational drug, and there is no randomization to a concurrent comparator group (e.g., placebo/standard of care)."

SECTION / LINES	GUIDANCE TEXT	COMMENT	PROPOSED CHANGE
	investigational drug, and there is no randomization to a concurrent comparator group (e.g., placebo/standard of care)."		
Lines 532-539	"As discussed in section III., Natural History Studies, when concurrent controls are impractical or unethical, clinical trials can rely on a historical control. …. However, initiation of prospective natural history studies should not delay interventional testing otherwise ready to commence for a serious disease with unmet medical need."	ARM interprets this language to mean that even if there is no feasible control group, and there is no natural history data, sponsors should not delay starting interventional testing. This recommendation supports efficient drug development for rare diseases with small patient populations and lack of natural history data, with extreme related challenges for drug development. ARM suggested FDA to further clarify whether a "lead in" observational period is needed in such cases.	Provide clarification regarding the need and for a "lead in" observational study as a control group in cases where start of interventional testing should not be delayed owing to lack of concurrent controls and natural history data.
2. Early randomization when feasible			
Lines			
C. Safety			
608-610	"Robust natural history data can also help distinguish drug-related adverse effects from underlying disease manifestations."	Proposed change suggested to clarify the intended meaning of the statement, and how i.e. on what basis sponsors can distinguish drug-related adverse effects from underlying disease manifestations	"Robust natural history data can also help distinguish drug-related adverse effects from underlying disease manifestations, for example by establishing background rates."
VIII. PHARMACEUTICAL QUALITY CONSIDERATIONS			

SECTION / LINES	GUIDANCE TEXT	COMMENT	PROPOSED CHANGE
Lines			
IX. ADDITIONAL CONSIDERATIONS			
Lines			
A. Participation of Patients, Caregivers, and Advocates			
B. Expedited Programs			
Lines			
C. Pediatric Considerations			
Lines			
X. INTERACTIONS WITH FDA			
Lines			
REFERENCES			
Lines			