Subject: Comment on FDA Draft Guidance for Industry Titled "Rare Diseases: Early Drug Development and the Role of Pre-Investigational New Drug Application Meetings"

Docket #: FDA-2018-D-3268

ARM is an international multi-stakeholder advocacy organization based in Washington, D.C. that promotes legislative, regulatory, and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM comprises more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. 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.

Many of the regenerative medicines and advanced therapies are being developed for the over 7,000 rare diseases, most of which do not yet have a cure. We applaud FDA's efforts in developing this new draft guidance to assist sponsors of drug and biological products for the treatment of rare diseases in planning and conducting more efficient and productive pre-investigational new drug application (pre-IND) meetings. Therapeutic product development for rare diseases has many challenges related to the nature of these diseases. We commend FDA for efforts to advance and facilitate the development of drugs and biological products for the treatment of rare diseases with the issuance of this new draft guidance.

In general, we agree with the draft guidance recommendations. We find the approach for the draft guidance structure— providing recommendations for quality, nonclinical, clinical pharmacology, and clinical considerations, as well as additional considerations— to be very helpful and logical. We especially appreciate the format for providing the recommendations i.e. by using bulleted lists to provide recommendations, to be clear and easier to follow. The bulleted lists clearly separate out different concepts and recommendations. The guidance provides robust recommendations for a broad array of topics to be considered for pre-IND meetings. We request FDA to clarify in the beginning of the guidance that not all of the recommended information is needed or expected in order for sponsors to request a pre-IND meeting. Sponsors' rare disease drug development programs may benefit from FDA's advice in a pre-IND meeting even if they

do not have all of the information recommended in the draft guidance. Accordingly, to the extent that there is information that FDA expects at a minimum in a pre-IND meeting, it may be helpful to clarify what that potentially limited set of data and information would be. Also, the draft guidance notes (for example in lines 75-77) that the recommended information is in addition to providing standard meeting background material, and references the draft guidance for industry entitled "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products." However, it appears that some of the information recommended in the draft guidance may also be considered part of the standard background material. It would be helpful if FDA could clarify what the expectations for standard pre-IND meeting background materials are, and which recommendations in this draft are considered additional detailed information to enable meaningful discussion of the specific questions that may be posed to FDA from a rare disease drug development perspective.

The draft guidance provides recommendations for a broad range of topics related to considerations for product development for rare diseases. However, not all of the recommendations would apply to all product development programs for rare diseases, as the draft guidance also notes in several places. For example, the draft guidance notes in lines 56-57 that issues discussed during pre-IND meetings may vary depending on the drug, program development stage, and targeted disease. We request FDA to consider providing examples, which would be very helpful in enhancing the understanding of the recommendations, and when they would apply. Some suggested topics that FDA may consider providing examples or more information to clarify the context include: consideration for how pre-IND meetings relate to pre-pre-IND meetings, the best ethical practices in rare diseases, novel endpoint development, choice of control group (when placebo are not ethical), nonclinical testing flexibility and nonclinical program that would support starting first in human trials in pediatric population, how many patients are needed in the clinical study(ies), and examples or range/scope of safety databases that support accelerated approval or standard approval.

FDA's openness to seamless clinical trials in recent statements by FDA leadership have been well-received by the industry. We request the FDA to consider including recommendations in the guidance acknowledging the prospect of acceptance of non-traditional clinical trial design, e.g. rather than a phase 1 study, a first-in-human study as a combined phase 1/2 study in the targeted patient population instead of in healthy volunteers. Further, we recommend that the FDA align the recommendation regarding clinical trial design in this guidance with FDA's recent guidance for gene therapy development for rare diseases. Specifically, the July 2018 FDA draft guidance for

industry entitled "Human Gene Therapy for Rare Diseases" recommends that sponsors "should consider designing 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."

The guidance recommendations specific to pre-IND meetings are very helpful to facilitate early drug development for rare diseases. To further facilitate and clarify the regulatory process for early drug development for rare diseases, it would be helpful to provide recommendations on how pre-IND meetings relate to pre-pre-IND meetings and INTERACT meetings available at CBER for gene therapy products.

In addition to the general comments above, we have included specific line item comments in the sections below, title "Appendix 1 – Detailed comments on FDA Guidance".

Overall, we would like to again commend the FDA for generating such a comprehensive guidance document on the important topic of early drug and biologic development for rare diseases and the planning of and participation in formal pre-IND meetings with the FDA for such programs. We see the release of such a robust and pragmatic guidance as a sign of the Agency's commitment to collaborate with industry to promote and facilitate drug and biologic development for rare diseases. Our members look forward to utilizing your revised guidance in generation of novel therapeutic products for rare diseases.

Respectfully Submitted,

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Appendix 1 – Detailed comments on FDA Guidance:

Line Number	Guidance Text	Comment and Rationale	Proposed Change / Recommendation (if any)
I. INTRODUCTION			
II. BACKGROUND			
III. REGULATORY AND SCIENTIFIC CONSIDERATIONS			
A. Pharmaceutical Quality Considerations			
92-93	"For biologics, a description of the potency assay and its relationship to the mechanism of action and, as applicable, a summary of information on viral clearance studies."	Consider providing flexibility with the potency assay because it may be refined after the pre-IND meetings. Consider separating out viral clearance studies as a separate or sub-bullet for cell and gene therapy products, instead of for all biologics.	"For biologics, a description of the **intended** potency assay and its relationship to the mechanism of action and, as applicable. **For cell and gene therapy product**, a summary of information on viral clearance studies **where applicable**."
98-99	"A description of any differences (e.g., manufacturing process, impurity profiles) between the nonclinical batch(es) and	Consider providing flexibility for autologous and "just in time" patient custom manufacturing, where there should be consideration for cost effective and actionable release testing.	

	the proposed clinical trial batch(es)."		
108-110	"A listing of the manufacturing facilities used to manufacture clinical lots and, if known, the proposed manufacturing facilities to be used for commercial manufacturing (if different) and a plan for the transition from the clinical manufacturing to the commercial manufacturing facilities.	Consider providing additional flexibility because a plan for transition from clinical to commercial manufacturing may not be possible at the time of pre-IND meeting request.	"A listing of the manufacturing facilities used to manufacture clinical lots and, if known, the proposed manufacturing facilities to be used for commercial manufacturing (if different) and a plan for the transition from the clinical manufacturing to the commercial manufacturing facilities **(if available)**."
B. Nonclinical Considerations			
115-121	"FDA can exercise flexibility in nonclinical programs where the proposed clinical indications are for treatment of rare diseases, particularly diseases that are serious and life threatening."	Consider providing additional flexibility for pediatric populations that are not accessible as adults or rare diseases that are strictly found and studied in pediatric population.	"FDA can exercise flexibility in nonclinical programs where the proposed clinical indications are for treatment of rare diseases, particularly diseases that are serious and life threatening**, or those that are only found as rare pediatric conditions**."
119	"FDA can exercise flexibility in nonclinical programs where the proposed clinical indications are for treatment of rare diseases, particularly	ARM requests examples of FDA's use of flexibility in nonclinical development programs. Consider providing 3 examples of how a more traditional nonclinical testing program was reduced or modified, in the case	

	diseases that are serious and life threatening."	of a few rare, serious and life-threatening diseases.	
153-156	"A nonclinical plan that supports the initiation of clinical studies by demonstrating the prospect of direct benefit in any planned pediatric age groups, as applicable. The plan should also include the selection of appropriate animal models and appropriate species for specific pediatric toxicity evaluation, as applicable."	Due to the relatively high prevalence of pediatric patients suffering from serious rare diseases (perhaps due to lack of treatment options which results in death prior to reaching adulthood), consider providing more guidance on nonclinical testing parameters that would allow for enrollment of pediatric patients in FIH studies of drugs in development for rare diseases. Consider providing at least one example of a nonclinical testing plan that allowed for a drug (small molecule) and a biologic (such as a cell or gene therapy) to enroll pediatric patients in a FIH study for an Orphan product. Lastly, we request FDA to consider removing the "specific pediatric toxicity evaluation" as such studies may not be feasible or warranted in all programs.	"A nonclinical plan that supports the initiation of clinical studies by demonstrating the prospect of direct benefit in any planned pediatric age groups, as applicable. The plan should also include the selection of appropriate animal models and appropriate species ~~for specific pediatric toxicity evaluation~~, as applicable."
C. Clinical Pharmacology Considerations			
		Consider providing a statement on pharmacokinetic (PK) (biodistribution) expectations for gene therapies in development for rare diseases, and the relevance of the key points outlined in lines 203- 226 for gene therapies, in general. For example, clarify	

		whether population PK expected for gene therapy programs.	
210-214	"A justification of the dose selection (e.g., dosing range, number of doses, dose interval, route of administration, pivotal biomarkers) and patient selection strategy (e.g., enrichment), including an assessment of factors that can contribute to variability in a patient's response to the drug. Modeling and simulations approaches can be used to inform the drug's dosing and elements of the trial design."	Adequately powered placebo-controlled studies for dose finding may not be feasible for rare diseases with limited patient population. Innovative strategies, such as sequential enrollment across dose groups with historical controls, may be more appropriate in some rare disease settings. Sponsors may want to discuss these approaches with the FDA during pre-IND meeting.	"A justification of the dose selection (e.g., dosing range, number of doses, dose interval, route of administration, pivotal biomarkers**, study design of dose finding study(ies) (approaches to randomization and control group(s)**) and patient selection strategy (e.g., enrichment), including an assessment of factors that can contribute to variability in a patient's response to the drug. Modeling and simulations approaches can be used to inform the drug's dosing and elements of the trial design."
225-226	"Plans for in vitro diagnostic development, including adherence to regulatory requirements for investigational devices, as applicable."	Plans for in vitro diagnostic development may not be clear or finalized at the pre-IND stage. Additional flexibility with this recommendation would be helpful	"Plans for in vitro diagnostic development, including adherence to regulatory requirements for investigational devices, as applicable**, and if known at the pre-IND stage."**
D. Clinical Considerations			
235-237	"Participants should be randomized from the first patient enrolled in a trial	While we agree with the recommendation, we especially appreciate FDA's indication of flexibility with the parenthetical "when	"Participants should be randomized from the first patient enrolled in a trial (when

	(when feasible) to help ensure interpretable results."	feasible" because it may not be possible to randomize participants from the first patient enrolled in a trial given the small patient populations and limitations of rare disease trials. We request the Agency to reflect additional flexibility to allay concerns with this recommendation and suggest alternate approaches to ensuring interpretable results."	feasible) to help ensure interpretable results. Sponsors may also use other approaches when it is not feasible to randomize participants from the first patient enrolled in a trial to help ensure interpretable results."
239-240	"Although FDA has no specified minimum number of patients needed to establish drug safety and efficacy, the number of patients should be adequate to assess benefit and risk."	To better inform industry expectations, consider providing historical data, and examples of the average and/or range in patient numbers that have supported licensure (accelerated and/or standard approvals) for rare diseases, and nonrare diseases for comparison purposes.	
245-247	"This approach reflects FDA's recognition that patients and physicians are generally willing to accept greater risks and side effects from treatment of life-threatening and severely debilitating diseases than they would for other diseases."	Consider providing further guidance on best ethical practices (or reference beyond 21 CFR 312.80, and a suggestion to seek expert ethical advice [line 350-351]), in situations, such as pediatric populations, and in rare diseases, in general, where, as noted in the draft guidance, physicians, patients and their caregivers may be willing to accept a higher risk/benefit profile than would be the case for other diseases with available therapies.	
260	"Description and rationale for the following: proposed clinical trial design(s), efficacy endpoints, biomarkers trial population, patient selection	Consider providing examples of control groups that FDA considered appropriate in rare diseases, in particular cases in which treatment with a placebo is not ethically acceptable. Use of alternatives to placebo control is important	"Description and rationale for the following: proposed clinical trial design(s), efficacy endpoints, biomarkers, trial population, patient selection

	criteria, choice of control group, methods used to minimize bias overview of statistical analysis plan (including the sample size and power calculation when possible), and statistical analysis methods."	for rare disease with limited patient populations and unmet medical need. Early input from FDA on strategies sponsors may plan to employ for use of alternatives to placebo control, such as natural history data or historical controls, can be helpful for the development programs. Also, please clarify if "biomarkers" and "trial population" are intended as separate terms or one term as "biomarkers trial population."	criteria, choice of control group **and alternatives to placebo control, such as historical controls**, methods used to minimize bias overview of statistical analysis plan (including the sample size and power calculation when possible), and statistical analysis methods."
285-287	"Considerations related to novel endpoints including the development of clinical outcomes assessments (e.g., patient reported, observer reported, clinician reported, performance outcome measures)."	Notwithstanding reference to "Patient-reported outcome measures: Use in Medical Product Development to Support Labeling Claims" consider including examples of novel efficacy endpoints successfully used in clinical studies of rare indications (as primary and/or secondary clinical study endpoints), and a comment on the expected rigor of novel endpoint development and/or validation for rare diseases, compared to expectations for similar work for use in large indications (such as cardiovascular diseases), including how to demonstrate concept saturation in a rare disease population where sample sizes are limited. As noted in the FDA's discussion document Discussion Document for Patient-Focused Drug Development Public 2 Workshop on Guidance 3: Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments	"Considerations related to novel endpoints including the development **or modification or use** of **existing** clinical outcomes assessments (e.g., patient reported, observer reported, clinician reported, performance outcome measures) **that are fit for purpose for the context of use in the new rare disease setting, where they may not have been used previously."**

		(available here), developing new endpoints and COAs in rare diseases is often complicated by additional challenges, including but not limited to small patient populations for inclusion in studies, cognitive and/or linguistic developmental differences, willingness, ability, and motivation to self-report by age subgroups, availability of few disease experts, and wide geographic dispersion of patients. We recommend FDA to encourage use of existing COAs, where fit-for-purpose COAs can be adapted as is or modified for the new context of use in the new rare disease setting where they may not have been used before. Also, note that the 2009 PRO guidance cited in the footnote will be superseded by the PFDD guidance 3, when issued. We recommend referencing the FDA PFDD guidance webpage for most recent guidance on the topic	
291-293	"Sponsors may consider the pros and cons of alternative study designs such as platform studies."	Sponsors may discuss the possibility of basket trials and multiple indications during pre-IND meeting.	
IV. ADDITIONAL CONSIDERATIONS			
A. Expedited Programs for Serious Conditions			

		It may be helpful to discuss the possibility of earlier Fast Track designation based on nonclinical data during a pre-IND meeting.	
B. Companion Diagnostics			
313-316	"Therefore, FDA recommends that sponsors discuss drug diagnostic codevelopment early in the drug development program if the drug is likely to only have a favorable benefit-risk profile in a biomarker-defined subtype of patients"	In some cases, such information may not be known or confirmed at the pre-IND stage. It would be helpful to clarify when this recommendation would apply and provide additional flexibility	"Therefore, FDA recommends that sponsors discuss drug diagnostic codevelopment early in the drug development program if **it is clear and known at the pre-IND stage that** the drug is likely to only have a favorable benefit-risk profile in a biomarker-defined subtype of patients."
C. Orphan Drug Product Incentives			
D. Pediatric Studies			
347-349	"Prospect of direct benefit can come from adult data, or in some instances, nonclinical animal disease models can also provide proof of concept that the investigational drug may have a beneficial effect in affected children."	It would be helpful if FDA could provide example(s) of what circumstances the FDA is thinking may support the use of animal models to provide proof of concept for beneficial impact in affected children.	
E. Data Standards and Electronic Submissions			