International Consortium for Innovation & Quality in Pharmaceutical Development

Comments on Draft Guidance:

Rare Diseases: Common Issues in Drug Development

Docket No. FDA-2015-D-2818

We are pleased to offer the following comments, prepared by the IQ Consortium. The IQ Consortium is a technically focused organization of pharmaceutical and biotechnology companies, whose mission is to advance science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators, and the broader R&D community.

We very much appreciate the opportunity to review the draft proposed guidance and share our feedback. Specific concerns and feedback on the draft guidance follow. Please contact Dr. Maggie Liu at the IQ Secretariat with any questions: Maggie.liu@dbr.com or 202-746-5620.

I. General Comments

IQ appreciates the Agency's proactive approach as it continues to address the many issues and challenges associated with drug development for rare diseases. In general, the draft guidance provides helpful information to address, at a high-level, the complex issues that Sponsors often encounter in rare disease drug development. FDA's acknowledgment "that study approaches for common diseases are not always feasible for rare diseases" and encouragement of early engagement/dialogue is welcomed. However, the guidance is insufficiently focused on the challenges of drug development for rare diseases and the Agency is asked to provide additional guidance and or clarity in the following areas.

- The guidance should provide recommendations regarding more efficient and focused approaches to endpoint validation for use in drug development programs for rare diseases.
- A more robust discussion of the use of biomarkers as surrogate endpoints should be provided, as this is important in the timely and efficient development of drugs for rare diseases. The current draft only focuses on the use of biomarkers for study design purposes and the biomarker section is particularly onerous in the setting of an orphan disease. Reference is provided to potential benefits in terms of adaptive and enrichment designs to improve clinical development efficiency. Greater guidance on how the existing FDA guidance on enrichment and adaptive trials can be applied to orphan indications is needed.
- The guidance should discuss the use of appropriate innovative statistics (eg, Bayesian Statistics) in the design and analysis of clinical trial in rare diseases. In the absence of clear guidance from FDA, the industry perception will remain that the FDA is reluctant to accept innovative adaptive design. The EMA has openly encouraged the use of Bayesian statistics in their guidance for rare diseases.

- The guidance may be misinterpreted as discouraging the use of historical controls.
- The section on natural history studies sets a higher bar/greater expectation for the conduct and use of these studies than appropriate to gather natural history of disease information.
- IQ recommends that the Agency add statements in the guidance that safety is about overall risk/benefit coupled with the extent of residual uncertainties.
- Given that the focus of research and development is rare diseases with either a high unmet medical need or serious and life threatening conditions, FDA should revise the guidance to specifically address such scenarios, where possible, highlighting and providing examples of abbreviated nonclinical or clinical programs that could be applied to these indications. Serious and life-threatening diseases within the rare disease arena should be viewed as analogous to advanced cancer therapies and as such the guidance proposed should be consistent with ICH S9[1] from a nonclinical perspective. The draft guidance would benefit from the inclusion of examples of regulatory flexibility regarding nonclinical studies, particularly regulatory expectations for nonclinical data that support a marketing application.
- The design and timing of toxicology studies based on ICH M3[2] and ICH S6[3] guidelines are considered in many cases too cautious for rare diseases that are considered life threatening. Specifically, we encourage the FDA to consider authorizing careful dose escalation and dose extension in patients without additional toxicology data beyond IND-enabling toxicology studies, provided the benefit outweighs the risks during early clinical evaluations. Also as outlined in ICH S9 and FDA's "Investigational Enzyme Replacement Therapy Products Draft Guidance[4]", a 3-month toxicology study in two species (one species if a second species is not relevant) together with embryo-fetal development studies (if appropriate) can be considered adequate for registration provided early clinical data from dose extension studies show benefit to patients and indicate no cause for concern for safety. If carcinogenicity studies or additional reproductive and developmental toxicology studies are required they can be conducted after registration and data from these studies together with clinical data could inform risk to patients.
- The draft guidance does not address the nonclinical considerations in support of early pediatric clinical trials (e.g., pediatric-first indications), where it would be helpful for the Agency to acknowledge the need for flexibility, early FDA dialogue and a case by case approach to the nonclinical testing program. In certain patient populations (eg, infant and child patient populations) and life-threatening indications certain components of the toxicology package (eg reproductive toxicology and/or carcinogenicity) can be eliminated or delayed until much later in the development process.
- The guidance makes numerous mentions of early and frequent interactions between a Sponsor and FDA. IQ recommends that the draft guidance be revised to include additional recommendations regarding FDA's preferred approach to establishing early and frequent interactions and to include additional detail regarding with whom these interactions should be with (i.e., Review Division, FDA's rare disease program staff, or both etc.).

2. Specific Comments on Text

Line No.	Comment and Rationale	Proposed change (if applicable)
17	Introduction: IQ recommends that this guidance present the concept of 'orphan equipoise,' making the most efficient experimental use of rare	

[1] International Conference on Harmonisation (ICH). S9. Nonclinical Evaluation for Anticancer Pharmaceuticals. December 2008
[2] International Conference on Harmonisation (ICH). M3(R2). Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. July 2008
[3] International Conference on Harmonisation (ICH). S6(R1). Preclinical safety evaluation for biotechnology-derived pharmaceuticals. June 2011
[4] FDA Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment Guidance for Industry (DRAFT GUIDANCE). May 2015.

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	disease populations by utilizing very efficient study designs, in the introduction.	
57-78	The Background section does not emphasize that in cases where there is a high unmet medical need for a serious and life-threatening condition that a rare disease could be subject to an expedited approval pathway.	Suggested addition to Background section: "Rare disease investigational drugs intended to address unmet medical need in the treatment of a serious or life-threatening condition may be eligible for expedited development and review programs." Add reference to the FDA guidance for Industry on Expedited Programs for Serious Conditions – Drugs and Biologics, 2014.
99	Consider revising the following bullet as it is currently very definitive. "defining the disease population, including a description of the full range of the disease manifestations and identification of important disease subtypes" Due to the heterogeneity of the clinical manifestations of many rare diseases it is not always possible to have an understanding of the full range of the disease. Suggest deleting full from the bullet.	Suggested deletion to line 99 "defining the disease population, including a description of the ~~full~~ range of the disease manifestations and identification of important disease subtypes"
120	Consider revising the following sentence in recognition that it can be challenging to "know which disease manifestations are likely to develop and when". "It is critical to know, for example, which disease manifestations are likely to develop and when, and which are likely to persist". The heterogeneous nature of the disease and the small sample size (even if a natural history study) preclude "knowing" the answer to this question.	Suggested addition to line 120: "Although challenging it can in some instances be critical to know, for example, which disease manifestations are likely to develop and when, and which are likely to persist".
129-135	Paragraph 129 – 135 regarding phenotypic variability in rare diseases. IQ suggests that the Agency consider re-drafting the paragraph to take account of the fact that in many rare diseases the phenotypic subsets are very limited because of the rarity of the disease. For example, severe Fabry Disease is very rare in females so even casting a wide net in a natural history study may not capture some subsets.	
164	With regard to control groups (concurrent or in limited and special circumstances, historical), it is recommended that additional text be incorporated to permit augmentation of internal concurrent placebo data with historic placebo data that has been obtained in a substantially similar patient population based on a substantially similar mode of data collection. This approach can make more efficient use of the available rare disease population whereby unbalanced randomizations (more patients on active treatment) may be utilized while preserving or increasing statistical power. Given ongoing industry initiatives to establish repositories of patient placebo data sets (TransCelerate), this modality is likely to be increasingly feasible and can strike the appropriate balance between use of internal concurrent control groups and external historic control groups.	Suggested addition to line 164: "In addition to a purely historical control, a placebo 'supplementation' strategy using partial historical or observational data addresses some, but not all of the issues with using historical controls. Nevertheless, with the use of partial replacement of placebo or other control groups does permit assumptions of similarity between the supplemental data and the data in the trial to be examined, and can be considered. Early consultation with the Agency on any proposed use of placebo supplementation is strongly suggested."
219-221	Regarding the following sentence "When such biomarkers are to be used in a	

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	drug development program, a reliable and sufficiently sensitive assay should be developed early in advance of initiating clinical studies that will rely on measurement of that biomarker." IQ considers that the statement … "early in advance of initiating clinical studies" maybe unrealistic for small companies or for ultra-rare conditions and hence should revised to introduce additional flexibility.	
240 -307	Nonclinical studies encompass more than toxicology studies (e.g., safety pharmacology studies are an important element of the nonclinical safety strategy).	Suggested alternative language to lines 240-307: Replace 'toxicology studies' with 'nonclinical safety studies' unless specifically discussing general toxicology studies.
241 -242 269-270	The sentence "Before first-in-human use of an investigational drug, FDA requires toxicology information from in vitro studies, animal studies, or both" could be interpreted as indicating that FDA requires toxicology information from in vitro and animal studies to support first-in-human or first-in-patient studies. Later in section V, FDA indicates that under limited circumstances, clinical studies can proceed in the absence of standard toxicology studies. IQ recommends addition of a sentence that discusses serious and life threatening conditions upfront in section V, with recognition that they can be abbreviated, deferred or omitted as per ICH M3[2] guidance. In very limited cases, this could take the form of not conducting any nonclinical safety studies.	Suggested alternative language to lines 241-242: "Before first-in-human studies of an investigational drug, FDA typically requires nonclinical safety studies which may include in vitro and/or in vivo studies. However, FDA may accept abbreviated nonclinical safety programs for drugs to treat serious or life threatening diseases where current treatments, if any, are inadequate."
244 and 247	Nonclinical studies can contribute more information that outlined in the following sentences. Revise the following sentence in 244 "Nonclinical studies can also contribute to a better understanding of drugs mechanism of action." Revise the following sentence in 247 "The nonclinical data may help guide patient eligibility criteria and will often determine some important safety monitoring procedures."	Suggested revision to line 244 Nonclinical studies can also contribute to a better understanding of drugs mechanism of action, therapeutic proof of concept in disease models and identification of pharmacologically active doses for the design of toxicity studies and selection of first in human clinical doses." Suggested revision to line 247 "The nonclinical data may help guide patient eligibility criteria and will determine some important safety monitoring procedures and potential patient toxicities."
258	Add the concept of benefit risk into the following sentence. "Among the factors FDA considers are the design and objectives of the proposed clinical investigations, the existing accumulated nonclinical and human data and the possible risk to humans".	"Among the factors FDA considers are the design and objectives of the proposed clinical investigations, the existing accumulated nonclinical and human data and the possible risk benefit to humans"
261	Please take account of other factors that can support abbreviated nonclinical toxicology programs in the following sentence. "Information from previous nonclinical and human use has the potential to decrease the amount of new toxicology data needed."	Suggested revision to line 261 " Information from previous nonclinical and human use, literature on the drug class and together with information on the severity of the disease and patient life span has the potential to decrease the amount of new toxicology data needed"

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278	Move sentence 278 " Toxicology testing in animal model might be performed ……" to line 255	
294-297	IQ suggests adding the phrase "appropriate and feasible" to the following sentence on adding safety endpoints to proof of concept animal studies in recognition that it may not in all instances be appropriate or feasible to do so.	Suggested revision to line 294: "If appropriate and feasible, and care is taken to preserve the organs, tissues and other samples during nonclinical studies focused on drug discovery and POC, toxicological analyses might be deferred on these samples until there is confidence that the specific molecule used in the animal study will be relevant to the human clinical trial."
300	We have a better understanding of the underlying issue with single gene genetic disorders than other disease areas; therefore, IQ recommends that flexibility should be given to the nonclinical studies required for biological replacement factors.	Suggested addition to line 300: "Biological 'replacement factors' – biological structures that replace a genetic or phenotypic missing protein - that are to be utilized in the clinic at levels designed to be consistent with normal in vivo levels can be the subject of flexibility in preclinical testing, and that this testing should largely be focused on characterization of potential excessive pharmacology."
312	It is important to highlight the general objective of using the most sensitive clinically meaningful endpoint to assess efficacy in rare populations who have large unmet medical need.	Suggested addition to line 312, after first sentence: "If there are multiple clinically relevant endpoints, it is appropriate to select the clinically relevant endpoint that is most suited to detect the effects of the specific mechanism of action."
332-335	Please consider taking account of patient interviews and patient reported outcomes (at least as secondary endpoints) in the following bullet "An understanding of which aspects of the disease are meaningful to the patient and might also be affected by the drug's activity. This evaluation is influenced by knowledge of the pathophysiology of the disease and prior experience (if any) with the drug or related drugs, including nonclinical and clinical effects and pharmacology." Patient interviews (either directly or via patient advocacy organizations) are a valuable source to understanding the disease signs and symptoms most meaningful to patients. Again, the challenge is the heterogeneous nature of most rare diseases.	
351-356	Please consider revising this sentence to account for another feasibility challenge e.g. where a clinical trial for rare disease drug is conducted in several countries and several sites within each country but with few patients per site. "For example, rare disease clinical trials are often conducted at a small number of centers that have the appropriate specialized equipment, and long travel distances for patients may be a barrier. In other cases, complex patient assessments capable of detecting small changes may rely upon procedures that are difficult and poorly accepted by the patient."	
358-360	Please consider revising these sentences to account for that fact that it may	Suggested revision to line 358-360 – "Although treatment-assignment blinding is important to

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	be impossible in some instances to ensure blinding. "Although treatment-assignment blinding is important to lessening the potential for bias in study results, ensuring perfect blinding is difficult for many treatments."	lessening the potential for bias in study results, ensuring perfect blinding is difficult for many treatments or may be impossible".
386-388	"As another example, effective blinding of treatments can reduce concern about bias in the subjective aspects of an assessment, as can conduct of endpoint evaluation by people not involved in other aspects of the trial (e.g., radiologists, exercise testers)."	Suggested revision to line 386-388 – "As another example, effective blinding of treatments (where feasible) can reduce concern about bias in the subjective aspects of an assessment, as can conduct of endpoint evaluation by people not involved in other aspects of the trial (e.g., radiologists, exercise testers)."
458-460	See above comments for line 164 for placebo augmentation.	Suggested addition to lines 458-460: "In limited and special circumstances, placebo augmentation may also be considered whereby, within the guidelines of the ICH E10[5] guidance and subject to appropriate sensitivity testing, data from the internal concurrent control group may be supplemented with historic data from an appropriately matched external control group." It would be helpful if the Agency could provide examples of circumstances where historical controls would be acceptable.
461	The standard clinic trials are challenging to conduct or not feasible for rare diseases when the population is small. Alternative novel and efficient study designs must be considered, keeping in line with the concept of orphan equipoise. Given the general nature of this guidance, it would be useful to provide examples of efficient study designs in this setting.	Suggested addition to line 461: "Study designs using the patient as their own control (such as blinded cross-over designs) can be very efficient and should be considered when clinically feasible and scientifically appropriate."

[5] International Conference on Harmonisation (ICH). Choice of control groups and related clinical trials E10. July 2000