February 5, 2018

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

RE: ACRO Comment on Docket No. FDA-2017-N-6476
"Pediatric Rare Diseases—A Collaborative Approach for Drug Development Using Gaucher Disease as a Model; Draft Guidance for Industry; Availability"

Dear Sir/Madam:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually.

ACRO welcomes this important draft guidance and is pleased to provide the following comments.

I. General comments

This draft guidance discussion of a controlled, multi-arm, multi-company clinical trial to facilitate the development of multiple drug products for a given rare pediatric disease provides an elegant solution to several problems that plague clinical drug development for rare diseases – including the scarcity of patients, ethical concerns related to control arms, and a lack of measurable and validated clinically relevant endpoints for study. However, the draft guidance omits consideration of two key topics. First, the document stops short of providing a discussion of the specific path to attainment of such a drug development transformation. The addition of an analysis of critical logistic concerns in the final guidance would help to ensure greater uptake of this model. Second, the draft guidance does not discuss the important topic of collaborative trial results and drug approval.

Discussion of logistic concerns is omitted from draft guidance

The primary financers of clinical trials are sponsor companies who rightly value confidentiality and control – working carefully to protect the market potential of their pharmaceutical assets. While sponsor companies are increasingly using third party vendors, such as clinical research organizations (CROs), to facilitate conduct of their clinical trials, they generally stay intimately involved, with careful oversight of daily activities to assure their investments are being handled appropriately. As long as there are financial benefits to being first-to-market, this approach is likely to persist. As such, it would be highly unlikely that any drug development company would enter into a partnership with one of their competitors to finance a multi-company clinical trial – even if agreements regarding cost-sharing, control, and confidentiality could be reached.

In order for sponsor companies to find a multi-company clinical trial appealing, the endeavor must propose to provide significant financial benefit with little to no added risk related to breaches of confidentiality. The financial benefit will come from the cost-sharing afforded by having several sponsor companies involved. However, assuring confidentiality within the partnership will be difficult. An unbiased, independent, and skilled third party facilitator for each trial will be needed to create sufficient distance between the involved sponsor companies so that each may have confidence in confidentiality assurances. Since each clinical trial will need to be customized with eligibility criteria, assessments, visit schedules, and safety precautions suitable for the specific disease under study, disease specific advocacy groups and organizations could facilitate. While some such organizations (e.g. Children's Oncology Group) will have the expertise needed to design and conduct an appropriate multi-company clinical trial, others may need to seek support from experienced CROs. Either way, the facilitator would need to contract with each drug development company independently and assure delivery of study data related to the control arm and the relevant arm(s) testing their investigational medical product(s) only. The facilitator would additionally need to maintain decision-making responsibility for trial conduct decisions in order to avoid conflicts of interest, but they could seek consultation and input from the various invested sponsor companies.

As with most endeavors this large, the hardest part is getting started. While the key players in Gaucher disease research may be close, other disease specific advocacy groups and organizations may need extra support and motivation to take on this task. They will need resources to draft an initial protocol or synopsis, formulate a conduct plan, and recruit sponsor companies to participate. If initial financing for these tasks could be supported via the Orphan Products Clinical Trials Grants Program, or a similar program, disease specific advocacy groups and organizations may find the motivation they need to initiate a controlled, multi-arm, multi-company clinical trial for their disease of interest.

Discussion of potential drug approval is omitted from draft guidance

It is not clear how the results of the collaborative trial will be interpreted in terms of potential drug approval. In other words, if two or more treatments show superiority (or non-inferiority) to the control ERT, would that be considered the basis for potential approval, or will that depend on the outcome (e.g. a new exploratory biomarker)? We assume this will be of great interest to sponsor companies at the time to make a decision to participate in the study or not.

II. Specific comments

Lines 136-142

It would be helpful to have some detail on the agency's position with regards to development of relevant endpoints and outcome measures in the context of a collaborative effort (e.g. collaborative natural history study or registry).

Lines 162-163

ACRO requests further clarification in terms of developing exploratory biomarkers in the context of a clinical trial or a natural history study.

Line 208
ACRO recommends clarification regarding whether the extrapolation plan should be combined for each new drug product or whether individual extrapolation plans should be prepared and maintained per company. Also, when adopting a multi-product, multi-company study, it is not clear whether the PSP applicant is expected to develop additional clinical studies in pediatric patients depending on the specific medicinal product/mechanism of action. ACRO recommends clarifying the sentence with the inclusion of the bolded words: *"An extrapolation plan **including each new drug product** could be formulated early during drug development . . . "*

Line 249
It would be helpful to have the Agency's current stance about some practical considerations such as the application process and management of the proposed multi-arm, multi-company trials. For instance, whether the trial application should be made by individual companies under their INDs or one of the companies could potentially take a lead sponsor role while others can just cross reference the trial; whether individual companies will share responsibilities with SUSAR reporting while DSUR updates are done for individual drugs' IBD; whether individual companies should archive the same trial-related data during the required retention period.

Line 252
If possible, some typical examples anticipated in practice will need to be presented for applicants' considerations about study design. For instance, the Agency's thoughts/suggestions on the form of investigational products in consideration of multiple placebos under the double-blinded design; the targeted pediatric subgroups should be the same; the treatment and follow- up periods of individual drugs.

252-255
It seems unlikely that two or more potential new therapies for a given condition would be at the same stage of clinical development at the same time, and the process for managing this is not given. For example, would one drug be "held back" at the FDA's request to allow one or two further drugs to reach the appropriate stage of development to allow them to commence the trial simultaneously? If so, would the period of exclusivity be extended to compensate for such a delay?

Line 253
Where "sponsorship" is concerned, if there is more than one company involved for each product, how will eligibility of individual products for specific designations or rewards be managed (e.g., orphan designation).

Line 254
It is not clear whether failure or clinical hold of an individual new drug product to demonstrate both safety and efficacy will have any impact on the continued development of the remaining new drug products or whether the arm for the drug product that has not demonstrated efficacy and safety can simply be closed moving the patients to another active arm.

257-259
Different therapies are unlikely to be sufficiently similar to one another with respect to the dosing route and regimen that a common placebo could be employed in a double-blind manner. Would each drug require its own placebo "nested" in an overall composite placebo group?

Line 267
Inclusion/exclusion criteria may differ between different products depending on the mechanism of action etc. This could limit patient enrolment for all treatment groups if patients are randomized. We suggest that the inclusion/exclusion criteria can be adjusted to accommodate all involved products.

Table
It is unclear how a single ERT drug product will be selected as a comparator, considering that there are two products approved (Cerezyme and VPRIV). This is also relevant for new exploratory biomarkers, as the response to ERT may not be known in terms of those.

Table
Bone manifestations do not include bone density, although BMD is mentioned on line 163.

Table
Efficacy: In the event that sequential analysis establishes that one of the drugs in the trial is effective, how would that be managed? Clinical equipoise no longer exists, and so continuing the trial would surely be unethical. That said, another drug in the trial may demonstrate a trend to efficacy which has not achieved a threshold level of significance, so what would happen to that drug, which retrospective analysis may establish was more effective than the first drug in a sub-group of subjects?

ACRO thanks the Agency for the opportunity to provide this comment on "Pediatric Rare Diseases—A Collaborative Approach for Drug Development Using Gaucher Disease as a Model." Please contact ACRO if we can provide additional details or answer any questions.

Respectfully submitted,

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