October 5, 2018

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

RE: ACRO Comment on—
FDA Draft Guidance for industry: Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics

Dear Sir or Madam:

As the voice and trade association representing the world's leading, global clinical research organizations, ACRO represents member companies that 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, ACRO member companies advance 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ACRO thanks the Agency for the opportunity to provide comment on this *Draft Guidance for industry: Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics.*

We have organized ACRO's feedback into general comments and line-specific comments immediately below.

General Comments
ACRO welcomes the draft guidance as a means of supporting innovation and efficiency in the development of cancer therapies, and considers that the draft guidance represents an innovative and important approach to facilitate the clinical assessment of a clinically important new compound more quickly, once a dose that appears to be well tolerated and potentially effective has been identified. The guidance notes that "because of the rapid enrolment and evolving nature of the information obtained in these trials, large numbers of patients are exposed to drugs with unknown efficacy and minimally characterized toxicity profiles."

ACRO concurs with FDA that the multi-arm expansion cohort approach described in the draft guidance can offer many opportunities for more efficient data generation, better use of resources and time, and a more patient-centric approach to outcomes measurement, while also presenting challenges that will require additional trial infrastructure to address consequences for patient safety

and informed consent. ACRO cautions that speed in and of itself is not a sufficient rationale as test compounds in oncology are often potent, and potentially unsafe when used improperly. ACRO recommends that the prerequisite criteria should be stated clearly and up front in this guidance. ACRO also recommends that the decision-making process should be clearly stated as well, with clear stopping rules, just like that of the dose escalation study in healthy subjects. Nonetheless, it is doubtful if all the important questions could be addressed in a single protocol. Realistically, we anticipate that a protocol would need to be amended numerous times in order to accomplish the objectives (see comments to lines 459-506 below).

Additionally, clinical trials designed specifically for older and frail adults are rare and this important patient population is probably underrepresented. This situation is concerning in oncology, considering that more than 60 percent of cancers (in the U.S.) are found in patients aged 65 years and older. Few industry-initiated studies seem to focus on the elderly cancer population, with fewer than 20 abstracts focused on elderly patients being presented at ASCO 2018. Interestingly, there appears to be no increased risk for discontinuation of the elderly due to safety reasons. As people are living longer, there is a need to target clinical trial development specifically in elderly cancer patients and the hope is that in coming years there will be more industry sponsored trials and presentations focusing on this patient population. Consequently, it would be helpful if this guidance included more information about the FDA's current thinking on this subject, and some references in the guidance that could encourage increased attention to study design and expansion cohorts in this important patient population.

Specific Comments on the Text

Lines 48-54: Phase I clinical trials in cancer patients often carry an additional objective of proof-of-mechanism and/or proof-of-concept. We recommend that this should be stated in this opening paragraph, especially because it sets the stage for the rationale of expansion cohorts.

Lines 75-77: The reference to a single protocol for FIH is confusing given the multifarious types of studies in FIH that have different protocols based on different endpoints. Also, there should be an established sentinel dose included in this language. Additionally, we note that the definition of a FIH multiple expansion cohort trial requires a single protocol with an initial dose-escalation phase. ACRO recommends that the guidance should specify whether this initial phase should be limited to single dose escalation (with exploration of multiple doses in an additional cohort of a multiple cohort expansion study) or also include multiple doses to establish the proposed dosing schedule. If the former, we recommend that Section V of the guidance should include an additional sub-section on moving from single to multiple dosing (see our comments on lines 150-154, below). ACRO recommends clarifying that, as a general rule, the expansion cohorts should start once the recommended phase II dose is identified in the initial dose-escalation portion of the trial.

Lines 107-108: This sentence appears to be incomplete. Perhaps it can be further expanded to describe the risk of exposing large number of patients to non-optimal doses. This would have to be considered a significant risk for patients.

Line 113: This states that the investigational product could be injected into one eye and the untreated eye is used as a control. Comparison of local effects can be facilitated in this way by eliminating inter-subject variation. This is not the best of controls as recent clinical trial data has shown that it is better to undertake a cross over design with the one eye.

Lines 116-118: Given the potential additional risks to patients resulting from the multiple expansion cohort approach to early clinical development, and the need to ensure that potential benefits outweigh the risks, ACRO agrees with the FDA view that the patient population should be limited to patients with serious diseases for which no curative therapies are available. It is possible that, as experience with the expansion cohort approach is gained, this criterion might be relaxed in the future but, at this time, ACRO supports this position. It is also possible that drugs that are classified in the "break-through" category could be a second criterion. This point is mentioned in lines 119 to 123, but the context of this message suggests this to be a sequential criterion rather than an equally important one. This should be clarified.

Lines 118-119: We recommend that the guidance should explain what the sponsor is obligated to include in the "robust rationale" beyond "diseases for which no curative therapies are available".

Lines 125-135: ACRO agrees that drug product formulations containing drug substances with the material attributes described may be more appropriate for multiple expansion cohort trials. However, such products may not be limited to the examples given in parentheses. For example, products with a biopharmaceuticals classification system class III designation may also be appropriate if the formulation does not change the permeability or gastro-intestinal duration time. Consequently, ACRO recommends that the text in parentheses is deleted and that an additional sentence is added to the paragraph to indicate that sponsors should discuss with the appropriate FDA review division the suitability of the drug product for expansion cohort development. Additionally, we recommend the development and inclusion of a decision tree to indicate when expansion cohorts are worth considering and *vice versa*.

Lines 150-154: Nonclinical testing of a new drug typically continues in parallel with clinical development. Consequently, ACRO recommends that expansion cohorts intended to further evaluate safety beyond the initial dose-escalation portion of a trial should be supported by detailed information from all available additional studies, both nonclinical and clinical, including available safety and pharmacokinetic data from the dose-escalation phase of clinical development and a summary of safety data from other expansion cohorts, if available. Additionally, as noted in our comment on lines 75-77 (above), if the initial phase of a multiple expansion cohort trial is to be limited to single dose escalation, we recommend that Section V should include a sub-section on moving from single to multiple doses.

Lines 173-174: For the reason noted in our comment on lines 150-154 (above), we also recommend that this bullet point states "Updated safety experience from any additional nonclinical studies, the dose-escalation portion and other expansion cohorts, as available."

Lines 187-327: We recommend that thorough QT studies should be included in this section, given their frequency in early phase studies, and that adaptive study design is another useful tool that should be considered for inclusion in this section.

Lines 231-232: Again, for the reason noted in our comments on lines 150-154 and 173-174 (above), we recommend that this bullet point states "Results of available nonclinical and clinical safety, activity, and PK information to support the new proposed dosage(s)."

Lines 297-327: ACRO is delighted to see pediatrics being considered from the outset in this document. Clarification on whether inclusion of a pediatric group in such a trial would require the trial to be included in a pediatric study plan (PSP) would be useful. In addition, we recommend that the guidance should clarify whether, for rare cancers, a pediatric cohort might provide sufficient evidence of efficacy/safety to bypass the PSP process. The ethical recommendations in the EU do not support the age-staggered approach to pediatric development other than in particular circumstances, and we are concerned that the FDA's proposed approach might reduce the possibility of conducting global pediatric oncology trials. Given that both EMA and FDA have expressed concern regarding the low number of drugs being evaluated or approved for pediatric oncology use, anything which compromised pediatric development would be unwelcome. In any case, we are concerned that the statement "In these situations, sponsors should consider staged enrollment of older children or adolescents before younger children" may not confer the desired protection to younger cohorts. Due to the many and significant physiological and metabolic differences between the various pediatric age groups, data generated in older children do not necessarily predict what will happen in younger cohorts, nor do they mitigate the risks. ACRO therefore recommends that the statement quoted above is replaced by one such as "In these situations, the specific pediatric population(s) to be included in the cohort should be determined by a risk-based assessment, with inclusion of appropriate mitigation measures in the trial protocol."

Lines 358-361: ACRO agrees that the sponsor is responsible for the activities described in this paragraph. Additionally, ACRO recommends that the guidance should add that the sponsor should ensure that the protocol requires immediate reporting of adverse events by investigators to the sponsor, that the sponsor should establish a process that allows for rapid evaluation of important safety information (i.e., one that is not dependent upon routine meeting dates of an independent safety assessment committee or independent data monitoring committee), and that the sponsor should establish a communication plan that ensures important safety information is provided rapidly to all investigators and is not delayed pending the preparation of protocol amendments and/or cumulative summary reports (but see also our comments on lines 403-421, below).

Lines 371-373: ACRO recommends that the guidance should specify that Medical Monitors should be haematologists/oncologists in these complex studies.

Lines 377-395: Membership of an independent safety assessment committee may include sponsor representation. In view of the increased risks to patients participating in FIH multiple expansion cohort trials, ACRO recommends that the guidance should include a statement to the effect that the

role and responsibilities of each member of the committee should be defined and documented before the member takes up their duties on the committee.

Lines 403-421: These paragraphs are confusing with regard to responsibility for the dissemination of safety information. As it is written, the sponsor notifies the investigator and then the investigator notifies the IRB. However, when a central IRB is used it is not clear if the IRB is ultimately responsible for dissemination of safety information to all investigators or if that is the sponsor's responsibility.

Lines 430-442: ACRO welcomes the flexibility shown in the draft guidance with regard to suitable approaches for IRB oversight, given the complexity of multiple expansion cohort trials and the potential increased risks to trial participants.

Lines 446-447: The statement "Informed consent documents should be updated as new information is obtained during the trial that may affect a patient's decision to participate in or remain in the trial" implies that any update to the informed consent documents would necessitate the re-consent of subjects already participating in the trial. ACRO recommends that the statement is clarified as re-consent may not always be necessary if the update is relatively minor in nature. ACRO also recommends that guidance should be included on what new information would imply an update of the informed consent document, in order to ensure a consistent approach across studies. However, if it is the FDA's intention that, in a multiple expansion cohort trial, any amendment of the informed consent documents should result in re-consent of the trial subjects, this should be clearly stated, but considerations should be made about the overall impact on study timelines.

Line 459-506: Most likely, the protocol will need to be amended numerous times in order to accomplish the objectives of expansion cohorts. Proactive decision-making mechanisms should be established to facilitate data collection, review and decision making. ACRO strongly recommends that this is specified very clearly and in detail in this guidance. It might be helpful to include discussion of the identification of "decision gates" that may allow timely execution of the above-mentioned activities. Additionally, a Safety Data Review Board would be a useful tool to facilitate this process.

Thank you again for the opportunity to comment on this draft guidance.
Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional information or details.

Respectfully submitted,

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