American Association for Cancer Research

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

Re: Docket No. FDA-2013-D-0576, "Draft Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products"

To whom it may concern:

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention, detection and cure of cancer through research, education, communication and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the July 2013 draft guidance on "Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products ."

The AACR applauds the FDA for developing detailed, forward-looking draft guidance on many of the key issues associated with early-phase trial design of cellular and gene therapy products. There are, however, a few areas in which we believe additional guidance would be beneficial. Specifically, the AACR requests the FDA to provide additional information with respect to assessment of "reasonable risk", dose exploration and selection, safety and activity assessment, appropriate study population selection, establishment of stopping rules and integrating validation procedures for large scale production into early-phase study design. With these additions, we believe this document will encourage innovative approaches to early phase clinical trials of cellular and gene therapy products in oncology accelerating development of these novel therapies and create new hope for cancer patients worldwide.

Elaborate on how to assess "reasonable risk" and dose selection based on preclinical data

The Agency notes that "the preclinical data generated for Cellular and Gene Therapy (CGT) products may not always be as informative as for small molecule pharmaceuticals, particularly since it usually is not feasible to conduct traditional preclinical pharmacokinetic (PK) studies with CGT products."
The Agency suggests that "Preclinical data generated from studies conducted in appropriate animal species and animal models of disease contribute to defining *reasonable risk* for the investigational CGT product." Since dose-selection is based on preclinical data and since risk

determination will influence further conduct of these studies, we request that the agency elaborate and clarify what it means by "reasonable risk". Further, if the agency could suggest alternate means of assessing risk or provide examples of preclinical studies that may aid in determining said risk and dose selection, it would aid sponsors in the design and conduct of these studies.

Dose Selection

The draft notes that in situations where there is uncertainty about the cell subset(s) responsible for the therapeutic or adverse effects, collecting data on various cell subsets in the final CT product, with a comparison of clinical outcomes associated with these different subsets, may help to identify the cell subsets most relevant to product safety and effectiveness. As this is a common problem associated with cellular-based therapies, it would be helpful to investigators if the agency could clarify what kind and level of data the agency would find acceptable.

The draft suggests that when there is no previous human experience with a specific dose treating several patients simultaneously with that dose may pose an unreasonable risk. Therefore, staggering administration to limit the number of subjects exposed is suggested. This is especially suggested in the context of dose escalation such that the first few individuals may be staggered followed by staggered cohorts. With certain CT products each individual dose may vary (cellular expansion *ex vivo*, transduction efficiencies etc.). Therefore, it would be helpful if the agency could clarify how sponsors can establish a staggered dosing protocol while balancing dosing variabilities that may arise due to product characteristics.

The agency notes that larger cohorts might be necessary to provide reasonable assurance of safety before escalating the dose of a product intended for a disease that is less serious and for which the tolerance for accepting risk might be lower. Smaller cohorts might be adequate for a product that is intended to treat a life-threatening disease where a greater potential benefit may justify a higher risk. Examples of what the agency considers "large" and "small" cohorts would be useful. This definition becomes especially relevant for autologous cell-based therapies and induced pluripotent stem cell therapies where a "cohort" is essentially the individual patient.

Clarify Safety Assessment in early-phase CGT studies

The Agency states that the primary objective for first-in-human studies should be **safety evaluation**. For CGT products this can involve assessment of safety related to specific dose levels as well as feasibility of administering certain doses as noted above. An additional consideration for CGT products is the risk that may be involved in administration of products. For example, CGT product administration may involve complicated procedures such as surgery. Therefore, it would be helpful to sponsors if the agency could clarify whether the route of product administration will impact the product's safety assessment by the agency.

Additionally, it would help if the agency could address monitoring of potential long-term safety concerns. This is especially important in the case of CGT products wherein some adverse effects

may not be evident during short-term monitoring. Sponsors could be invited to collect and archive post-treatment safety data from several early studies in order to develop long-term safety databases. It would be extremely helpful if the agency could provide some guidance and/or examples on what types of safety data and what level of detail should be collected in early phase studies. Early-phase studies usually involve small study populations. Therefore, having the flexibility to pool safety data from several different early-phase studies (e.g. exploratory studies of multiple products within a single class or studies that employ a common route of administration) in order to develop and implement a robust long-term safety monitoring protocol would be useful.

Address the Complexities involved in Dose Exploration

Recognizing the complications of performing dose explorations with CGT products, the agency suggests that in certain cases, limiting dose exploration to determine the biologically active or optimal effective dose would suffice. Further, since there may be significant practical limits on the dose of the product that can be produced or delivered, investigators may focus on characterizing the safety profile of the feasible dose or doses, rather than finding the Maximum Tolerated Dose (MTD). Given the uniqueness of CGT products it would be helpful if the agency could clarify how the agency might accommodate for the fact that MTD and biologically active "dose" for these products may sometimes vary for each patient and therefore efficacy and toxicity may vary as well. For certain CGT products a standard "feasible dose" may never be achieved (E.g. Chimeric Antigen Receptor T-Cell therapy). In such cases it would be helpful if the agency can accommodate for variable dosing of the study population by the sponsor. This in turn leads to another issue- if base-dosing parameters are established such that different sub-populations are to be treated with different doses; it would be helpful if the agency could clarify whether multi-dosing protocols would be permissible in later-stage study designs. It would also be useful if the agency could provide examples of what kinds and levels of data should be collected in early stage studies to provide the scientific rationale to establish multiple dosing regimens in later studies of these products.

For certain CGT products MTD may never be achieved which may impact the agency (and sponsor's) assessment of later stage dosing studies. It would be helpful if the agency could explicitly state whether failure to establish a MTD for these products in early-stage studies will constitute a problem in subsequent studies.

Agency notes that for life-threatening diseases, such as cancer, some toxicities may be acceptable. It would be helpful if the agency could elaborate or give examples of "acceptable toxicities". Further, it would be helpful if the agency could clarify if toxicities would be acceptable if they are anticipated and/or can be managed.

Clarify the Process of Product Activity Assessments

Agency notes that a secondary objective of early-phase studies is to obtain preliminary assessments of product activity that could suggest potential efficacy. Given the complicated nature and mechanism of action of some CGT products, it would be helpful if the agency could clarify how it will distinguish between product activity, bioavailability and product efficacy. This is especially pertinent to products that may have long-term beneficial effects but have no immediate signs of benefit for the patient or even display short term toxic effects in the patient. It would also be helpful if the agency can clarify whether a sponsor is required to collect and/or submit these data even if preliminary product activity cannot be determined and/or distinguished in early studies. In case the agency does require this data to be submitted, it should clarify what exactly constitutes product activity data and whether alternate or surrogate data points indicative of product activity can be substituted. Further, in these cases, it would be helpful if the agency can clarify whether early study data can be retrospectively analyzed to establish and validate surrogate markers/endpoints in subsequent studies.

Choosing an Appropriate Study Population

The draft notes that "for most CGT trials, the risk-benefit profile is not acceptable for healthy volunteers." However, it is inevitable that situations will arise where these products will warrant testing in a healthy volunteer population. Therefore, the agency could give examples of cases wherein healthy volunteers can be enrolled to aid sponsors.

The Agency acknowledges that patients with severe or advanced stage disease are more likely to accept the risks inherent in experimental therapies and therefore more likely to enroll in trials. However, the draft suggests that patients with less advanced or more moderate disease may be more appropriate. The draft also suggests that co-morbidities in patients with advanced disease may complicate data interpretation and that patient enrollment must be done keeping in mind the ultimate target population for the treatment.

Given the above, it would help if the agency could give examples or specify situations wherein enrollment of patients with less severe disease would be appropriate. Often, early-phase studies can be exploratory with a goal of identifying the ultimate target population profile. In such cases, the sponsor would pursue studies in a variety of populations in early stages. Therefore, it would be helpful if the agency could elaborate on how such an exploratory study may be pursued.

The draft states that the "decision about the severity of disease to be studied in an early-phase trial should be made only after considering the estimated nature and magnitude of the risks to the subjects, and the implications of those risks, for various stages or severity of the disease." Further, in considering and balancing risk-benefit profile, the potential for individual benefit should be balanced against an assessment of overall risk-benefit. In early-phase studies, the complete risk-benefit profile of the treatment is still not completely understood. Given that, it

would be helpful for the Agency to provide examples wherein individual benefits may outweigh overall risks.

The Agency cautions that risk of the administration procedure (for invasive or otherwise risky administration) is also an aspect of the overall treatment that needs to be evaluated. Given that it may not be advisable to administer a placebo using an invasive or otherwise risky procedure; it would help sponsors if the agency could elaborate on how it will parse out the risk posed by the administration procedure versus the risk posed by the treatment itself.

Clarify appropriate use of Stopping Rules

Due to the uncertain and high-risk nature of CGT treatments, the agency recommends including stopping rules in early phase study protocols. Stopping rules may not necessarily terminate a trial and well-designed stopping rules may allow sponsors to assess and address risks identified as the trial proceeds, and to amend the protocol to mitigate such risks or to assure that risks to patients remains reasonable. It would help if the agency could detail how data gathered to stop the study can be used to amend the protocol and/or be analyzed to assure that risk to patients is reasonable.

Integrating validation procedures for large scale production

Early phase studies with CGT products involve small batch testing. However, in order to proceed to the next phase of testing, production must be "scaled up". Large scale manufacturing of CGT products can be complicated as cellular potency, *ex vivo* expansion etc. can vary between batches. Therefore, the process for large scale production should be validated such that the quality of the product is consistent and is not compromised during scale up operations. Consequently, if the validation process for large scale production could be integrated into early phase study design, the sponsor would be prepared to advance to the next stage of the study without undue delay. Hence, it would be helpful if the agency could provide some guidance on how sponsors may seek to validate the process for scaling up manufacture of these products during early phase studies. Further, the agency, given its expertise and experience with these products and the problems that arise during large scale production, could also provide sponsors with guidance regarding common potential production problems to be alert to and the means to alleviate the same.

The AACR commends the FDA for its commitment to incorporating scientific advances into its regulatory framework. The AACR is pleased to extend its resources and broad expertise to the FDA as the Agency further refines its guidance for early-phase studies of cellular and gene therapy products to support the approval of human drugs and biological products as well as other critical issues. If you have any further questions or require follow up, please contact Rasika Kalamegham, PhD, Senior Science Policy Analyst at 267-765-1029 or rasika.kalamegham@aacr.org.

Sincerely,

Frank McCormick, Ph.D., F.R.S.
Chair, Regulatory Science & Policy Subcommittee

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