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June 14, 2022

Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Draft Guidance for Industry — *Considerations for the Development of Chimeric Antigen Receptor T Cell Products* (Docket No. FDA-2021-D-0404)

Dear Dr. Califf:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) on the Agency's draft guidance on *Considerations for the Development of Chimeric Antigen Receptor T Cell Products* (Docket No. FDA-2021-D-0404).

ASH represents more than 18,000 clinicians and scientists worldwide committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell disease, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

The Society is pleased to provide comments on the Draft Guidance related to development of Chimeric Antigen Receptor T (CAR T) Cell products. ASH members are at the forefront of this therapy, conducting research and providing this potentially curative treatment to patients today with multiple myeloma, certain types of lymphoma, and leukemia. Overall, the Society is supportive of the recommendations included in the document. We are pleased to share comments about areas where additional clarification would benefit researchers, in the order in which they appear in the draft guidance document:

Serial Administration of CAR T: For section III, section C, while the FDA's recommendation to evaluate previously administered CAR T cell levels in the cellular starting material seems reasonable in theory, this could be challenging to do in practice since primers and probes for evaluating the circulating CAR T are usually proprietary for each company. Additional guidance from the FDA on how to conduct such evaluations will be useful. The FDA should clarify the statement in line 165 regarding "life threatening risk of myeloablation." Since studies giving CAR-T (as a tool to achieve remission) followed by myeloablative preparative regimens have shown high survival -- higher than that of chemo followed by hematopoietic cell transplantation – it is unclear how such serial administration of CAR-T products poses a life-threatening risk.

Cryopreservation: For section III, section D, the Agency notes "We generally recommend cryopreservation when CAR T cells are manufactured at a central location and shipped…." Because of the clinical condition of patients receiving these therapies, many will not be able to receive the CAR T at the time of CAR T release. Thus, the risks of lost product and failure to infuse are high with fresh products. ASH recommends the FDA consider recommending cryopreservation for all studies unless there is a reason not to. Also, while ASH concurs with the importance of maintaining integrity of the product during shipping, having to change an IND because of a change in courier services may be a burden. We ask that the FDA provide guidance on how investigators can quickly and easily update the IND in such cases to minimize administrative burden or pausing the study.

Risk-Benefit Calculations: In Section IV A 1, ASH supports the discussion that addresses many of the key considerations of risk-benefit calculations, including limiting potentially life-threatening early phase trials to those who truly merit this risk, while also acknowledging there may be patients with minimal to no options for whom the risk-benefit ratio has to carefully consider first-in-human studies.

Pediatric Patients: In section IV A 4, ASH recommends that the Agency soften the wording for the 'usually obtain safety and tolerability data in adults' to 'where possible obtain safety and tolerability data in adults.' Many pediatric tumors will lack adult correlates and there is precedent for pediatric-first in human studies in phase I trials. It would be helpful for the FDA to provide guidance about studies that include both adults and children.

Autologous Leukapheresis: For section IV B, ASH notes that the Guidance indicates that autologous leukapheresis does not require donor eligibility determination. Our clinician experts note that they typically include donor eligibility determination for auto products, including determination for collection of unmanipulated hematopoietic cell transplantation (HCT). ASH recommends that FDA update the guidance to state that "donor eligibility determination" be made a requirement.

Dose Escalation: In section IV B 1 B, the Guidance states that a continual reassessment method (CRM) is inappropriate because of concern about making decisions based on just one patient. However, it is possible to use a CRM variant that has decision rules similar to a 3+3 design that can estimate a proportion of dose limiting toxicities (DLTs) in the population at each dose. We ask the FDA to clarify the Agency's preference for the 3+3 dose escalation studies vs other designs such as the CRM that may have some value in effectively and efficiently capturing dose limiting toxicities.

Immunogenicity: The recommendation to develop immunogenicity tests may be a challenge for some researchers. This is not as difficult when there is a murine construct but may be more difficult for some humanized mouse constructs. ASH also recommends that the Agency clarify that murine vs. human CAR as a factor for CAR T immunogenicity, along with the other elements noted in section IV C 3.

Cytokine Release Syndrome (CRS) Monitoring: In the section VI D discussion of CRS monitoring, while it is good to monitor cytokine levels, it is worth noting that most clinicians will not receive levels soon enough to treat CRS. CRS and ICANs can emerge rapidly and treatment should not wait for results/proof. Rather, they tend to use these levels retrospectively to interpret what happened clinically. Thus, ASH recommends that the "algorithm based on the cytokine level as an adjunct to the clinical decision for administering…" language be modified. It is also important to include that treating facilities have CRS medication (tociluzumab) stocked prior to starting CAR T therapy (this is standard of care for most cellular therapy centers). Finally, all grade 4 CRS are defined as being DLTs in section IV D 3. But, if CRS reverses in one day after tocilizumab administration, this should not be defined as a DLT.

Graft Versus Host Disease (GVHD): For section V, section C, ASH agrees that allogeneic T cells may cause GVHD or host rejection. However, the Society does not believe that mixed lymphocyte reactions are informative to evaluate immunogenicity of products that are modified to reduce the risk of GVHD since such reactions have been poorly predictive of GVHD. Furthermore, the use of these lymphocyte reactions spans two distinct scenarios with

different risks. If a patient is already fully engrafted with a donor cells without graft versus host disease, the likelihood is lower that donor-derived CAR T would induce GVHD. However, in the setting of low mixed chimerism or an entirely allogeneic CAR T from the donor immune system, the risk of GVHD would seem very high without further genetic modification. ASH encourages FDA to clarify this section of the guidance.

Cellular Depletion: Finally, the guidance does not mention the capture of expected/associated cellular depletion, for example, the duration of B cell lymphopenia after CD19 CAR T. This is important to note, in addition to the evidence of CAR T persistence, as CD-19 B cell depletion far exceeds the CAR T detection and requires additional therapies.

ASH appreciates the opportunity to provide these comments. Please consider ASH a resource; we would be pleased to provide additional information or support. If you have any questions, please use ASH Deputy Director of Government Relations and Public Health Stephanie Kaplan (*skaplan@hematology.org* or 202-776-0544) as your point of contact.

Sincerely,

Jane N. Winter, MD
ASH President