Draft Guidance: **Considerations for the Development of Chimeric Antigen Receptor T Cell Products; Draft Guidance for Industry; Docket No. FDA-2021-D-0404**

Comments submitted by International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

GENERAL COMMENTS ON THE DOCUMENT
We recommend adding a reference to Quality by Design as the guidance focuses on testing and there may be inherent flaws in some of the test methods (e.g., sterility testing). Encouraging QbD could mitigate some of the risk solely relying on end product testing to demonstrate CQA are achieved.
Additional visual representations/diagrams for CAR-T construct would be useful.
We recommend adding patient population (age, demographics, gender) considerations.
We recommend that the guidance include the limitations of CAR-T cell therapy such as Antigen Escape.
We recommend that the guidance identify the key considerations for setting and determining appropriate trial endpoints.
We recommend that the guidance include quality considerations (QMS development) for preclinical through late-stage development.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Line 260	"endotoxin"	"endotoxins"	This aligns with the USP test (<85>) for this contaminant
Line 280	"… any wash steps or cryopreservation procedures."	"…any wash steps**, contamination control,** or cryopreservation procedures."	To ensure steps to control (microbial) contamination are described and aseptic manipulation is encouraged.
Lines 340-343	"For example, we recommend that human or animal-derived components are not sourced from geographical areas of concern for potential viral and/or transmissible spongiform encephalopathy (TSE) agent contamination and that components be tested appropriately for adventitious agents."		Please clarify whether TSE/BSE certificate (that derived components are not sourced from a geographical area of concern) be a regulatory expectation or will testing for TSE be the only requirement.
Lines 349 -356	"To assure product safety,……. And validated test method.		It may be more appropriate to highlight in-process testing for bioburden when process volume is sufficient, since these products cannot be terminally sterilized and due to the inherent flaws in product sterility testing. Or a clear comment could be provided if in-process bioburden is a recommendation.
Line 404	"…phenotype, CAR expression)."	"…phenotype, CAR expression**, bioburden)**.	Due to the inherent risks associated with the aseptic manufacture of CAR T products and the inability to terminally sterilize them, it may be beneficial to stress the importance of in-process bioburden testing by highlighting this additional in-process test.

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Line 694	"…be considered new chemistry information…"	"be considered ~~new chemistry~~ **CMC** information…"	Chemistry is a regulatory review discipline, not a regulatory application section. The information to be provided to support manufacturing changes are considered CMC (chemistry, manufacturing and controls) submission. The manufacturing changes may represent other regulatory disciplines needing to review it (e.g., microbiologists, process, facilities, or their integration reviewer).
Lines 293-295	We recommend that you test the leukapheresis starting material for microbial contamination (e.g., sterility or bioburden) prior to initiating CAR T cell manufacturing or that you retain a sample for post hoc testing in the event of a DP sterility test failure.	We recommend that you test the leukapheresis starting material for microbial contamination (e.g., sterility or bioburden) prior to initiating CAR T cell manufacturing ~~or that you retain a sample for post hoc testing in the event of a DP sterility test failure.~~	Microbial/Contamination control strategy for CAR-T products requires final product sterility to ensure patient safety (as noted on Line 349). We suggest it is more appropriate to forward process patient material at risk while awaiting sterility result of apheresis material and terminate manufacture in the event of a sterility positive result. This could enable faster turnaround for re-apheresis of the patient and subsequent remanufacture. Please clarify whether the expectation is that sterility positive drug product results is expected given the inability to sterilize/reduce bioburden during manufacturing.
Line 609 Line 650	Change management		We understood that this guidance document pertains to IND submissions, but principles related to ICHQ12 and associated lifecycle management would be beneficial to ensure principles pertaining to ICH Q12 are

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			embedded earlier in product development to enable benefits associated with rapid lifecycle changes in the future. Commentary speaking to established conditions and use of post approval change management protocols in development of lifecycle strategies would be beneficial.
Line 739	However, if product manufactured from healthy donors is not adequate to assess product comparability for autologous CAR T cells, the comparability study should include evaluation of CAR T cells manufactured from patient cellular starting material.		Given the criticality of split runs evaluating comparability pre/post changes, further comment on situations where healthy donor material is not appropriate would be helpful. Otherwise, experimentation with patient material cells is implied, which does not aid in treatment. A clinical evaluation prior to executing comparability would be needed to ensure the patient is properly treated ultimately.
117 to 121	Long term follow up is recommended for products that include integrating vectors, because integrating vectors may increase the risk of delayed adverse events (Ref. 10). The predicted risk of delayed adverse events is thought to be low for non-integrating vectors and generally long term follow up would not be needed		Please elaborate on the impact of the unknown risk of integrating vector to the patient and can potentially have on the DNA.
154 to 155	Therefore, evaluation of the previously administered CAR T cell levels in the cellular starting material may be appropriate.		The addition of evaluation questions that can be asked or considered to assess the previously administered CAR T Cell impact would be helpful.

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155 to 159	Additionally, due to the risks associated with increased vector integration frequencies, CAR T cell testing should include evaluation of the vector copy number (VCN) in the final product both for the newly introduced and previously administered CAR T cells, if the previously administered CAR T cells are detectable.		Please add the FDA recommended guidance on what the VCN should be. Please clarify how the patient data and VCN are to be evaluated of a previously administered CAR T cell therapy if the manufacturing companies are different.
301 to 305	Autologous leukapheresis starting material does not require donor eligibility determination (Ref. 23), screening or testing (21 CFR 1271.90(a)(1)). Allogeneic leukapheresis starting material, on the other hand, does require donor eligibility determination and screening and testing for relevant communicable disease agents under 21 CFR Part 1271, Subpart C		Please expound upon the considerations for donor eligibility determination, screening and testing.
777 to 782	We recommend you submit data, ideally from qualification runs using the same cellular starting material, performed at each site to demonstrate analytical comparability of the products manufactured at each site, including a list of the methods used for testing and the predefined acceptance criteria used for determining analytical comparability.		This should specify what that the “same cellular starting material” means. Line 142 to 144 states “The starting material for CAR T cell manufacture is generally obtained by leukapheresis of patients (for autologous products) or healthy donors (for allogeneic products).” Please clarify that this means the same patient for autologous, and the same healthy donor for allogenic.