Draft Guidance: **Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry; Docket No. FDA-2021-D-0398**

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

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 218	"…an existing IND or **Master File**."		Please verify that it is appropriate to submit this information in a Master File, as FDA has considered referencing a MF for CDER regulated biologic products in a BLA inappropriate, and another current draft guidance (*Considerations for the Development of Chimeric Antigen Receptor T Cell Products; Draft Guidance for Industry; Docket No. FDA-2021-D-0404. P*g. 10, line 388) mentions that this information should not be in a DMF.
Line 239-240	"…, such as purity and functionality..."	"…, such as **microbial control,** purity and functionality"	Suggest adding "microbial control" as this is a significant concern for these aseptically manufactured components/API (and ultimately) products with multiple manipulations
Line 249	"… on measures taken to ~~ensure~~ aseptic processing"	"… on measures taken **towards ensuring** aseptic processing"	There is no way to test, demonstrate or prove that aseptic processing is 'ensured'.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
376	The animal species and/or models selected for in vivo studies…	Please clarify how organoid and/or complex tissue models would be viewed.	Organoid and/or complex tissue models could provide insight beyond traditional monoculture in vitro testing. In certain products where the MOC is unique to humans might provide a more relevant demonstration of a biological response than animals. These models could provide biological response for rare or personalized treatments. (Ronaldson-Bouchard, K., Teles, D., Yeager, K. *et al.* A multi-organ chip with matured tissue niches linked by vascular flow. *Nat. Biomed. Eng* **6,** 351–371 (2022).) However, it is unclear if the FDA will only view organoid and/or complex tissue models as in vitro testing only, capable of demonstrating activity, or, if these models could substitute for animal models with justification.
513-515, 525-531	Therefore, first-in-human trials involving such products generally should be designed to enroll only subjects for whom no other treatment options are available or acceptable.	Therefore, first-in-human trials involving such products generally should ~~be designed to enroll~~ **evaluate enrolling** only subjects for whom no other treatment options are available or acceptable.	