Response to a request for comments Docket No. FDA-2023-D-2436 "***Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry"***

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

General Comments
The CGT specific recommendations for managing manufacturing changes are welcome. The incorporation of concepts and terms noted in the internationally agreed guideline, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management ICH Q12 should be included in this guidance in order to set the framework around those specific recommendations included in this draft guidance. Examples are i) providing an overview of the concept of established conditions before the example on operating ranges for a cell wash process in lines 116-119 ii) highlighting active knowledge management as part of the Pharmaceutical Quality System and change management process in developing control and/or scalability improvements. In the effort to deliver safe and effective medicines to patients with no/limited treatment options, process control strategies, and scalability improvements are not fully developed until the product is available to address the patient population's needs. Post-approval Change Management Protocols and Product Lifecycle Management documents should be mentioned as a means to manage the knowledge around these potential changes. The establishment of an ICH Q12 framework will provide the industry with a more efficient manner to address new challenges globally as technology advances.
Emphasis on statistical approaches to comparability is provided, but in many cases for cellular-derived processes, this is challenging to implement. The difficulty in risk-assessing changes is acknowledged in line 412. The draft guidance should consider these challenges. The absence of the ability to apply statistical approaches could be addressed by using more rigorous risk management exercises involving an interdisciplinary team (e.g. discovery scientists, clinical experts, and drug product administration experts)

6110 Executive Blvd., Suite 600, North Bethesda, MD 20852 USA **T** 1 301-364-9201 **F** 1 240-204-6024 **ispe.org**

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
99-100	For investigational products, maintaining product quality by control of CQAs and critical process parameters (CPPs) during manufacturing changes is important for obtaining interpretable clinical study data that can support licensure	~~For investigational products, maintaining product quality by control of CQAs and critical process parameters (CPPs) during manufacturing changes is important for obtaining interpretable clinical study data that can support licensure.~~ Fully **defining CQAs and CPPs may be challenging in the early stage of development because of limited and evolving understanding on product and process; however, introducing these concepts in the very beginning and keeping them evolving should be considered to support licensure.**	The definition and determination of CQAs and CPPs is normally evolving during clinical development, as product and process knowledge becomes available, particularly in early clinical programs and when developing products in accelerated programs, for example, breakthrough therapy. We recommend FDA clarify the expectations on CQAs and CPPs in a way that reflects this progression of knowledge, for example use of phase-appropriate language - early stage, late stage, and post-approval.
109 - 110	Therefore, we recommend that you apply a systematic approach to quality risk management designed to identify, assess, analyze, and mitigate potential risks. Such an approach can facilitate science-based decision-making and enable a risk-based evaluation of manufacturing changes (Ref. 1).	Therefore, we recommend that you apply a systematic approach to quality risk management designed to identify, assess, analyze, and mitigate potential risks **by involving subject matter experts in the risk assessment.** Such an approach can facilitate science-based decision-making and enable a risk-based evaluation of manufacturing changes (Ref. 1).	We recommend that FDA consider introducing language that sponsors should consider involving discovery scientists, clinical experts, and drug product administration experts in an interdisciplinary team during risk management exercises. **(e.g. discovery scientists, clinical experts, and drug product administration experts)**

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Section or Line Number	Current Text	Proposed Change	Rationale or Comment
174-176	For post-licensure manufacturing changes, there may be a need to generate real-time stability data with post-change product to demonstrate a lack of adverse effect on product quality,…	For post-licensure manufacturing changes, ~~there may be~~ **science- and risk-based approaches may identify** a need to generate real-time stability data with post-change product to demonstrate a lack of adverse effect on product quality,…	Consider revising text for consistency with ICH Q12 (Section 9) principles.
211-213	If comparability studies demonstrate that the manufacturing change does not adversely affect product safety but are insufficient to exclude an adverse impact on product effectiveness,…	If comparability studies demonstrate that the manufacturing change does not adversely affect product safety but are insufficient to exclude an ~~**adverse**~~ impact on product effectiveness	Consider removing **"adverse"** throughout where the impact could be an enhancement which could be a cause for failed comparability (e.g., increased potency).
477-479	We recommend that you submit a detailed study protocol (comparability protocol) and request feedback from the FDA (section VII of this guidance) on the study design and statistical approach.	We recommend that you submit a detailed study protocol (comparability protocol) and request feedback from the FDA (section VII of this guidance) on the study design and **any statistical approach which could be supported by data.**	Statistical approaches may not always be possible, particularly during the IND phases when sufficient data may not be available.

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