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Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Docket Number: **FDA-2023-D-2436**

Dear FDA Dockets Management Staff,

I am submitting comments to Docket Number FDA-2023-D-2436, **Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products, Draft Guidance for Industry** on behalf of the National Institute for Innovation in *Manufacturing* Biopharmaceuticals (NIIMBL). NIIMBL, a part of the ManufacturingUSA network, is a public private partnership of approximately 200 members in academia, government service, and across the biopharmaceutical supply chain. NIIMBL collected feedback on this Draft Guidance from its membership and aggregated the responses.

NIIMBL, on behalf of our community, recognizes the individual efforts involved in generating the Draft Guidance and we appreciate the opportunity to comment. This Draft Guidance does not represent a significant departure of philosophy or practice from previous FDA guidance and it is reassuring that CBER is committed to regulating cell and gene therapy (CGT) products within the current FDA and ICH regulatory framework. The feedback provided in this response to the docket focuses on assuring the utility of the document for advancing risk-based, patient-centered biopharmaceutical manufacturing through clarity of expectation, consistency with existing guidance and regulation, and technical excellence.

We recommend providing additional clarification around the following major points:

1- **Patient-Centered Risk & Clinical Relevance**. Global trends in regulatory oversight and risk management are moving towards probabilized, patient-centered risk management. A focus on clinical relevance of observed variation is appropriate in this environment, where all source variance and analytical measurement uncertainty are both large. It would be helpful if the guidance were explicit in identifying a central role for clinical relevance, in addition to measurement uncertainty and variance in risk assessment.

2- **Measurement Uncertainty**. Similarly, it would be helpful to explicitly state that variation within the measurement uncertainty of an assay should not be a basis for decision making within the process control strategy, especially not in lot release. Variation within the measurement uncertainty cannot be assigned a relevance in process or product control.

3- **Site to Site Comparability & Distributed Manufacturing**. It is understood that when CGT processes are transferred from site to site, assurance of comparability is critical to the patient yet burdensome and expensive. It would be useful for the guidance to comment upon differences in expectations for asserting site to site comparability

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associated with a manufacturing transfer and site to site comparability in a distributed manufacturing setting. It would be useful to clarify whether the biosimilar standard of "highly similar with no clinically relevant differences based upon the totality of the evidence" is applicable in site transfers or distributed manufacturing strategies for CGT products.

4- **Statistical Analysis.** Statistics is one of many tools to aid decision making and drawing conclusions, but it is not decisional in itself. It is also useful to note that the statistical tools used in CMC processing are quite different from those used in clinical assessments of populations. In CMC processing, "n" can be quite small, especially in CGT manufacturing, and the cost of increasing "n" solely for process and product characterization can be prohibitive. Sometimes measurement uncertainty error greatly exceeds response thresholds and sometimes patient to patient uncertainty or clinic to clinic uncertainty greatly exceeds that of CMC control. It would be helpful to clarify that statistical analysis of development and manufacturing lots may be informed by all source data enrichment and mathematical models built upon first principles and/or related processes. We recommend providing guidance around low lot numbers (for example, $n < 3$) where statistics are not practical.

5- **Resource Constraints**. The document recommends that sponsors discuss changes with the agency. As the number of CGT submissions and companies increase, it becomes clear that there will be capacity constraints on the ability to grant meetings. It would be helpful to have clarity around when meetings are an expectation or to remove references to meetings in this document.

6- **Appendix or FAQ Document**. There are many places in the document where additional clarification or examples might help sponsors apply the guidance to their own unique situations. However we recognize that too many examples might limit the utility of the document or make it overly prescriptive. A collection of these examples, either as an appendix or as an FAQ document would be helpful. Some examples might include:
   - "Reporting Manufacturing Changes to an IND or BLA" – what are some changes that might not require additional studies?
   - What are some examples of the types of changes the agency anticipates might require nonclinical studies?
   - Are there different considerations for different product types (e.g. in vivo AAV, gene editing, CAR-T), especially when study material is limited?
   - … and others

7- **Shipping Stability**. The guidance recognizes the importance of managing stability during shipping and handling but is silent on expectations for shipping validation, point of use testing, and related label or package insert instructions to users. It would be useful for the guidance to confirm that expectations for CGT biologics are no different than those for 351(a) submissions in general or to clarify additional expectations for CGT products. As written the guidance highlights a clinically relevant concern but does not comment on mitigation of the concern.

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8- **Accelerated Stability Studies**. Consistent with prior guidance, stability studies must be fit for purpose at time of use. The document suggests that accelerated stability studies may be helpful. The relevance of accelerated stability studies (e.g. higher temperatures, shear) has been increasingly brought into question because the major degradation pathways for biologics tend to be physical (e.g. aggregation, higher order structure disruption) rather than chemical. We appreciate that the Agency uses the word "may" when referring to the use of accelerated stability studies, but as a practical matter, we recommend that the guidance note that accelerated stability studies may be helpful if predictive of the major degradation pathways in commercial or clinical settings.

We also suggest edits to address the following minor points:

9- **Lines 240-241.** We suggest rewording these lines since it is hard to prove a negative. An alternate way to phrase this might be: "In order to approve manufacturing changes, analytical and/or nonclinical comparability studies, or other sound scientific arguments must demonstrate that manufacturing changes have no adverse effect on product quality."

10- **Lines 265-287**. To be consistent with prior practice and to accommodate the systems burden associated with increased submissions and healthcare solutions within the space, we suggest that "… or IND Amendment" be added to the title of this section. This section may be unintentionally confusing and suggest to sponsors that process changes accommodated by IND Amendment now need a new IND.

11- **Line 886**. The link is broken (Guidance for Industry: Q9 Quality Risk Management)

We appreciate this opportunity to provide feedback to this request and would be happy to follow up.

Kind Regards,
Gene Schaefer
NIIMBL Senior Fellow
