590 Avenue 1743
Newark, DE 19713
P 302.831.0663

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

Docket Number: **FDA-2021-D-1047**

Dear FDA Dockets Management,

I am submitting comments to Docket Number FDA-2021-D-1047, Q13 CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS 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 is sponsored by the Department of Commerce, administered through the National Institute of Standards and Technology (NIST), and supported by State, Federal, and private funding. NIIMBL has a Collaborative Research and Development Agreement (CRADA) with the United States FDA and the relationship between FDA and NIIMBL's Federal Sponsors is expanded upon in MOU 225-21-006 dated January 15, 2021.

NIIMBL collected and analyzed anonymized feedback on this Draft Guidance from its membership and then led discussions based on this feedback at NIIMBL Regulatory Considerations Committee meetings. All responses acknowledged the magnitude of the task and were appreciative of the individual efforts involved in generating the Draft Guidance. The feedback provided in this response to the docket focusses 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 in manufacturing controls.

We recommend revising the document to address the following concerns:

- It is important for the document to be explicit about differences in the application of general principles of practice to the continuous manufacture of synthetic small molecule drugs and to the continuous manufacture of biologics. While many technical matters are no different between these two classes of pharmaceuticals; regulatory review, inspection, and management of post-launch process changes can be quite different due to complexity of the products and residual uncertainty associated with first principle understanding of critical quality attributes. Rather than being silent on these differences, we suggest the document be explicit about differences in quality assurance and regulatory oversight between biologics and small molecule drugs. Being clear about these differences mitigates unintended outcomes and facilitates regulatory convergence.
- Part I of the document describes general regulatory considerations and Part II provides Annexes with examples of application, *e.g.*, Annex III – Continuous manufacturing of therapeutic protein substances. It would be helpful if the document were explicit about regulatory considerations applicable to all product classes and regulatory considerations primarily applicable to, for instance, non-sterile oral dosage forms but not to biologic parenterals or to solid powders but not bulk solutions. This would also allow the guidance to insert a "why" or "because" statements, as appropriate, in Regulatory Considerations. The current construction of the document, generalizing

590 Avenue 1743
Newark, DE 19713
P 302.831.0663

the small molecule principles and specifying the biologic exceptions, can lead to unintended suggestion of regulatory hierarchy and unnecessary confusion.

- Definitions of batch and lot are critical to deployment of continuous manufacturing technologies. For clarity, the guidance should explicitly confirm that the definitions of batch and lot, especially for biologics, are consistent with those in ICHQ7 and 21CFR210.3.
- Nomenclature and lexicons used in this guidance should be harmonized and consistent with those of the other ICH Guidance documents. The introduction of new terms for established practices or new or nuanced definitions of established terms without harmonized adjustment of antecedent guidance is not helpful and can compromise the goals of the guidance outlined in the Introduction.
- It is clear that dynamic, real-time measurements are central to the deployment and control of continuous manufacturing technologies. The guidance as written does not address considerations for data or process stream sampling such as: measurement uncertainty or calibration and maintenance practices assuring accuracy and precision of integrated sensors specific to a continuous process. We recommend the guidance be amended to include validation of dynamic (continuous flow) in-process assays, measurement uncertainty, maintenance, and responses to special cause signals and common cause data drift.
- The guidance addresses use of closed bioprocess manufacturing systems in Annex III but does not specify the definition of the term. In general, current practice for proof of closed systems focuses on bioburden, cleanliness, and integrity to prevent adventitious contamination. Assurance of viral inactivation or clearance is an additional special case for mammalian cell culture derived products. We encourage reference of the commonly accepted standard *International Society of Pharmaceutical Engineering Baseline Guide, Volume 6: Biopharmaceutical Manufacturing Facilities, 2nd ed.* for definition and practice in proof of closure.

Taken together, the feedback that we have collected suggest a need for significant edits to assure harmony with existing guidance, clarity of messaging, and appropriate application across product classes, especially biologics. We appreciate the FDA providing the public and technical communities of practice an opportunity to comment on this Draft Guidance.

Submitted on behalf of NIIMBL,

Gene Schaefer

Senior Fellow and Chair Regulatory Considerations Committee
National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL)
590 Avenue 1743
Newark, DE 19713
gene@udel.edu

cc:
Dr. Kelvin Lee, Director of NIIMBL
Dr. John Erikson, Acting Chief Technical Officer NIIMBL
CDR James Coburn, USPHS, FDA Liaison to NIIMBL
FILE