Request for Information; Identifying Ambiguities, Gaps, Inefficiencies, and Uncertainties in the Coordinated Framework for the Regulation of Biotechnology

Docket ID No. APHIS-2022-0076

A response on behalf of the
National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) Community

OVERVIEW

These comments are submitted to **Request for Information; Identifying Ambiguities, Gaps, Inefficiencies, and Uncertainties in the Coordinated Framework for the Regulation of Biotechnology as announced in the 87 FR 77900 Dec 20, 2022** 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. It is recognized that this RFI and related activities associated with the National Biotechnology and Biomanufacturing Initiative in the United States are endeavoring to strengthen and enable the US Bioeconomy in its most aspirational sense. Our comments to the docket are focused on the needs of the biopharmaceutical industry, the primary focus of NIIMBL's expertise. The biopharmaceutical industry provides advanced health care solutions for patients, provides high value, low volume, low emission manufacturing opportunities. The Coordinated Framework for the Regulation of Biotechnology as currently established is highly effective in the vast majority of applications. It is important to address exceptions, but these exceptions should not drive gross revisionism. In our responses to specific questions, we highlight some areas where additional clarity would be welcome, and aim to provide suggestions that improve the experience of our stakeholders, particularly around consistency within and between agencies.

COMMENTS

1. Describe any ambiguities, gaps, inefficiencies, or uncertainties regarding statutory authorities and/or agency roles, responsibilities, or processes for different biotechnology product types, particularly for product types within the responsibility of multiple agencies.

a. Describe the impact, including economic impact, of these ambiguities, gaps, inefficiencies or uncertainties.

While the Coordinated Framework for the Regulation of Biotechnology is effective in a majority of cases, there are some ambiguities, gaps, inefficiencies, and uncertainties related to implementation for biopharmaceutical products. Biopharmaceutical companies work with different centers at the FDA (CBER, CDER, CDRH, ORA) as well as other other regulatory authorities.

Harmonization

- Global regulatory divergence and intra agency divergence within the U.S. FDA is a hurdle to manufacturers producing biologics for a global market with respect to support speed to launch activities as well as post-approval modernization.
- Lack of consistency in global regulations and enforcement of current regulations is a hurdle to innovation, contributes to complex inventory management challenges, and can lead to serious drug shortage situations.
- A specific example of domestic divergence is oversight of PHSA Sec 351 approved biologics by FDA: ORA, CBER, and CDER. Specific examples or variance in review and

inspection practices are available, although there is an understandable reluctance by the regulated industry to threaten a critical relationship with regulatory authorities. As a practical matter, FDA should acknowledge and resolve discrepancies in review, supplement, and inspection practices between FDA Centers and ORA for PHS Sec 351 approved products. This could be addressed by having a single PM or inspection function for biologics within FDA or by separating review of biologics organizationally within FDA. It is recognized that different types of biologics address different patient centered risks but increased regulatory divergence within FDA in unnecessarily burdensome and confusing to practitioners and the public and is, in many cases, not science or patient need based. Furthermore, it is critical to advancing and protecting the public health as well as the bioeconomy that avenues for the development of shared understanding of risk-based decisions in case of discrepancies or lack of clarity. The current framework does not provide a concerted appeal process or mechanism for requesting science centered of divergence in review and inspection.

2. Provide any relevant data or information, including case studies, that could inform improvement in the clarity or efficiency (including the predictability, transparency, and coordination) of the regulatory system and processes for biotechnology products.

In general, we will refrain from providing specific case studies as examples because of the proprietary nature of the biopharmaceutical industry. In 2019, NIIMBL conducted an active listening activity around hurdles to adoption of new manufacturing technologies where many regulatory challenges were identified [1]. Here we present several suggestions and archetypal examples that could inform improvement in clarity and efficiency:

Clarity

- Providing a regulatory liaison function within the government to provide plain language recourse in the case of discrepancies or lack of clarity
- Provide a third party portal for highlighting discrepancies within and between agencies as well as assessing application of regulatory
- Minimize divergence in principles of practice and within the regulatory framework and focus on scientifically-centered risk-based assessments

Processes and Efficiency

- Greater structure and predictability in processes for information requests would benefit both agency and sponsors.
- Change controls, and particularly post-approval change management, can vary in level of detail required between product types. Further, relief in the number and type of changes requiring a submission, consistent across all product types, would allow manufacturing processes to be updated more readily and would facilitate continuous improvement.
- Training of field inspectors on new technologies to ensure alignment between “the podium” and “the field”. For example, agency initiatives and reviewers might favorably view changes to environmental design and control of manufacturing spaces needed with the adoption of closed manufacturing systems but there may be hesitation to implement

these changes in a manufacturing setting due to perceived questions, scrutiny, or observations during inspections.
- Electronic drug labels should be permitted in the United States.

3. Describe any specific topics the agencies should address in plain language on the regulatory roles, responsibilities, and processes of the agencies.

FDA should address and develop a consistent approach for the routine cGMP assessment of biomanufacturers across geographies. Risk elements associated with the location of a site should be included in inspection approaches and OAI assignment. FDA could more consistently enforce the elements of FDASIA Title VII as written.

4. Describe any specific issues the agencies should consider in developing a plan to implement regulatory reform, including any updated or new regulations or guidance documents.

- The concept of "mandatory" guidance to industry from FDA should be critically reviewed as a policy construct, especially when issued from a single Center rather than the Agency. Requirements of additional reporting to the Agency by the regulated industry on approved processes, products, or inventories as well as requirements of specific formatting of documents and data beyond those of the ICH eCTD should not be exempt from the Paperwork Reduction Act of 1995.
- Acknowledge and resolve discrepancies in review, supplement, and inspection practices between FDA Centers and ORA for PHS Sec 351 approved products. This could be addressed by having a single PM or inspection function for biologics within FDA or by separating review of biologics organizationally within FDA. It is recognized that different types of biologics address different patient centered risks but increased regulatory divergence within FDA in unnecessarily burdensome and confusing to practitioners and the public and is, in many cases, not science or patient need based.
- Resolve the role of USP monographs in labelling biologics.
- Modernize or consolidate outdated guidance documents. In general, guidance should be subject to periodic review every 5-10 years to ensure they are current and not barriers to implementing innovative manufacturing technologies that did not exist when the guidance was first drafted.

5. Describe any new or emerging biotechnology products (*e.g.,* microbial amendments to promote plant growth; food plants expressing non-food substances or allergens from non-plant sources) that, based on lessons learned from past experiences or other information, the agencies should pay particular attention to in their evaluation of ambiguities, gaps, or uncertainties regarding statutory authorities and/or agency roles or processes.

Technologies involving engineering microbes, for example with intended release into the environment or delivery to the human gut and subsequent impact to wastewater, are worth

consideration. It's important to consider how to balance assessment within a drug framework with environmental impact.

6. Describe any new or emerging categories of biotechnology products on the horizon that the regulatory system and processes for biotechnology products should be preparing to address. Describe any specific recommendations for regulating these new or emerging categories of biotechnology products to guide agency preparations.

Technologies relevant to the biopharmaceutical industry include gene editing technologies and engineered microbes used as human therapeutics.

7. What is the highest priority issue for the agencies to address in the short term (*i.e.,* within the next year) and in the long term?

The highest priority issues are those that benefit both agencies and the regulated industry. A relatively simple place to focus on the short term could be to provide a third party portal for highlighting and resolving discrepancies within and between agencies. An important long-term goal should be to pursue practical mutual recognition agreements with other major international regulatory agencies. Standards around manufacturing, analytical testing, and compliance expectations make this objective increasingly achievable and could allow for better utilization of available inspectorial resources. Companies would benefit from streamlined expectations, reduced inspection time, and clarity of commonly accepted standards. Harmonization would enable reduced risk around incorporation of innovative and advanced manufacturing technologies and reduce the regulatory burden on sponsors to maintain separate processes and inventories.

References

1. Mantle, J.L., & Lee, K.H. (2020). NIIMBL-Facilitated Active Listening Meeting between Industry and FDA Identifies Common Challenges for Adoption of New Biopharmaceutical Manufacturing Technologies. *PDA Journal of Pharmaceutical Science and Technology, 74*, 497 - 508.