July 14th, 2021

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency Guidance for Industry, Updated Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers, and Resiliency Roadmap for FDA Inspectional Oversight

Dear Sir/Madam:

BIO appreciates the opportunity to provide our input to FDA's Guidance for Industry *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency*. BIO also appreciates the May 2021 update to the *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers* Guidance and the May 2021 *Resiliency Roadmap for FDA Inspectional Oversight*. Taken together these three regulatory documents provide a path forward for inspections during and after the COVID-19 public health emergency. Additional detail regarding how FDA is utilizing this suite of tools to address the inspectional backlog created by the COVID-19 public health emergency, how certain inspections will be prioritized, and the time needed to reduce the backlog as well as how these alternative tools fit into the larger inspectional paradigm would be helpful. We provide comments and suggestions for each of these documents below.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

I. Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency Guidance for Industry

BIO believes that the *Remote Interactive Evaluations* Guidance is an important step in providing clarity regarding important inspectional activities during the COVID-19 pandemic. It is also an important step in discussions regarding modernizing inspectional activities and providing FDA and Sponsors additional tools to complete these activities in the future. While we understand this Guidance is only "in effect for the duration of the public health emergency related to COVID-19" we believe many of the concepts introduced should be retained after the public health emergency ends and become another set of tools in FDA's toolbox for inspectional activities, utilizing a risk-based approach.

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We appreciate that a remote interactive evaluation (RIE) may be used in advanced or in conjunction with a records request and/or in-person inspection in order to reduce the staff needed and time spent onsite. We believe this approach could be used in the future to better distribute FDA resources for inspections, ensuring the most amount of staff time is focused on places where in-person assessment is truly needed, and information cannot be obtained via another method.

We applaud FDA's willingness to discuss and facilitate planning of the RIE with Sponsors once an RIE has been requested and agreed to. Pre-planning and understanding expectations up front is critical to a successful evaluation. We believe the list of items to be discussed in advance of an RIE (pages 9-10 of the Guidance) are appropriate and cover the major items BIO and our members have identified for preparing for a successful remote interaction. To this end, it would be helpful to add clarity in the Guidance on the timeframe and mechanism by which FDA targets having a discussion with Sponsors regarding an RIE to ensure appropriate logistical and technical considerations have been accounted for (especially if live streaming might be required).

While we generally believe that the RIE Guidance is helpful we have identified a number of areas where additional clarification or detail would be helpful, particularly as it relates to the final RIE report. We offer the following to bring additional clarity to the RIE Guidance.

A footnote in the Guidance (page 10) states "For a remote interactive evaluation supporting a pending biologics license application, FDA usually will expect a facility to provide for livestream video of the manufacturing operations described in the application." We request that FDA add a caveat for accepting pre-recorded videos when manufacturing is batched and may not be ongoing during the time the RIE is scheduled or where other operational or safety issues may prevent live video recording.

We understand that FDA will usually provide a list of observations at the closeout meeting of the RIE and provide a copy of the final RIE report to the facility after the conclusion of the evaluation. However, as it is clear that an RIE is not an inspection, and FDA will not be issuing Forms FDA 482 or 483, it would be helpful to have additional information regarding how the RIE will be captured in the GMP history of the facility or be utilized for documentation of cGMP and requests of CPPs or cGMP declarations (typically done with Establishment Inspection Reports (EIRs) and Decisional Letters). It would be helpful for the RIE Guidance to include information regarding the timing for receipt of the final RIE report, what information will be included in the report (e.g., outcome of evaluation, GMP compliance, whether an on-site inspection will be needed), as well as how Sponsors should respond to observations articulated during the closeout meeting, as there is no FDA Form 483.

In the RIE Guidance, FDA notes that the RIE will be used to "meet user fee commitments and to update FDA's relevant internal databases". We request additional information regarding whether and how an RIE will update a facility's classification in the Inspection Classification Database and how that information will be communicated to the facility as well as what information will be publicly available.

II. Updated Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers

BIO appreciates the updates and clarifications made in May 2021 to the *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers* Guidance. The additional detail regarding communication of issues identified during records requests (Q5) and decisions regarding applications (Q6) is particularly appreciated.

Clear communication of expectations and how FDA will be utilizing Complete Response Letters (CRLs) or deferring action on an application is important for Sponsors as well as the broader drug development ecosystem as the issuance of a CRL, or confusion regarding its use, can have implications far beyond a single product application. We appreciate the clear statement in the Q&A Guidance that if a needed inspection cannot be completed due to travel restrictions but there are no other deficiencies (site/facility or otherwise in the application), FDA will defer action, rather than issuing a CRL. We also appreciate the statements that FDA will communicate with the applicant as soon as possible during the review cycle regarding deficiencies found in the application or the facility. This early communication may allow Sponsors to resolve issues prior to the issuance of a CRL.

Finally, the inclusion of question and answer 7 regarding prioritization of inspections as travel restrictions are eased or lifted is an important addition to the Guidance. Additional information regarding how FDA plans to address the backlog of inspections during the pandemic, including for applications that have received a CRL or been deferred, would be helpful.

III. Resiliency Roadmap for FDA Inspectional Oversight

BIO appreciates the robust dataset in the *Roadmap* articulating where inspections have been able to be completed and where they are outstanding. We also appreciate the discussion of the three scenario-based estimates. It is clear that even in a best-case scenario, only a small number of needed inspections will be able to occur this Fiscal Year (FY). It remains important that FDA communicate with Industry and broader stakeholders regarding not only progress in conducting inspections, including the use of alternate tools, but also how FDA will address consequences of the lack of inspections. For example, biopharmaceutical companies rely on inspectional documentation for other purposes such as CPPs or GMP declarations for other countries. Additional detail regarding how FDA is utilizing this suite of tools to address the inspectional backlog created by the COVID-19 public health emergency, how these tools fit into the larger inspectional paradigm, how remaining inspections will be prioritized, and estimates regarding the resolution of the current and additional backlog would be helpful.

We applaud FDA's leveraging of information shared by trusted regulatory partners through mutual recognition and confidentiality agreements and encourage FDA to continue this practice after the end of the public health emergency as supply chains and manufacturing facilities are global. We also encourage FDA to look to expand the number of trusted regulatory partners to increase efficiencies.

Additionally, we urge FDA to take lessons learned from the COVID-19 public health emergency related to challenges and the use of alternate tools, including RIEs, for inspectional activities to identify how these challenges can be mitigated and where alternate tools could be utilized more robustly in the future, including after the conclusion of the

public health emergency. This will include building on the use of alternate tools, ensuring consistency across and modernizing existing guidances.

IV. Conclusion

BIO appreciates this opportunity to submit comments regarding FDA's Guidance for Industry *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency,* the May 2021 update to the *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers* Guidance and the May 2021 *Resiliency Roadmap for FDA Inspectional Oversight*. We would be pleased to provide further input or clarification of our comments, as needed, as well as continue discussions regarding the use of virtual tools and technologies for inspectional activities in the future.

Sincerely,

/S/
Victoria A. Dohnal, RAC
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization