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Dockets Management Staff
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2022-D-0810

Conducting Remote Regulatory Assessments-Questions and Answers; Draft Guidance for Industry

To Whom It May Concern,

Biotechnology Innovation Organization (BIO) welcomes the opportunity to comment on the Food and Drug Administration (FDA or Agency) draft guidance for industry entitled "Conducting Remote Regulatory Assessments – Questions and Answers". We recognize the potential for Remote Regulatory Assessments (RRAs) to improve and streamline processes related to oversight, risk mitigation, meeting critical public health needs, and maximizing compliance of FDA-regulated products, as exemplified by their use throughout the COVID-19 pandemic. Guidance and transparency explaining FDA's current thinking regarding the use of RRAs can benefit industry and regulators alike, and ultimately, our patients.

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.

We are pleased to provide the following comments regarding the Agency's use of alternative inspection tools such as RRAs. We generally support the modernization of inspection activities and appreciate the development of this draft guidance to assist industry with the conduct of RRAs. The following comments summarize recommendations that would provide additional clarity and transparency to establishments undergoing RRAs.

(1) Applicability of RRAs during pre-approval/pre-licensure and routine surveillance inspection scenarios

BIO understands that FDA has used RRAs to support the approval or authorization of marketing submissions during the COVID-19 pandemic. While the draft guidance states that RRAs "complement FDA's authority to conduct inspections under section 704(a)(1) of the FD&C Act and other applicable FDA authorities", further clarification would be helpful to understand the intended scope and role of RRAs relative to pre-approval/pre-licensure inspections (PAI/PLI).

For example:

- We strongly suggest that FDA provides additional details describing scenarios where RRAs may lead to regulatory decisions, especially the approval of applications, in lieu of inspections.
- BIO requests additional details describing scenarios where RRAs may or may not be used to mitigate delays on the approval or authorization of marketing submissions, especially when such delays are caused by the Agency's inability to conduct a foreign inspection.
- Similarly, BIO strongly recommends that FDA explains the potential role of RRAs with respect to activities conducted under Mutual Recognition Agreements (MRAs), e.g., whether outputs of RRAs would be made available by FDA to other health authorities.
- BIO strongly recommends that FDA clarifies whether RRAs may continue to result in advisory and/or enforcement actions independently, i.e., when not conducted in conjunction with an inspection, and describe FDA's current thinking on this topic in additional detail.
- We recommend that the Agency clarifies whether it intends to use RRAs to support the review of supplements, i.e., sNDA/sBLA, as well as originals, i.e., NDA/BLA.

We understand the potential benefits of leveraging RRAs to assist FDA's surveillance activities and recommend that FDA considers RRAs as part of its routine surveillance process. For example, FDA might consider whether RRAs could fulfill surveillance inspection needs for GxP facilities, allowing the facility to expect its next surveillance inspection in alignment with a risk-based schedule after completion of the RRA.

We also note that when RRAs are used, there is no visible or apparent indication that FDA considers the establishment to be operating under cGMP/GLP since RRAs are not considered to be inspections. This could create unintended consequences, such as the appearance that a facility has not had recent surveillance activity, which could cause challenges during scenarios when other health authorities would like to review documentation of recent inspections (or the equivalent of GMP certificates) when looking for measures to recognize MRAs or other alliances (e.g., PIC/s members). We recommend connecting RRAs with a method to show publicly FDA's oversight of facilities, e.g., updating cGMP declarations to include RRAs, updating FDA Dashboard to show oversight activities, etc., to strengthen the benefits of RRAs for industry, FDA, and other health authorities. FDA could also consider implementing the issuance of GMP certificates to provide a mechanism that demonstrates continued oversight of establishments through FDA's various inspection tools.

(2) Details about RRA processes and parameters

BIO recommends that the Agency clarify the similarities and differences between what an establishment might expect to happen during voluntary and mandatory RRAs. For example:

- We recommend that the guidance explains whether "limited" voluntary RRAs can be performed, e.g., an establishment could agree exclusively to conduct virtual interviews.
- Similarly, BIO requests clarification about whether an establishment's refusal to provide access or records during a voluntary RRA would be deemed an establishment that "delays, denies or limits inspection" under FD&C 501(j).

BIO also suggests that FDA provides additional details about general RRA processes, such as criteria that inform decisions on whether RRAs should be conducted and what potential outcomes can be. For example:

- We suggest that FDA clarifies whether establishments can request onsite inspections in lieu of RRAs without such a request being considered a refusal.
- BIO suggests that the guidance clarifies criteria that will be used to determine whether a given RRA will be voluntary or mandatory.
- We recommend that the guidance clarify whether FDA can request RRAs for establishments that the Agency has never previously inspected.
- BIO recommends that FDA includes details about how an establishment can provide necessary supplemental explanations about data or documents requested under an RRA.
- In general, BIO recommends that FDA explains the desired outcomes and expected benefits caused by the ongoing use of RRAs outside of public health emergencies and provides metrics by which potential impact could be evaluated. Since our members report that RRAs are more resource intensive for establishments (e.g., implementation of information technology, audio/visual, and secure data exchange capabilities) compared to inspections, such metrics would be helpful to ensure the use of RRAs works as intended.

Please consider the following table outlining granular comments on specific language in the draft guidance.

SECTION	ISSUE	PROPOSED CHANGE
I. BACKGROUND		
Line 117-118	Definition of “establishment”	Please clarify whether FDA will use RRAs as part of oversight activities for manufacturers of active pharmaceutical ingredients (API)
II. QUESTIONS AND ANSWERS		
Line 124, 246, 318, 362, 371	Document speaks to live streaming; explain how this is managed to ensure privacy of company and personal information.	Please provide recommendations on how to ensure privacy of personal and proprietary information during live streaming
Line 257-260	“Having an RRA precede an inspection under section 704(a)(1) of the FD&C Act could reduce resource expenditure by (1) potentially reducing the time FDA is present at the establishment, and (2) helping optimize FDA's time on-site, by reducing the extent of records to be reviewed during the inspection.”	Member experiences with FDA 4003 records requests submitted prior to inspections have been that the investigators/inspectors that arrive to conduct the inspection did not have prior access to the files submitted under the FDA 4003 records request. Also, the investigators/inspectors did not have access to FDA’s Box platform to access the files. Files previously submitted under the 4003 records request needed to be supplied again to FDA during the inspection.

SECTION	ISSUE	PROPOSED CHANGE
		Proposal: FDA should ensure that investigators and establishments have access to FDA's Box platform during the records request and the inspection.
Line 265-266	"Providing FDA additional information to incorporate into a risk-based inspection schedule, thereby helping FDA use inspectional resources more efficiently and effectively."	We recommend connecting RRAs with a method to show publicly FDA's oversight of facilities, e.g., updating cGMP declarations to include RRAs, updating FDA Dashboard to show oversight activities, etc., to strengthen the benefits of RRAs for industry, FDA, and other health authorities. FDA could also consider implementing the issuance of GMP certificates to provide a mechanism that demonstrates continued oversight of establishments through FDA's various inspection tools.
Line 312	"FDA requests and reviews records, documents, and other information (such as electronic systems, and source records from non-clinical and clinical studies)."	Please clarify how FDA expects to review electronic systems and source records, e.g., whether this requires remote access to these systems and records.
Line 314-326	BIO's understanding is that information beyond mandatory records requests are voluntary. However, Question B.9. implies that virtual meetings, livestream, and/or pre-recorded video could be a component of either voluntary or mandatory RRAs. Question B.9 presents a scenario where a video-streaming RRA (i.e., voluntary RRA) could be held along with a 704(a)(4) records request (i.e., mandatory RRA); no description is provided on how this approach would be initiated or managed.	We recommend changing Q.9 to "What might an establishment expect to happen during a voluntary RRA?" Additionally, we recommend expanding the language in lines 323-326 into a separate Q&A discussing combination scenarios of mandatory and voluntary RRAs. We would appreciate that FDA address whether simultaneous mandatory and voluntary RRAs could occur, and if so, whether the two RRAs would be requested together or sequentially.
Line 339-342	"FDA may consider other actions …. such as an inspection."	We recommend that FDA provides additional examples of what "other actions necessary to verify information submitted to FDA" could be.
Line 478	EIRs and 483s are utilized to show GLP compliance to other health authorities (HAs) during submissions. It is unclear whether FDA will issue an official report and whether FDA is working with other	We propose FDA issue an official report at the conclusion of an RRA and work with global HAs to support their acceptance.

SECTION	ISSUE	PROPOSED CHANGE
	HAs to support sharing and acceptance of any RRA reports.	
Line 480, 502, 506:	RRA completion is unclear: "FDA may….." This language should be clarified to indicate how FDA will ensure firms that RRAs have been minimally successfully responded to	Please clarify how FDA will communicate that the RRA's requests have successfully been completed and that there are no outstanding items associated with it.
Line 480-482	"Upon completion of an RRA … FDA may present a written list of RRA observations, if any, and describe and discuss any observations in sufficient detail to enable understanding and foster an appropriate response." It would be helpful to clarify whether there is potential for an establishment to receive observations without a closeout meeting or discussion.	Please clarify if there is potential for an establishment to receive RRA observations without a closeout meeting, and provide details on how establishments will receive, and respond to, any FDA observations in these cases. Additionally, the guidance does not provide clarity on how FDA will close voluntary RRAs. We propose FDA includes details regarding documentation/form type and timeline to close voluntary RRAs. Similarly, the guidance does not provide clarity on closure of mandatory RRAs (e.g., FDA 4003 records request). Industry receives FDA 4003a, "confirmation of receipt of records", but this does not provide clarity regarding closure of the RRA. We propose that FDA clarify whether the FDA 4003a is considered closure of a mandatory RRA.
Line 502-506	Line 502- 506 states that FDA will provide a written copy of the RRA report to the establishment. However, there may be some instances where a report will not be written or provided. This should be clarified.	Please clarify in what situations FDA will, or will not, provide a written copy of the RRA report. Additionally, we propose splitting this section on closure into separate sections on closure for Voluntary RRAs and closure for Mandatory RRAs. This section appears to only provide detail for closure of Voluntary RRAs.
Line 504	The timing by which the establishment will receive the written copy of the narrative portion of the RRA report is unclear.	Please provide clarification regarding the timing of issuance of any closeout report or "narrative" as well as

SECTION	ISSUE	PROPOSED CHANGE
		example situations when reports would or would not be written.
Line 506	It is unclear whether FDA intends to post RRAs on FDA.gov.	Please clarify whether FDA intends to post RRAs on its website proactively.

Conclusion

BIO appreciates this opportunity to submit comments regarding FDA's draft guidance for industry entitled "Conducting Remote Regulatory Assessments – Questions and Answers". As FDA continues to consider the implementation and use of RRAs, we would welcome future opportunities to discuss these points.

Sincerely,

Alex May, M.S.
Director, Science & Regulatory
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