Biotechnology Innovation Organization
1201 New York Ave, NW
Suite 130
Washington, DC, 20005

November 21, 2023

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

Re: FDA-2023-D-3031; Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the **Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications**

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.

Sincerely,

/s/
Sam Gunter
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

General Comments

There seems to be no description of approved means of sharing documents with FDA. Inconsistent use of technological approaches places strain on sites and information technology services as they implement and adjust to new methods. IT tools to support virtual inspections are a significant challenge and put huge pressure on sites at the kickoff of an inspection as even within FDA there isn't a consistent approach to what tools are used. When using virtual interactive technologies to communicate intricate narratives or complex subject matter, a significant amount of time is required to ensure proper understanding. It would be helpful to know how much notification a site gets to be able to support the use of virtual tools.

We would like clarification on whether FDA will consider pre-license inspections (PLIs) and pre-approval inspections (PAIs) conducted by a foreign regulatory authority as amended by the Food and Drug Omnibus Reform Act of 2022. In addition, we would like to know if the review team uses an alternative tool (AT) to assess a manufacturing facility and if there is a requirement that the facility is in production and manufacturing the product for which a biologics license is desired. Clarification is also needed on what advanced notice and details a site will receive to support the inclusion of FDA Remote SMEs.

It is not completely clear from the text whether the decision to supplement a PLI or PAI with remote resources will always be made in advance of the inspection or whether it could be decided once the inspection is ongoing and as needed. In addition, the guideline suggests that it is expected that a facility can employ virtual interactive technologies. This could result in a disadvantage for applicants with limited resources and potentially negatively impact FDA's inspection.

Whenever a virtual interaction with a remote FDA resource potentially leads to an observation, the FDA should ensure adequate time and interactions for the manufacturing facility to respond directly to the remote FDA resource before the conclusion of the on-site PAI or PLI.

FDA should expand use of MRAs to PAIs and PLIs to further enhance the Agency’s ability conduct oversight and review applications in a timely manner. FDA should also be more transparent in their use of MRAs, which should include metrics. In addition to FDA expanded use MRAs to include PAI and PLI, it would also be helpful if FDA included additional modalities such as advanced therapy medicinal products (ATMP) or more specifically adeno-associated virus (AAV) based gene therapy products.

Specific Comments

I. Introduction

It is unclear what these post approval inspections are. They are not surveillance, for cause or BIMO, because those are described in bullet points below in this section. We recommend including examples of post approval inspections that are out of the scope of this guidance.

III. Risk-Based Use of Alternative Tools

It seems that FDA may approve an application without performing an inspection or using alternative tools. We would like clarification on whether this interpretation is accurate. A risk based approach to determine remote interactive evaluation (RIE) inspection support is a great idea. We suggest more transparency in scoring to help the industry. A robust and previously successful audited pharmaceutical quality system (PQS) should be considered. We propose a ranking matrix list that is available to companies like an enhanced Significantly Regulated Organizations (SRO) list. Companies should strive to be on this list.

As written, "... and the proposed operations in the application are the same as or sufficiently related to existing operations covered in previous inspections" implies that FDA may rely on manufacturing processes/products that are not the ones being assessed in the submission.

IV. Considerations for Alternative Tools

Will the Agency communicate its intent to use AT to assess a manufacturing facility at least 60 days in advance and no later than mid cycle as stated in the commitment letters for PLIs/PAIs?

A. Remote Regulatory Assessments

Will the review team conduct multiple rounds of AT during a review cycle? Or will it be limited to one AT, like inspections, within an application review cycle?

The guidance does not state that FDA will notify the establishment that the agency intends to initiate a mandatory remote regulatory assessment (RRA), as opposed to a voluntary RRA. We request that the guidance be revised to state that if FDA is initiating a mandatory RRA under this guidance, then the initial communication notifying the establishment of the mandatory RRA will explicitly state its mandatory nature, to ensure it is clear to establishments when FDA is initiating a mandatory RRA as opposed to requesting a voluntary RRA (e.g., remote interactive evaluation, or RIE).

Request revisions to clarify that FDA considers all RIEs to be considered voluntary, even those conducted in the context of a mandatory RRA. Lines 173 to 180 of the guidance indicate a mandatory RRA could include “[c]onducting an RIE during application assessment.” However, Line 199 of the guidance states “In contrast, a facility’s participation in an RIE is voluntary.”

The discussion of an RRA conducted under section 704(a)(4) does not indicate the minimum amount of time the agency intends to give establishments to respond. Request that the guidance be revised to state the minimum amount of time FDA will allow for an establishment to respond to an initial request for information (RFI) submitted in connection with a mandatory RRA. While the agency often employs 15 working days for response times, this minimum should be at least 20 working days, as the resources required to respond to a mandatory-RRA-related RFI have the potential to be substantial.

FDA’s related Conducting Remote Regulatory Assessments Questions and Answers: Draft Guidance for Industry (July 2022) (hereinafter “the RRA Q&A Guidance”) indicates FDA’s expectation that documents maintained in paper form be scanned and submitted electronically. Such an expectation in the context of a mandatory RRA could be extremely burdensome to an

establishment. We request that the guidance be revised to clarify that FDA will not mandate that paper-based documents be submitted to FDA under a mandatory RRA. If the production of paper records is necessary, then the guidance should state FDA's intention to limit such requests to only those portions that are necessary (e.g., allowing establishments to submit the excerpts necessary to answer FDA's question), so as to limit the substantial resources that may be needed if FDA includes broad requests that could encompass large numbers of documents in paper format.

The RRA Q&A Guidance states that "FDA will provide a secure means to send requested records and information." This commitment could be fulfilled by FDA simply allowing establishments to follow the traditional method of submitting documents via email (e.g., a standard email address maintained by FDA's Office of Regulatory Affairs). However, using email can pose technological challenges when submitting large files and/or large numbers of files (e.g., companies often set limits on the size of outgoing emails). We have seen the agency begin to offer secure file-sharing web-portals, but to date whether these portals are made available appears at the sole discretion of the FDA personnel requesting information. We request that this guidance be revised to commit that if FDA is conducting a mandatory RRA, then FDA will provide, upon request, another means that is conducive to submitting large files and/or large numbers of files, such as a secure file-sharing web-portal.

The guidance references FDCA section 501(j), without providing guidance specific to the context of RRAs and RIEs, particularly as it relates to technical challenges. Request the guidance be revised to clarify how FDA will deal with technical challenges in the context of a mandatory RRA (e.g., issues uploading documents to a file share device; inability to join a virtual meeting). Alternatively, this clarification could be provided in FDA's Conducting Remote Regulatory Assessments Questions and Answers: Draft Guidance for Industry (July 2022) (hereinafter "the RRA Q&A Guidance") or FDA's Guidance for Industry: Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection (December 2022).

B. Inspections Conducted by Trusted Foreign Regulatory Partners

Other sections describe notifications to the facility of the type of inspection but are lacking in the Foreign Regulatory Partners section. We request clarity on the methods of notifications.

2. Foreign Regulatory Inspections with FDA Remote Participants

Other sections describe notifications to the facility of the type of inspection but are lacking in the Foreign Regulatory Partners. Please provide details on how FDA will provide notification around remote FDA participation.

It is unclear if the Agency would classify collaborating with foreign regulators who use innovative regulatory approaches and virtual interactive tools may as an inspection or as a RIE.

The utilization of the approach described in this section has the potential to negatively impact the outcome from either FDA or the foreign regulatory agency. In adopting this approach, we request that the agency include specific provisions for ensuring alignment between FDA and the foreign regulatory agency, both at the leadership level and the investigator level. We also request that provisions be added to make clear that it is the responsibility of FDA and the

foreign agency, not the establishment, to resolve any issues that might arise during such a collaborative visit.

C. PAIs and PLIs With FDA Remote Subject Matter Experts

Are the remote participants considered as voluntary based on the facility's capability to support remote activities?

It is not completely clear from the text whether the decision to supplement a PLI or PAI with remote resources will be made always in advance of the inspection or whether it could be decided once the inspection is ongoing, as needed. In addition, the guideline suggests that it is expected that a facility can employ virtual interactive technologies. This could result in a disadvantage for applicants with limited resources and potentially negatively impact FDA's inspection. We recommend including "in advance" here: "When FDA anticipates using remote resources during an inspection, the Agency intends to notify the facility IN ADVANCE by electronic correspondence or by telephone..."

The guidance states that “facility agreement to the involvement of remote Agency personnel is voluntary,” which indicates that the establishment is allowed to refuse the involvement of remote Agency personnel prior to the start of an inspection but does not address whether the establishment is allowed to end the involvement of remote personnel during the inspection. We request that the guidance clarify that this agreement is also revokable during an inspection (e.g., due to technical issues), similar the portion of the guidance that states that a “facility may decline participation in an RIE (or a particular RIE request) before or during the RIE”.

V. The Effects of Using Alternative Tools

The guidance does not address the situation when the use of an alternative tool results in no observations. As a matter of standard practice, FDA should issue a closure memorandum whenever no observations are found (or detailed "narrative report" like the establishment inspection report) following the conclusion of an RRA or other AT.

It is unclear whether "observations" refer to Form FDA 483 observations and are considered equivalent to on site observations. This raises the question of whether the use of alternative tools will be considered an inspection and be used to update the FDA inspection dashboard. It would help if the use of the word "observation" was clarified and if it refers to Form FDA 483 observations.

LINE-BY-LINE RECOMMENDED EDITS

SECTION/LINE	ISSUE	PROPOSED CHANGE
I. Introduction		
39-40	It is unclear what these Post approval inspections are. They are not surveillance, or for cause or BIMO, because those are described in bullet points below. There are instances when an PLI/PAI is combined with a surveillance inspection. This seems to infer that these types of combined inspections would not use the alternative tools, leading to potential inefficiencies and multiple visits/requests by FDA.	Include examples of Post approval inspections that are out of the scope of this guidance. Suggest FDA to be explicit about the potential to use these tools for combined inspections (PAI/PLI with surveillance coverage) so that internal FDA processes will facilitate the use of the alternate tools for these types of situations, if appropriate.
II. Background		
III. Risk-Based Use of Alternative Tools		
102-104	This sentence suggests that FDA may approve an application without performing an inspection or using alternative tools	Provide clarification on whether this interpretation is accurate
116-117		Risk based approach to determine RIE inspection support is a great idea. Suggest more transparency in scoring to help the industry. A robust and previously successful audited PQS system should be considered
119-121		Propose a ranking matrix list that is available to companies, some sort of

SECTION/LINE	ISSUE	PROPOSED CHANGE
		enhanced SRO list. Companies should strive to be in this list.
123-126	As written, "... and the proposed operations in the application are the same as or sufficiently related to existing operations covered in previous inspections" implies that FDA may rely on manufacturing processes/products that are not the ones being assessed in the submission	Request FDA to clarify/confirm whether operations that are similar to those in the application under review can be used in the context of alternative tools.
IV. Considerations for Alternative Tools		
144-147	Will the Agency communicate its intent to use AT to assess a manufacturing facility at least 60 days in advance and no later than mid cycle as stated in the commitment letters for PLIs/PAIs?	
A. **Remote Regulatory Assessments**		
	The guidance does not state that FDA will notify the establishment that the agency intends to initiate a mandatory RRA, as opposed to a voluntary RRA.	Request that the guidance be revised to state that if FDA is initiating a mandatory RRA under this guidance, then the initial communication notifying the establishment of the mandatory RRA will explicitly state its mandatory nature, to ensure it is clear to establishments when FDA is initiating a mandatory RRA as opposed to requesting a voluntary RRA (e.g., remote interactive evaluation, or RIE).
	No description of approved means of sharing documents with FDA. Inconsistent use of technological approaches places strain on sites/IT as they implement and adjust to the new methods.	We request clarity on the approved methods of document sharing and how FDA will provide updates on these methods (e.g. use of Box.com or Teams.)
162-163	Will the review team conduct multiple rounds of AT during a review cycle? Or it will	

SECTION/LINE	ISSUE	PROPOSED CHANGE
	be limited to one AT, like inspections within an application review cycle?	
173-180	The language in this section could be clearer regarding the mandatory nature of RIEs.	Request revisions to clarify that FDA considers all RIEs to be considered voluntary, even those conducted in the context of a mandatory RRA. Lines 173 to 180 of the guidance indicate a mandatory RRA could include "[c]onducting an RIE during application assessment." However, Line 199 of the guidance states "In contrast, a facility's participation in an RIE is voluntary."
173-189	The discussion of an RRA conducted under section 704(a)(4) does not indicate the minimum amount of time the agency intends to give establishments to respond.	Request that the guidance be revised to state the minimum amount of time FDA will allow for an establishment to respond to an initial request for information (RFI) submitted in connection with a mandatory RRA. While the agency often employs 15 working days for response times, this minimum should be at least 20 working days, as the resources required to respond to a mandatory-RRA-related RFI have the potential to be substantial.
173-189	FDA's related *Conducting Remote Regulatory Assessments Questions and Answers: Draft Guidance for Industry* (July 2022)(hereinafter "the RRA Q&A Guidance") indicates FDA's expectation that documents maintained in paper form be scanned and submitted electronically. Such an expectation in the context of a mandatory RRA could be extremely burdensome to an establishment.	Request that the guidance be revised to clarify that FDA will not mandate that paper-based documents be submitted to FDA under a mandatory RRA. If the production of paper records is necessary, then the guidance should state FDA's intention to limit such requests to only those portions that are necessary (e.g., allowing establishments to submit the excerpts necessary to answer FDA's question), so as

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		to limit the substantial resources that may be needed if FDA includes broad requests that could encompass large numbers of documents in paper format.
173-189	The RRA Q&A Guidance states that "FDA will provide a secure means to send requested records and information." This commitment could be fulfilled by FDA simply allowing establishments to follow the traditional method of submitting documents via email (e.g., a standard email address maintained by FDA's Office of Regulatory Affairs). However, using email can pose technological challenges when submitting large files and/or large numbers of files (e.g., companies often set limits on the size of outgoing emails). We have seen the agency begin to offer secure file-sharing web-portals, but to date whether these portals are made available appears at the sole discretion of the FDA personnel requesting information.	Request that this guidance be revised to commit that if FDA is conducting a mandatory RRA, then FDA will provide, upon request, another means that is conducive to submitting large files and/or large numbers of files, such as a secure file-sharing web-portal.
192-197 (Including Footnote 32)	The guidance references FDCA section 501(j), without providing guidance specific to the context of RRAs and RIEs, particularly as it relates to technical challenges.	Request the guidance be revised to clarify how FDA will deal with technical challenges in the context of a mandatory RRA (e.g., issues uploading documents to a file share device; inability to join a virtual meeting). Alternatively, this clarification could be provided in FDA's Conducting Remote Regulatory Assessments Questions and Answers: Draft Guidance for Industry (July 2022) (hereinafter "the RRA Q&A Guidance") or FDA's Guidance for Industry: Circumstances that Constitute Delaying,

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		Denying, Limiting, or Refusing a Drug or Device Inspection (December 2022).
199-202	If the review team uses an AT to assess a manufacturing facility, is there a requirement that the facility is in production and manufacturing the product for which a biologics license is desired	
B. **Inspections Conducted by Trusted Foreign Regulatory Partners**		
	Other sections describe notifications to the facility of the type of inspection but are lacking in the Foreign Regulatory Partners.	We request clarity on the methods of notifications.
225-228	Section 316 (c) in the Food and Drug Omnibus Reform Act of 2022 amends Section 809 of the Federal Food, Drug, and Cosmetic Act by inserting ‘‘preapproval or’’ before ‘‘risk-based inspections’’	Clarify whether FDA will consider PLIs and PAIs conducted by a foreign regulatory authority as amended by the Food and Drug Omnibus Reform Act of 2022.
1. Information Sharing by Trusted Foreign Regulatory Partners		
2. Foreign Regulatory Inspections with FDA Remote Participants		
	The utilization of the approach described in this section has the potential to negatively impact the outcome from either FDA or the foreign regulatory agency.	In adopting this approach, request that the agency include specific provisions for ensuring alignment between FDA and the foreign regulatory agency, both at the leadership level and the investigator level. Also request that provisions be added to make clear that it is the responsibility of FDA and the foreign agency, not the establishment, to resolve any issues that might arise during such a collaborative visit.
	Other sections describe notifications to the facility of the type of inspection but are lacking in the Foreign Regulatory Partners.	Please provide details on how FDA will provide notification around remote FDA participation.

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245-247	It is unclear if the agency would classify this type of assessment as an inspection or as a RIE?	
C. **PAIs and PLIs With FDA Remote Subject Matter Experts**		
199-202	If the review team uses an AT to assess a manufacturing facility, is there a requirement that the facility is in production and manufacturing the product for which a biologics license is desired	
266-268	Are the remote participants considered as voluntary based on the facility's capability to support remote activities?	
277-281	It is not completely clear from the text whether the decision to supplement a PLI or PAI with remote resources will be made always in advance of the inspection or whether it could be decided once the inspection is ongoing, as needed. In addition, the guideline suggests that it is expected that a facility has the ability to employ virtual interactive technologies. This could result in a disadvantage for applicants with limited resources and potentially negatively impact FDA's inspection	Include " in advance" or "before the inspection starts" or similar e.g: "To support a PAI or a PLI with remote resources, FDA will request "IN ADVANCE" confirmation of a facility's..."
282-283	The guidance states that "facility agreement to the involvement of remote Agency personnel is voluntary," which indicates that the establishment is allowed to refuse the involvement of remote Agency personnel prior to the start of an inspection, but does not address whether the establishment is	Request that the guidance clarify that this agreement is also revokable during an inspection (e.g., due to technical issues), similar the portion of the guidance that states that a "facility may decline participation in an RIE (or a particular RIE request) before or during the RIE".

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	allowed to end the involvement of remote personnel during the inspection.	
288-292	It is not completely clear from the text whether the decision to supplement a PLI or PAI with remote resources will be made always in advance of the inspection or whether it could be decided once the inspection is ongoing, as needed. In addition, the guideline suggests that it is expected that a facility has the ability to employ virtual interactive technologies. This could result in a disadvantage for applicants with limited resources and potentially negatively impact FDA's inspection	Include "in advance" here: "When FDA anticipates using remote resources during an inspection, the Agency intends to notify the facility IN ADVANCE by electronic correspondence or by telephone..."
318-323	How much notification does a site get to be able to support the use of virtual tools? As noted above, IT tools to support virtual inspections/ elements of them are a significant challenge and put huge pressure on sites at kick off of an inspection as even within FDA there isn't a consistent approach in tools used. When using virtual interactive technologies to communicate intricate narratives or complex subject matter, a significant amount of time is required to ensure proper understanding.	Please clarify what advanced notice and details a site will receive to support the inclusion of FDA Remote SMEs. Whenever a virtual interaction with a remote FDA resource potentially leads to an observation, the FDA should ensure adequate time and interactions for the manufacturing facility to respond directly to the remote FDA resource by the conclusion of the on-site PAI or PLI.
V. The Effects of Using Alternative Tools		
323-340	The guidance does not address the situation when the use of an alternative tool results in no observations.	As matter of standard practice, FDA should issue a closure memorandum whenever no observations are found (or detailed

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		"narrative report" similar to the establishment inspection report) following the conclusion of an RRA or other alternative tool.
332-334	It is unclear whether "observations" refer to 483 observations and are considered equivalent to on site observations. This raises the question of whether the use of alternative tools will be considered an inspection and be used to update the FDA inspection dashboard	Clarify the use of the word "observation", whether it refers to 483 observations.