

8 May 2026

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
via online submission to <https://www.regulations.gov/>

RE: [Docket No.FDA-2025-D-1504](#): *Responding to FDA Form 483 Observations at the Conclusion of a Drug CGMP Inspection: Draft Guidance for Industry*

Dear Sir or Madam,

The International Society for Pharmaceutical Engineering (ISPE) appreciates the opportunity to comment on the above-referenced draft guidance.

ISPE appreciates the FDA's efforts in issuing this guidance, as the document provides detailed step-by-step instructions for responding to FDA Form 483 observations following cGMP inspections and will be greatly beneficial to industry. ISPE's comments are the voice of the ISPE members, based on a range of experiences responding to observations in Form 483 and producing acceptable responses within the required timescale.

In addition to specific suggestions listed in the attached pages, ISPE requests that FDA consider revising Section IV, as several of the recommendations are ambiguous. For example, recommendations to examine internal audits (ref. line 200) or perform specific investigative activities (ref. line 326) could be interpreted as requests to include internal audit findings and detailed investigative steps as part of the response to the FDA 483. ISPE recommends that FDA state that the elements discussed throughout Section IV should be considered as part of the development of the FDA 483 response, but not all the elements may be relevant to include in the FDA 483 response. The establishment should determine, based on the criticality, severity, global nature, and patient impact of the observation, which of the elements in this section are most applicable and include them as part of the 483 response.

ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. ISPE's 25,000+ members lead scientific, technical, and regulatory advancement across the pharmaceutical lifecycle in more than 90 countries worldwide. ISPE does not take a political position or engage in lobbying activities or legislative agendas.

We appreciate the opportunity to submit these comments for your consideration. Please do not hesitate to contact me if you have any questions.

Respectfully,

Michael S. Martin
ISPE President & CEO
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Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strike through~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Footnote to lines 23-26	The purpose of this guidance is to assist drug manufacturers who choose to respond to FDA when they receive an FDA Form 483 Inspectional Observation (FDA 483) at the conclusion of an inspection to assess conformity with current good manufacturing practice (CGMP).	ISPE recommends that the guidance includes a new footnote after this sentence: <u>Remote Regulatory Assessments (RRA) are out of scope of this guidance. Refer to the FDA guidance “Conducting Remote Regulatory Assessments: Questions and Answers; Guidance for Industry” issued in the Federal Register on June 28, 2025.</u>	For clarification and to eliminate any confusion, ISPE recommends that FDA add a new footnote after this section, explicitly stating that Remote Regulatory Assessments (RRA) are out of scope for this guidance.
55-68	Responding to an FDA 483 gives an establishment an opportunity to provide, among other things...	ISPE recommends including the following text as a fifth bullet after line 68: <u>Evidence documenting a misunderstanding that occurred during the inspection, which may have resulted in an observation, including a referenced violation of a specific regulation to which the firm disagrees</u>	The inspected facility should have the opportunity to provide this type of documentation as part of the firm’s response to FDA Form 483. If no resolution or consensus is reached, the ombudsman process can be initiated as outlined in Section V. of the guidance.
70-72	The FDA 483 response can also address observations of a verbal nature (including non-reportable observations and discussion items) that are not listed on the FDA 483, but which FDA representatives discussed during the inspection.	ISPE recommends deleting the text in lines 70-72: The FDA 483 response can also address observations of a verbal nature (including non-reportable observations and discussion items) that are not listed on the FDA 483, but which FDA representatives discussed during the inspection.	Verbal comments and recommendations from agency representatives often reflect advisory discussion rather than documented violations of current Good Manufacturing Practice requirements. Recommending firms prepare formal responses within the 15-business-day timeframe for matters not deemed

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70-72(cont.)			significant enough to appear on the Form 483 imposes an undue burden and diverts limited compliance resources from documented observations that present real regulatory risk. Removing this statement also eliminates subjectivity and potential misinterpretation or misunderstanding of verbal topics discussed during the inspection that are not specifically included in the FDA 483.
91	The FDA 483 response should include a table of contents and at least the following elements:	Regarding a table of contents, ISPE recommends that the FDA 483 response should include a table of contents with at least the following elements, <u>unless not applicable to the specific response:</u>	Not all listed elements will be applicable in every response. Updating the text will reduce uncertainty about what must be included when certain items don't apply.
97-111	<p>(2) A copy of the FDA 483 issued at the close of the inspection.</p> <p>(3) The identity of the response preparer, and if not prepared by the establishment, the preparer's relationship to the establishment (e.g., the establishment's consultant, U.S. agent, or outside counsel).</p>	<p>ISPE recommends deleting items (2), (3), editing (4), and also deleting (5).</p> <p>(2) A copy of the FDA 483 issued at the close of the inspection.</p> <p>(3) The identity of the response preparer, and if not prepared by the establishment, the preparer's relationship to the establishment (e.g., the establishment's consultant, U.S. agent, or outside counsel).</p>	<p>ISPE recommends deleting items (2), (3), and (5) in this section for the following reasons.</p> <ul style="list-style-type: none"> Regarding item (2), FDA has access to the complete 483 and should not need the manufacturer to submit a copy with the response. Regarding item (3), typically, multiple people are involved in preparing the 483 responses, so it would not be appropriate to name a single "response preparer".

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	<p>(4) The identity of the signatory of the written response.</p> <ul style="list-style-type: none"> The written response should be signed by a person in the establishment’s executive management who allocates resources and has the authority to implement commitments. <p>(5) Any letters of authorization, if the establishment has retained a consultant or outside counsel.</p>	<p>(4) The identity of the signatory of the written response.</p> <ul style="list-style-type: none"> The written response should be signed by a person in the establishment’s executive management <u>the most senior responsible person at the inspected establishment</u> who allocates resources and has the authority to implement commitments, <u>for example, a site head or other officially designated senior representative with authority for the inspected establishment.</u> <p>(5) Any letters of authorization, if the establishment has retained a consultant or outside counsel.</p>	<ul style="list-style-type: none"> ISPE considers the requirement in item (4), as amended by ISPE, sufficient. <p>ISPE recommends amending the text in item (4). The term “executive management” can be ambiguous in large organizations, and could cause unnecessary delay and administrative burden, while not necessarily reflecting the role with the authority for site-level commitments. It may not be feasible for the establishment’s executive management to sign the written response, especially for global companies, as this individual may be in another country or not available at the inspected facility to sign the written response in a timely manner. The most responsible person at the inspected facility who is responsible for facility compliance and oversight of facility resources and commitment implementation should be the appropriate level within the inspected establishment to sign the written response.</p> <ul style="list-style-type: none"> Regarding item (5), FDA should not need a letter of authorization, therefore, we recommend deleting this item.

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116-137	<p>(7) An executive summary of all remediation activities with key details, as well as a more detailed description of each observation or grouped observations and associated remediation activities, including each of the following:</p> <ul style="list-style-type: none"> • A patient- and product-focused risk assessment of the observations, with an assessment of inventory and distributed drugs still within expiry and any possible effects on safety, identity, strength, quality, and purity of potentially affected drugs. • A detailed investigation report with scope; summary; list of associated drug(s) and lot number(s); identified root cause(s) of the observation and any related systemic issues; the CAPA plan; a summary of completed actions, including interim actions; and a planned effectiveness evaluation, with results if available. • Attachments related to the associated observation. Attachments can include 	<p>ISPE recommends clarification of text as follows to reflect the variation in length and detail of responses to observations.</p> <p>(7) An executive summary of all remediation activities with key details, as well as a more <u>Where more detail is warranted, an executive summary of all remediation activities with key details, as well as a more detailed description of each observation or grouped observations and associated remediation activities.</u> including each of the following. You may consider including the following as part of any remediation activities:</p> <ul style="list-style-type: none"> • A patient- and product-focused risk assessment of the observations, with an assessment of inventory and distributed drugs still within expiry and any possible effects on safety, identity, strength, quality, and purity of potentially affected drugs. • A detailed investigation report with scope; summary; list of associated drug(s) and lot number(s); identified root cause(s) of the observation and any related systemic issues; the CAPA plan; a summary of completed actions, including interim actions; 	<p>ISPE recommends the following changes to this section of the guidance to address feedback from establishment responses given the variation of 483 observations.</p> <p>Not all observations require detailed investigation and remediation. A more flexible, risk-based approach regarding the expectations around executive summary, description of observations, remediation activities, and supporting documentation will ensure that time is spent on the critical content for each response, and that a complete and appropriate response is submitted within 15 business days.</p> <ul style="list-style-type: none"> • Although an executive summary may assist with review of the 483 observation responses, the level of detail is better and more effectively captured in the detailed response to each of the FDA 483 observations. Additionally, an executive summary may not be warranted if there is a small number of observations or if this level of detail is not needed, for example, if only one observation was received. • CAPA effectiveness may not be completed in the timescale and

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116-137(cont.)	documents, pictures, video, diagrams, or data. All attachments should be signed, indicating support for the contents contained therein. All documents provided by a consultant, including attachments, should be signed by the consultant.	<p>and a planned effectiveness evaluation., with results if available.</p> <ul style="list-style-type: none"> Attachments related to the associated observation. Attachments can include documents, pictures, video, diagrams, or data. All attachments should be signed, indicating support for the contents contained therein. Electronic signatures that comply with existing regulatory requirements are permitted. All documents provided by a consultant, including attachments, should be signed by the consultant. 	<p>thus would not be available to include in the 483 response.</p> <ul style="list-style-type: none"> Signing all pages of all attachments is not necessary if the source of the document is a validated document management system with version control and an audit trail, since the validated version of a particular document can be retrieved. This requirement requires extra work with little benefit.
134- 137	<p>Tables could be used to organize this information in the executive summary, for example:</p> <p>Example of Executive Summary Format</p>	<p>Tables could be used to organize this information in the executive summary, for example: summarize the items in the Executive Summary (if included). Organize this information in the executive summary, for example:</p> <p>Example of Executive Summary Format</p>	<p>ISPE recommends deleting the Table. Including a Table may be useful to summarize the response; however, the style and content of any table should be based on the observations and response. The example given contains details that may not be relevant to the variations in the types of responses.</p>

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275-277	An establishment's management should form a multidisciplinary investigation team with clear roles and responsibilities to understand an observation and set the foundation for a robust investigation.	Based on risk, A n establishment's management should may form a multidisciplinary investigation team with clear roles and responsibilities to understand an observation and set the foundation for a robust investigation."	ISPE recommends that the text be modified to include a caveat that a multidisciplinary team should be used based on risk, consistent with ICH Q9(R1). Additionally, a multidisciplinary investigation team is not always needed.
289-290	FDA recommends establishments prepare an investigation plan and include a detailed protocol and methodology.	FDA recommends establishments prepare an investigation plan and include a detailed protocol and methodology <u>on a risk basis consistent with ICH Q9(R1) or an equivalent approach.</u>	ISPE recommends that the guidance include a caveat that the investigation plan, protocol, and methodology should be based on risk and consistent with ICH Q9(R1) or an equivalent. A detailed investigation plan, protocol, and methodology are not always needed, or the plan and protocol may be relatively simple and not contain much detail, and a protocol may not be necessary – this should be risk-based.
317-320	A methodical approach to identifying the root cause(s) is important, including identifying potential causes (there may be more than one), investigating each potential cause individually, and testing product or systems using scientifically supported approaches for verification.	A methodical approach to identifying the root cause(s) is important, including identifying potential causes (there may be more than one), investigating each potential cause individually, and testing product or systems using scientifically supported <u>risk-based approaches for verification. to verify they are fit for their intended use.</u>	ISPE recommends revising this sentence to include risk-based approaches to system verification to ensure fitness for intended use, in alignment with FDA's Q9(R1) Quality Risk Management guidance, GAMP® principles, and good industry practices.

End of Comments