24 March 2025

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
via online submission to https://www.regulations.gov/

RE: Docket No.***FDA-2024-D-5374 Considerations for Complying with 21 CFR 211.110***

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Society for Pharmaceutical Engineering (ISPE) appreciates the opportunity to comment on the above-referenced draft guidance.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 to continue to review 21 CFR 211.110. In general, it is welcomed that the FDA provides their thinking on matters related to advanced manufacturing or technology use, as this can help industry gain clarity on current expectations.

In this case, while the document provides a detailed contextual explanation, its core message appears to be concentrated in lines 199–215. As currently written, this section categorically excludes the use of process models solely for compliance with the requirements of 21 CFR 211.110. Such a strict exclusion of process models as the primary or sole means of control could significantly hinder the advancement of innovative manufacturing control strategies, extending beyond continuous manufacturing and the specific applicability of 21 CFR 211.110. ISPE recommends removing or substantially revising lines 199–215 to mitigate this potential impact.

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 22,000+ members lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world. 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.

On behalf of ISPE,

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Response to a request for comments ***FDA-2024-D-5374 Considerations for Complying with 21 CFR 211.110***

Comments submitted by the International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

GENERAL COMMENTS ON THE DOCUMENT
GENERAL COMMENTS ● In general, it is welcomed that the FDA provides its thinking on matters related to advanced manufacturing or technology use, as this can help the industry clarify current expectations. ● In this particular case, however, beyond the detailed explanation of the context, the core message of the current document seems to be in lines 199-215. Currently, these seem to categorically rule out the use of process models only to comply with the requirements of 21 CFR 211.110. It is curious why this interpretation is issued at this point, vs. continuing to rely on the scientific and risk-based approach outlined, for example, in lines 86, 121, and especially line 130 about the spirit of flexibility that regulations provide. The somewhat categorical exclusion of the use of process models as the main or only means of control could have a significantly detrimental effect on the development of advanced manufacturing control strategies for process models, in general, beyond the case for continuous manufacturing or the 21 CFR 211.110 applicability. ISPE suggests removing or significantly revising sections 199-215.
The current draft appears to be based on one specific example from small molecule drug product processing. While a conservative approach might be justified in this case, there are additional modeling applications that have a different context of use and lower immediate, irreversible impact on product quality. This is mentioned in lines 113-119 of the current draft as well. To illustrate a wider range of model applications, minimize misunderstandings and further encourage the use of process models in drug manufacturing, it would be relevant and added value for both industry and FDA reviewers and inspectors to include additional examples where process models do not need verification by in-process testing or process monitoring as mentioned in lines 113-119.

Specific Comments on the Text

ISPE indicates text proposed for deletion with strikethrough and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Line 199-225	FDA is aware of industry's interest in using in-process control strategies that rely solely on process models to satisfy the requirements of § 211.110. This includes interest in strategies that use process models in continuous manufacturing to predict in-process material uniformity and homogeneity without any testing or examination of the in-process material (whether direct or indirect). However, to date, FDA has not been made aware of process models that demonstrate that: (1) the underlying assumptions of the process model will remain valid during routine manufacturing; and (2) the manufacturer can detect if an underlying assumption is no longer valid (e.g., a continuous mixing model that assumes uniform mixing would be unable to detect that uniform mixing is no longer occurring due to material agglomeration on the walls of the mixer). In other words, current process models cannot ensure the continued validity of all of the model's underlying assumptions at all times, particularly during certain unplanned disturbances. In the event of an unplanned disturbance that is not accounted for by the model's underlying assumptions, such control strategies would be unable to prevent nonconforming in-process materials (e.g., nonhomogeneous powder blend) from continuing through	The guidance should not limit application of technology for process models in lieu of testing but should provide risk-based considerations for potential future applications. Consider removing lines 199-215 or significantly revising it in order to avoid the categorical exclusion of the use of process models only for control of uniformity. ISPE recommends including an example where models can be used without verification by in-process control or process monitoring in order to illustrate the guidance provided in lines 113 - 119 and minimize misunderstanding that, in general, all process models in scope of this guidance need verification by in-process testing or process monitoring.	Additionally, although not explicitly stated, the guideline seems to have a narrow view of process models that are used as a critical part of a control strategy. The guideline should be consistent with the ICH Q8/9/10 Points to Consider and ICH Q13 that process models could be used for development or as part of a control strategy. The content of lines 199-215 could have a significantly detrimental effect on the development of advanced manufacturing control strategies for process models, in general, beyond the case for continuous manufacturing or the 21 CFR 211.110 applicability.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
	production and being used “in manufacturing or processing operations for which they are unsuitable.”27,28 Therefore, control strategies that rely solely on current process models would be insufficient to satisfy the requirements of § 211.110.		

End of Comments