

December 17, 2008

Division of Dockets Management HFA-305
Food and Drug Administration
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Reference Docket Number FDA-2008-D-0559, Guidance for Industry. Process Validation: General Principles and Practices.

Thank you for the opportunity to comment on the modernized and much-improved guideline to process validation.

Clarifications of Policy

This guide addresses many longstanding misunderstandings. There are four additional areas of ambiguity within the regulated industry that this guide, when finalized, should address.

1. In-process acceptance criteria.

The guide is clear that validation runs should be subject to enhanced sampling and in-process control.

- (a) Should there be acceptance criteria on the in-process controls? Or is it sufficient to evaluate the in-process results against unwritten standards and apply criteria only to the final tests?
- (b) Assuming that there are criteria on in-process controls and a validation run fails a criterion, but the same control passes later in the process or during final product testing, does the validation effort pass or fail?

2. Parameters and Criteria.

Does FDA expect acceptance limits on process inputs? Should a protocol establish criteria on, for example, equipment speed or temperature? There is no controversy that the process should be described in detail: the question is whether the validation fails if one or more validation runs exceeds those process settings but the resulting product meets limits. Or should acceptance criteria only apply to the output of the process?

3. Repeating validation following a failure of an acceptance criterion.

If a validation effort fails one criterion, the validation fails. The process must be changed or adjusted to address that failure, and the validation will be repeated. In this instance, must the second validation repeat all of the validation, or can the repeated validation address only those attributes that are related to the change?

Consider the scenario where a biotech API process fails an endotoxin limit. Investigation identifies that a process hold time was too long during a late stage of purification. Would the upstream processes (fermentation and recovery) need repeated validation with the enhanced sampling and acceptance criteria? Would the firm need to demonstrate impurity reduction for downstream purification? In this scenario, the process change between the first and second validation effort (reducing the process hold time) would have no effect (or slightly improve) impurities.

4. Reliance on representations from equipment and instrument vendors.

It has become fashionable to rely on documentation from the vendors of complex pieces of equipment for much of the qualification effort. These documents may be called “equipment turnover packages” or “factory acceptance tests.” Companies maintain:

- Some tests are complex and can only be performed with the expertise and specialized equipment at the vendor, and
- Repeating the tests at the drug manufacturer’s site is redundant.

This concept frequently extends to WFI systems – the same engineering company may weld and inspect the welds.

To what extent can a drug manufacturer rely on qualification data provided by the equipment vendor?

FDA may consider the policies on these topics to be so obvious that no clarification is needed. Unfortunately, there is a great deal of ambiguity within certain segments of the industry. We would greatly appreciate clear statements in the final guidance.

Status of guidance

Finally, the guidance would be less controversial in years to come if the degree of requirement were clearer. The application of *should*, *essential*, and *must* need to be consistent with the status of the guidance.

Should

Even though *should* is defined in line 60, the word appears in contexts that are inconsistent with that definition in the following places:

- Line 58, in the previous sentence: “guidances ... should be viewed only as recommendations”
- Line 82: “The basic principle of quality assurance is that a drug should be produced that is fit for its intended use;”

- Line 180, where *should* is not a recommendation but a regulatory requirement cited in the previous sentence: “Accordingly, in-process material should be controlled to assure that the final drug product will meet its quality requirements.”
- Line 246. If *should* is applied as defined, FDA is suggesting that it would be hypothetically acceptable for viral clearance studies to not be performed under CGMP conditions or to have approval by the quality unit: “viral clearance studies to viral and impurity clearance studies have a direct impact on drug safety and should be performed under CGMP conditions, even when performed at small scale. The quality unit should be involved with these studies as is typical during commercial production.”
- Line 380. Is there a scenario where FDA would accept a “decision to begin commercial distribution” that would not “be supported by data from commercial batches?”

Essential

Along the same line of inquiry, what is the relative status of *essential* in the guidance compared to *should*? The word *essential* appears in sentences starting at lines 190, 216, 284, 301, 333, 415, 498, 590, 593, and 619. At line 619, *essential* refers to something which is explicitly required by regulation.

Are *essential* items required, or are there alternative approaches that would suffice?

Must

Generally but not entirely, *must* appears in the guidance where there are explicit references to the CGMP regulations in 21 CFR 211. The scope of the guide includes APIs, though, which are outside the scope of 21 CFR 211. Does the guidance limit the application of *must* only to finished pharmaceuticals, or do the *must* sentences establish requirements (as opposed to recommendations) for APIs?

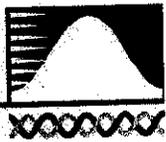
Thank you for your consideration,



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