

CPG Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval

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BACKGROUND:

This Compliance Policy Guide (CPG) explains the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Veterinary Medicine (CVM) enforcement policy regarding the timing of the completion of certain process validation activities for the products covered by this CPG.

This policy guide covers sterile as well as non-sterile manufacturing processes, but it does not address the methods and controls designed to ensure product sterility (e.g., aseptic fill validation). New drug applications for sterile products include information about the intended sterilization or aseptic processing procedures. The Centers evaluate this information as part of the application review process. CDER, CBER, and CVM may also issue assignments to the appropriate ORA offices (Office of Pharmaceutical Quality Operations (OPQO) or Office of Biological Product Operations (OBPO)) to audit and assess the filed information as well as any additional information that demonstrates the adequacy of the sterile process.

This CPG does not address products approved by a Biologics License Application (BLA) or recombinant protein drug products submitted in a New Drug Application (NDA).

Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110), and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. The proof of validation is obtained through rational experimental design and the evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase. Refer also to [Guidance for Industry Process Validation: General Principles and Practices \(January 2011, presently recognized by CDER, CBER, and CVM\)](#).

Before commercial distribution begins, a manufacturer is expected to have accumulated enough data and knowledge about the commercial production process to support post-approval product distribution. Normally, this is achieved after satisfactory product and process development, scale-up studies, equipment and system qualification, and the successful completion of the initial conformance batches. Conformance batches (sometimes referred to as "validation" batches and demonstration batches) are prepared to demonstrate that, under normal conditions and defined ranges of operating parameters,

the commercial scale process appears to make acceptable product. Prior to the manufacture of the conformance batches the manufacturer should have identified and controlled all critical sources of variability.

POLICY:

1. Conformance batches:

New drug applications may be approved by the Center prior to the completion of the initial conformance batch phase of process validation. The manufacture of the initial conformance batches should be successfully completed prior to commercial distribution, except as identified below.

2. Inspection of validation activities during a pre-approval inspection:

If a pre-approval inspection is performed, the inspection team should audit and assess any available process validation protocols, activities, data, and information, whether or not completed, and report to the firm any deficiencies. The appropriate division within the OPQO or OBPO should recommend withholding approval of an application, if any completed validation efforts include data of questionable integrity or demonstrate that the process is not under control and the firm has not committed to making appropriate changes. Refer also to the Center pre-approval inspection compliance programs for additional guidance.

If during a pre-approval inspection, process validation activities are found significantly deficient for an approved product made by a process similar to that of the subject of the pre-approval inspection and for which a warning letter or regulatory action will be proposed, the appropriate division within the respective OPQO or OBPO should recommend withholding approval of the application.

3. Inspection of validation activities during a post-approval inspection:

If the initial conformance batch validation activities for a particular approved product were not substantially inspected and found satisfactory during the pre-approval inspection, the appropriate division within OPQO or OBPO should cover this activity for the approved application or a substantially similar process/product during the next routine CGMP inspection (see Compliance Programs 7356.002 for human drugs, and 7371.001 for animal drugs).

The appropriate division within OPQO or OBPO **should inspect** the firm's validation activities for the new product **within the first year of manufacture** at commercial scale (if not inspected during the pre-approval inspection), if any of the following conditions apply:

- a. the new drug is the first produced by the manufacturing site;
- b. the firm has had previous problems validating a similar process for another product;
- c. the product is manufactured by equipment or process that is substantially different from equipment or processes previously used by this firm; or,

- d. the product is made by a process involving inherently variable unit operations or complex operations or procedures (see Compliance Programs 7356.002 for human drugs, and 7371.001 for animal drugs; and consult further with the respective Center's reviewing office for the product being inspected and/or the Office of Compliance subject contact for further guidance).

If none of the above conditions apply, the district should evaluate validation activities for new products during the next routine CGMP program inspection (7356.002). Alternatively, for sites with a history of successful validation efforts for related products made by similar processes the appropriate division within OPQO or OBPO may request the process validation protocol and report to be sent to the appropriate division office within OPQO or OBPO for audit and assessment. Based on the review of this information, additional on-site inspection, evaluation, and documentation of the information received may, or may not, be conducted at the appropriate OPQO or OBPO division office discretion unless directed otherwise.

If a firm's validation activities for the new product are found to have significant deficiencies (e.g., the initial conformance batch phase was not completed, the protocol was not followed or is inadequate, or validation data indicates process is not adequate), and one or more batches have been distributed, the appropriate division office within OPQO or OBPO should recommend regulatory action.

Seizure of distributed batches should be considered when there are significant deficiencies with validation or the evidence demonstrates the product does not comply with specifications. Injunction should be considered when there are significant deficiencies or data demonstrating the process is not capable of producing product meeting the established specifications.

4. Completion of initial conformance batch manufacture prior to commercial distribution:

For some products, the completion of the initial conformance batch phase of process validation before the distribution of any one batch would require the manufacture of unneeded batches (e.g., certain orphan drug products), which would not be in the interest of public health. In addition, the completion of multiple batches before first distribution may also be impractical for a product with a very short shelf-life or that is intended for limited use (e.g., some radiopharmaceuticals). Therefore, the need to manufacture multiple conformance batches in advance of initial product distribution may not be needed under these circumstances. In such cases, product distribution may have occurred concurrently with the release (or approval for release) of each conformance batch.

The agency's evaluation of a firm's decision to release batches concurrent with the manufacture of the initial conformance batches should include review and/or audit and assessment of:

- a. the firm's basis for justifying the distribution of individual batches prior to completion of the initial conformance batches (to include review of the product/process development effort);

- b. the firm's protocol/plan and available data to verify that there are adequate batch controls and testing prior to release for distribution of each batch, and provides for adequate and timely assessment of the validity of the process once all initial conformance batches have been manufactured; and,
- c. the firm's program for monitoring distributed batches and provisions for a rapid response to information suggesting the process is not under control (e.g., subsequent batch failures, production problems related to process design or equipment performance, complaints).

Advanced pharmaceutical science and engineering principles and manufacturing control technologies can provide a high level of process understanding and control capability. Use of these advanced principles and control technologies can provide a high assurance of quality by continuously monitoring, evaluating, and adjusting every batch using validated in-process measurements, tests, controls, and process endpoints. For manufacturing processes developed and controlled in such a manner, it may not be necessary for a firm to manufacture multiple conformance batches prior to initial distribution. Agency staff (field and Center) should discuss the need for conformance batches prior to distribution with the designated agency contacts, when inspecting firms employing these advanced pharmaceutical science and engineering principles and control technologies.

The appropriate division within OPQO or OBPO should consult with the appropriate agency contact before initiating regulatory action based on insufficient validation under the above circumstances.

5. Active Pharmaceutical Ingredients:

Under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Act, process validation, including the manufacture of initial conformance batches, is also expected for Active Pharmaceutical Ingredients (APIs), but the specific expectations differ somewhat from those required for dosage form products. Refer to the [Guidance for Industry, Q7A, GMP Guidance for Active Pharmaceutical Ingredients, issued August, 2001](#), for details.

If the API for an application under review is already used in other approved or marketed dosage form products, and is being made by substantially the same process and scale as for the application under consideration for approval, the inspection should cover full process validation data and activities (including conformance batches), unless covered during a previous inspection of the API manufacturer. If validation is covered and significant deficiencies are found, the district is to recommend withholding approval of the dosage form application and consider proposing action to address the use of that API in other dosage form products.

If the API for an application under review is a new molecular entity or is being manufactured by a process substantially new in design or scale to the site of manufacture, approval of the dosage form incorporating the API is not to be delayed by the performance of initial conformance batches for the API. However, the inspection team is to audit and assess any available process validation protocols, activities, data, and information, whether or not completed, and report to the firm any deficiencies. The

appropriate division office within OPQO or OBPO should recommend withholding approval of an application if any completed API validation efforts include data of questionable integrity or demonstrate that the API process is not under control and the firm has not committed to making appropriate changes.

Some biotech NDAs include information about the validation of the manufacturing process for the API, and this information is reviewed in conjunction with the other chemistry, manufacturing, and controls information in the application. In these cases, the inspection team should audit the accuracy and completeness of the data and information submitted to the application. Potentially objectionable findings should be handled consistent with the applicable compliance program and include consultation with the respective Center reviewer and/or compliance officer before making any formal objection to the firm.

If during a pre-approval inspection of the API manufacturer, process validation activities are found significantly deficient for an API made by a process similar to that of the API under inspection, and for which a warning letter or other regulatory action will be proposed, the appropriate division office within OPQO or OBPO should recommend withholding approval of the dosage form application. The appropriate division office within OPQO or OBPO should also recommend withholding approval if the API firm has not established or is not following an adequate initial conformance batch validation plan/protocol or when the process is not under control, as demonstrated by repeated batch failures due to manufacturing process variability.

If batches have been distributed, the appropriate division office within OPQO or OBPO should consider recommending an appropriate regulatory action.

NOTE: This compliance policy guide (CPG) also applies to pre-market approval applications submitted to the Center for Veterinary Medicine (NADAs or ANADAs). The CPG reference may be found at Sec. 638.100 (7125.38).

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