



**Do CGMPs require three successful process validation batches before a new active pharmaceutical ingredient (API) or a finished drug product is released for distribution?**

No. Neither the CGMP regulations nor FDA policy specifies a minimum number of batches to validate a manufacturing process. The current industry guidance on APIs (see [ICH Q7A](#) for APIs) also does not specify a specific number of batches for process validation.

FDA recognizes that validating a manufacturing process, or a change to a process, cannot be reduced to so simplistic a formula as the completion of three successful full scale batches. The agency acknowledges that the idea of three validation batches has become prevalent, in part due to language in its own guidance documents. However, FDA is now clarifying current expectations on process validation. The 1987 *Guideline of General Principles of Process Validation* is currently being revised to address this issue. The emphasis for demonstrating validated processes is placed on the manufacturer's process design and development studies in addition to its demonstration of reproducibility at scale, a goal that has always been expected.

However, a minimum number of conformance (a.k.a. validation) batches necessary to validate the manufacturing processes is not specified. The manufacturer is expected to have a sound rationale for its choices in this regard. The agency encourages the use of science based approaches to process validation.

In March 2004, FDA revised the Compliance Policy Guide (CPG) (Sec. 490.100) on [Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval](#). The CPG describes the concept that, after having identified and establishing control of all critical sources of variability, conformance batches are prepared to demonstrate that under normal conditions and operating parameters, the process results in the production of acceptable product. Successful completion of the initial conformance batches would normally be expected before commercial distribution begins, but some possible exceptions are described in the CPG. For example, although the CPG does not specifically mention concurrent validation for an API in short supply, the agency would consider the use of concurrent validation when it is necessary to address a true short-supply situation, and if the concurrent validation study conforms to the conditions identified in the CPG (See paragraph 4. a-c).

The conditions outlined in the CPG include expanded testing for each batch intended to address a short-supply situation. Expanded testing, conducted according to an established validation protocol could provide added assurance that the batch meets all established and

appropriate criteria before the API is used in the finished drug product. Additionally, confidence in the API manufacturing process may be gained by enhanced sampling (larger sample size representative of batch) and perhaps the testing of additional attributes. Validated analytical methods are needed for testing every batch, including validation batches. The agency would also expect the manufacturer to use a validation protocol which includes a review and final report after multiple batches are completed, even though the earlier batches may have been distributed or used in the finished drug product.

References:

- [21 CFR 211.100](#): Written procedures; deviations
- [21 CFR 211.110](#): Sampling and testing of in-process materials and drug products
- [CPG 490.100](#) Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval.
- [ICH Q7A](#) Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

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