Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion
This document provides document to determine if validation of re-work and / or re-processing steps is required for Active Pharmaceutical Ingredient (API) processes.

This document provides recommendations for evaluating the potential impact on product quality to determine if a given re-work or re-process step requires validation.

This document applies to critical steps of API manufacturing via chemical synthesis and the isolation steps for APIs produced by classical fermentation. It does not apply to biopharmaceutical API manufacturing or drug product manufacturing. Recovery of materials by 2nd crop production is not included within the scope of this document.

Compliance with regulatory filings, consideration of impact on product stability, and deviation investigation activities should be evaluated, but are outside of the scope of this document. For further information regarding regulatory filing compliance, stability and deviation investigation, please refer to relevant documents.

To clarify validation considerations for re-processing and re-work steps, definitions of these terms are listed below:

Re-process – Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process.

Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not re-processing.

Re-work – Subjecting an Intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., re-crystallizing with a different solvent).

The determination of whether a remediation procedure is considered to be re-processing or re-working should be done on a case-by-case basis. This determination should be performed relative to commitments and descriptions of the process in the regulatory filing. Subsequent to this determination, the potential impact of the re-processing or re-work step(s) on the quality of the final API should be identified. Additional evaluation may be needed to determine if validation of the re-work or re-processing step is required. Not all re-works will necessarily require validation (e.g. re-work of non-critical, non-registered intermediate process step), but they do require consideration of validation.

for impact on validated control of the process, while introduction of a new CPP requires validation of this control. For further information on CPPs, refer to relevant document.

7. Are there changes in equipment used in the process? If yes, validation activities may be required, per normal site change management system.

8. What potential impact is there on product homogeneity? If the batch size is outside the validated batch-size range, then a homogeneity study may be required to show that product prepared at the modified scale is homogeneous. For further document on homogeneity, please refer to relevant document

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9. Is it intended that the material will be re-processed or re-worked more than once? If so, an evaluation of the cumulative potential impact of multiple re-process or re-work steps on the same batch is required. The evaluation, including requirements for validation should include the considerations indicated in this section. If multiple iterations are proposed, one should determine if alternative methods for remediation have been considered.

10. Batches that have different reasons for re-processing or re-work may be combined to perform the proposed remediation, if there are data and/or rationales (such as blend uniformity) available to support that the re-processing or re-work would be effective on each individual batch. Validation considerations for these combined batches can be determined using the flow-chart provided. Per ICH Q7A, “Out of specification batches should not be blended with other batches for the purposes of meeting specifications”.

The effectiveness of this procedure was demonstrated by lab studies that showed the impurity was diminished by the modified crystallization that is within the proven acceptable ranges and registered ranges for the process. The modified isolation temperature was not originally identified as a critical parameter for the process, but is now considered a CPP. This crystallization at a higher temperature has not been used before on commercial scale and has not been validated.
Here, validation of the proposed remediation procedure should be done, because the isolation temperature is critical to product quality. Also, since the isolation of the crystals at a warmer temperature is likely to provide a lower than usual product yield from the crystallization, the size of the re-processed batch may fall outside the validated batch size range. If this is the case, homogeneity of the product batch should be included as part of the validation activities to show the smaller batch size on the same size filter still provides a homogeneous product.

Other considerations that may need evaluation for this example could include the potential impact of different temperatures for generating other impurities and the potential for different physical characteristics (such as crystal morphology or particle size distribution).

Example 2
Batch B of a final API is found to contain an unacceptable amount of a known process-related impurity. Investigation of the incident reveals the root cause of the problem, and the corrective action for Batch B relies on process knowledge that indicates an elevated amount of this impurity cannot be removed by the normal product purification procedure. During process development, an alternate crystallization solvent mixture was shown to effectively control elevated amounts of this impurity. Use of this procedure did not become part of normal processing because of poor product yield from the solvent mixture. This re-work procedure has not been used before during commercial-scale manufacturing and therefore has not been previously validated.

This example would require validation in order to evaluate the potential impact of the remediation processing on impurity profile. The validation study should at a minimum, include evaluation of equivalence to historical product quality results, especially for process impurities such as solvents and process-related impurities. Because in this example the yield is expected to reduce the output batch size below the validated range, homogeneity testing of the final product should also be included in the validation.

Other considerations that may need evaluation are similar to those for Example 1:

- Is there any potential for new impurities (or differing impurity levels) above the qualification threshold because of the use of a different crystallization solvent?

- Is there a potential for different physical characteristics such as crystal morphology or particle size distribution?

- What is the impact on the drug product manufacturing process, or on the quality of the drug product?

