

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.

ICH Q7A require that re-work steps be validated for those portions of a process that are critical to API quality. There can be steps after introduction of API Starting Material that are not critical steps and rework may not require validation for those steps.

Validation of re-work and/or re-processing steps can be concurrent and may only include 1 batch since re-work and/or re-processing steps are typically not conducted frequently and there may never be more than 1 batch.

Where validation of the remediation is necessary, a concurrent validation approach can be suitable. In cases where there is already a concurrent validation exercise in existence for a given remediation procedure, further validation runs conducted using this remediation procedure can be added to the existing validation exercise provided suitable justification for inclusion and possible scope expansion is provided.

The following questions are provided for guidance when conducting an impact assessment, in order to determine what aspects of validation may be needed. An impact assessment conducted to determine whether validation is required or not should be documented and approved as part of the deviation investigation.

The flow-chart provided on the pages below is intended to provide guidance for the determination of validation activities for re-processing and re-work procedures.

1. Frequency of failure requiring re-processing/re-work. How often has use of the proposed remediation process been needed? If the number of production batches over a period of time that have needed this remediation exceed that allowed by site policy for failure rate, one should ask if control of the routine production process is still in a validated state.
2. If it is an intermediate that is to be re-processed or re-worked, is it produced prior to the introduction of the API starting material (as described by ICH Q7A)? If yes, then validation of the step is not necessary, and by extension validation of the re-process or re-work to remediate the quality of the intermediate is also unnecessary.
3. If the material is the product of a step in the process containing one or more Critical Process Parameters (CPPs), validation of the proposed remediation may be needed. Is the re-work /re-process step covered by an existing validation study? If yes, then validation of the proposed procedure may have already been addressed. For example, re-processing steps that address chemical issues (e.g. recrystallization to reduce normal process impurities), as well as re-processing steps to remove physical contamination (assuming it