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

5. Is the material prepared by the remediation procedure isolated as a solid or not? While this may not be important to the determination of whether or not validation of the remediation procedure is needed, it may influence where in the process to evaluate the effectiveness of the remediation procedure.

6. Is there an impact on an existing critical process parameter (CPP), or introduction of a new CPP? A change to an existing CPP should be evaluated 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 guidance.

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 guidance on homogeneity, please refer to relevant guidance

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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?

