Examples provided in the two tables are generalizations. Every proposed change should be assessed to determine the potential impact of the change and to consider the potential impact to product quality from the adopted change. This assessment must be documented. Sampling and testing, as needed, should be carefully considered to provide meaningful measurements of the impact of the change. In some cases evaluation of the adopted change might include extended monitoring or statistical trending of the performance of the process that has adopted the change to provide additional assurance that the modified process continues to perform in a validated state.

Evaluation of the validation impact of the proposed change(s) should include assessment against pre-established acceptance criteria, including (where applicable):

- Impact on product acceptability: Documentation of the nature of the change and its expected impact(s) on Critical Quality Attributes (CQAs) of the final API or drug product;

- Impact on product equivalence s: Does the quality of material produced by the changed process compare favourably to acceptable material prepared previously? Consider all CQAs that may be affected by the change.

- Impact on control of critical process parameters (CPP): It is recommended that the CPP risk assessment be re-evaluated to determine if the proposed change alters the risk associated with control of process parameters that impact product quality.

- Impact on product uniformity (e.g. homogeneity of API or blend uniformity of DP); and

- Impact on ability of process to consistently provide product that meets all quality expectations.

Evaluation of the quality impact of the change should take place as close as practical to the step in the process where the change was made. The system owner or Technical Services may typically propose the change and should participate in assessing the impact of the change. The Quality organization must be included in approval of the assessment of impact of the change to a validated process.

When assessing and evaluating the impact of a change, in some circumstances it may be preferable and appropriate to address only that part or step of the process including the change, rather than assessing validation of the entire process. The approach chosen for evaluating the process incorporating the change should include determining expectations for commercial release of the product made using the changed process (e.g., prospective, concurrent, or Continuous Quality Verification [CQV] approaches) . In some cases CQV and statistical analysis may be very appropriate for continued monitoring of the impact of a change that has been implemented rather than performing a more traditional validation of the changes.

process to another (e.g., oven bed, fluid bed, microwave) • change that impacts ability to meet a CPP, or that may otherwise impact product quality; • significant change in equipment size; • change in type of equipment used for isolation and drying of final API or DP (e.g, centrifuge, pressure filter-drier, tray drier)	Does change in equipment impact residual solvent levels in API?
For API, use of a previous unused/unvalidated rework or alternate processing option for a critical process step.	Validation required for rework processing that provides an API, but may not be required for an intermediate process step of an API manufacturing process.

Table 2. Types of Minor Changes and Points to Consider with this Change

This table provides some examples of minor changes to an established process.
Type of change applies to all (API, DP and packaging) except where noted otherwise.

Type of Minor Change	**Points to consider with this change**
Source or specification of non-critical process materials such as: - non-registered intermediates, -reagents, -solvents, -process aids (e.g. chromatography resins, filter aids); - non critical excipients -substances used with manufacturing equipment that do not become part of the product (e.g., machine nitrogen, dusting powders, lubricating oils) -implementing the use of recycled or recovered solvent into the same step of an API manufacturing process.	Does the change have any impact on product quality? Is the change supported by data from a development lab? See also example 2 below. Implementing use of a recovered solvent may prompt examination of solvent recovery process.
Pore size of filter media used for isolation of API	If change impacts a CQA (e.g., particle size distribution or impurity profile), this could be regarded as a major change.

Example 2:
A new source for the API starting material is being evaluated. Qualification studies may be needed to show that the new supplier's material meets specifications and that the final

API made from it meets specifications. Availability of a supplier assessment and use test results will influence the decision of what validation, if any, is needed for this type of change. Validation may not be necessary if the impurity profile of the final API is unchanged. However if it is necessary to show that the process can adequately control product quality for a different impurity profile, validation is needed.

Example 3:
A significant process change to the API manufacturing process typically prompts activities to qualify the API made by the modified process in the DP manufacturing process. The impact of changes made in the API process may not be revealed in the routine quality testing performed on the API so examination of the DP may be performed. It is a good practice for API manufacturing to notify DP manufacturing when a process change is adopted, even when there is no apparent impact on API quality from the change.

Example 4.
A change made to an API process that is shown to not impact product quality could be regarded as a minor change (with respect to its validation impact) independent of the regulatory impact of this change. For instance, addition of salt to the aqueous phase might be recommended to improve separation of the aqueous and organic phases during an extraction, where the use of salt in this step was not previously included in the regulatory filing. In this instance a Product Change Proposal (at a minimum) would be needed [4]but a validation assessment might conclude that it is a minor change with respect to validation impact.

Regardless of how the assessment of the expected validation impact of a proposed change is documented, it is important that documentation provides a description of the change, the impact assessment and acceptance criteria, if any, for evaluation of the change. When validation is executed to demonstrate acceptability and consistency of the process with the adopted change, the acceptance criteria should be determined on a case by case basis.

Acceptance criteria for evaluating the change should focus on elements that may be impacted by the change; some criteria and/or validation sampling used for the original validation may not be necessary for revalidation.

An additional consideration is the trail of documentation that accounts for all the changes in the process since it was last validated. At some point, it may be desirable to update the validation documentation for the process into a comprehensive summary rather than continuing to add individual documents to a collection through which it may be difficult to trace the impact assessments of all the changes since the last validation.

