Evaluation of Changes for Potential Impact on Process Validation

Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion:

This document provides recommendations and examples for evaluating the process validation impact of changes to manufacturing processes used for manufacture of Active Pharmaceutical Ingredients (API), Drug Products (DPs), drug substances made by biopharmaceutical processes and DP packaging processes.

This document applies to validated processes and identifies examples of changes for which examining the validation impact of a change should be considered. It does not apply to cleaning processes or laboratory test methods. In general, all changes that may affect product quality, patient safety, or reproducibility of the process shall be evaluated by using an established change management system. This evaluation should include assessment of the validation impact of the change. Major changes require validation, while documented evaluation of minor changes are typically documented using the site change management system.

Evaluating proposed changes to a process shall include a documented assessment of the validation impact of proposed changes. Where appropriate, use of a risk assessment in evaluation of proposed changes is recommended.

Examples of major changes are provided in Table 1.

A validation protocol is typically used to describe the validation for major changes. Assessment of the validation impact of minor changes is typically documented using the site's change management work process.

Examples of minor changes are provided in Table 2.

The level of knowledge of the proposed change (e.g., support of the change by lab or pilot studies) may help justify that the risk is lower than might otherwise have been assumed, allowing some proposed changes to be treated as minor changes.

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.

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For medical devices, a change that affects form, fit, or function of the device, such as material, components, manufacturing or assembly process, and replacement of equipment For a biopharmaceutical process, a change to a critical step such as: • to filtration, concentration or mixing parameters • lengthening maximum hold time • any change of scale. • shipping conditions	recommended. Scale change: With biopharma processes it is typical to redo validation of any scale change unless rationale is provided to explain why it is not required. Consider: • Is the original viral clearance study still applicable with the changed scale? • Is the effectiveness of mixing speed impacted by the scale change?
A change to the packaging process or technology, such as: • change to primary packaging component (structure, vendor, etc.) • major equipment change, equipment operating speed, pressure or temperature change with impact on critical packaging characteristic • change to different packaging line • change to primary packaging method (e.g. heat sealing to induction)	Validation of part or all of process is recommended.
First-time manufacture of an existing product (API, DP or packaged product) at a different manufacturing site or in a different facility at existing site	Should validate the process at the new site to show process performs consistently in new/different facility when run by personnel previously unfamiliar with process. Moving process to similar equipment within same facility might be a minor change if sufficiently justified – see Table 2 for considerations.
Process changes that can affect the release, metering or other characteristics of the DP dose delivered to the patient, for example: • change to the API or critical excipients (e.g. site of manufacture, route of synthesis, impurity profile, particle size • change such as one to achieve operational efficiency gains or to address EHS issues that adversely impacts API or DP quality	Validation of part or all of the process or that part of the process which has been changed is recommended. Assessment should include impact of any changes that impact CQAs. Evaluate if dissolution profile test with f_2 comparison [10] will be included as part of the evaluation. See also Example 3 below.

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Changes to optimize a process that are unlikely to have measurable impact on product quality or process performance, as determined by risk assessment.	Does the change have any impact on ability to meet defined process controls or CPPs, or on final product (API or DP) quality? See also Example 4 in the text.
Change to equipment with the same design and operating principle	A change to use of a different work center using the same equipment design and operating principles at the same manufacturing site could be considered a minor change if adequately justified. Proceed with care when assuming that equipment items are equivalent because small differences in design specifications, controls and performance could have unanticipated effects on behavior of process and quality of product. At a minimum, impact assessment should include comparison to quality of material produced prior to change.
Linear change to batch size of an intermediate or an API, within site SOP allowances	Investigation of homogeneity is usually not needed for small scale changes. Evaluating the impact of scale change should consider if equipment controls are capable of meeting process needs at the new scale.
Change in method of controlling process (e.g., from manual to automated control, or installation of a new computerized control system) when shown to deliver equivalent processing control	Process validation may be unnecessary if a change in method of process control is unlikely to have measurable impact on product quality or process performance, as determined by risk assessment. Review of equipment qualification/ verification is needed and this type of change may be regarded as major if assessment identifies increased risk in providing prescribed control.
Change in existing code imprint on the DP	Examples include:

