## Guidance Number: 023

**Table 1. Types of Major Changes and Points to Consider with this Change**

**Legends**:

**CQA** : Critical Quality Attributes
**API** : Active Pharmaceutical Ingredients
**DP** : Drug Products
**CPP** : Critical Process Parameters
**QAAL**: Quality Assurance Action limit
**CQV** : Continuous Quality Verification

| Type of Major Change | Points to consider with this change |
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| A change to the API or DP manufacturing process or technology, such as:<br><br>• Change in critical unit operations (e.g., addition, deletion, change in order of steps, repetition of an existing unit operation on a routine basis);<br><br>• Change of source or specification of a critical material (e.g., regulatory intermediate or API starting material);<br><br>• Modified operating conditions (e.g.time, temperature, pH, reagent stoichiometry) that impact CQAs;<br><br>• Change that could impact acceptable microbiological quality of the product. | Validation of part or all of process is recommended. Process validation is needed if a change in the process is expected to have measurable impact on product quality or process performance, as determined by risk assessment. Is the change supported by data from a development lab? Is the process still capable of providing good quality product if a material specification is relaxed? Tightening of a specification may not require validation as this will typically not challenge the capability of the process. Is stability of API or DP affected?<br>See also example 1 in the text. |
| 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 | Validation of part or all of process is recommended |
| 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 | Validation of part or all of process is 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: |

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| For a biopharmaceutical process, a change to a critical step such as:<br>• to filtration, concentration or mixing parameters<br>• lengthening maximum hold time<br>• any change of scale.<br>• shipping conditions | • Is the original viral clearance study still applicable with the changed scale?<br>• Is the effectiveness of mixing speed impacted by the scale change? |
| A change to the packaging process or technology, such as:<br>• change to primary packaging component (structure, vendor, etc.)<br>• major equipment change, equipment operating speed, pressure or temperature change with impact on critical packaging characteristic<br>• change to different packaging line<br>• 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.<br>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:<br>• change to the API or critical excipients (e.g. site of manufacture, route of synthesis, impurity profile, particle size<br>• 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. |
| For API, DP or packaging process:<br>• Change in acceptable range of a CPP or planned shift of the normal operating range that increases the risk of deviation and has | Validation of such a change is typically performed. Consider: -Reevaluate risk assessment to determine if there is an increase in the risk of deviation. |

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| the potential to adversely impact product quality.<br>• Recognizing or adding a new CPP for control of a critical quality attribute.<br>For API, linear scale change of final product step involving increase or decrease of batch size by more than limits specified in site SOP (e.g., greater than 10 %). | -Are planned operating ranges within equipment qualification? See example 1 below.<br>Any change in batch size should be evaluated in relation to the equipment. Are equipment controls still capable of meeting process needs?<br>Does scale change affect ability to complete reaction? Process parameters could also be impacted.<br>Does scale change impact product homogeneity? Allowed minor scale changes should be indexed to the batch size range that has been validated. |
| Batch size change for DP process or packaging of liquid, semisolid and powder forms of DP. | Demonstration of homogeneity or content uniformity is typically expected for a non-liquid DP process batch size change. |
| Addition of code imprint on a dosage unit | Validation is recommended since change requires addition of a process step and use of a material (ink) new to the process, also has direct impact on appearance CQA. |
| Change of an imprint on a modified release dosage form | Validation is recommended since this type of change could impact dosage release. |
| Change to major equipment, such as:<br>• Design or principle of operation (e.g., change from dry to wet granulation or vice versa), or change from one type of drying process to another (e.g., oven bed, fluid bed, microwave)<br>• change that impacts ability to meet a CPP, or that may otherwise impact product quality;<br>• significant change in equipment size;<br>• change in type of equipment used for isolation and drying of final API or DP (e.g, centrifuge, pressure filter-drier, tray drier) | Is material produced equivalent in quality to acceptable material prepared in previous equipment?<br>Could equipment change impact product homogeneity or uniformity?<br>Does change in equipment impact residual solvent levels in API? |
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| 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**

| Type of Minor Change | Points to consider with this change |
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| Source or specification of non-critical process materials such as:<br><br>- non-registered intermediates, -reagents, -solvents, -process aids (e.g. chromatography resins, filter aids);<br><br>- 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?<br>Is the change supported by data from a development lab?<br>See also example 2 below.<br>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. |
| Change of Quality Assurance Action limit (QAAL)/target limit for a CQA | This is a minor change if the existing process is capable of routinely meeting the tighter quality limit. If tighter process control is needed to consistently meet QAAL/target limit then validation may be needed. |
| 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?<br>See also Example 4 in the text. |

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| 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.<br><br>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.<br><br>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.<br>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:<br>- Change in coding, such as from numeric to alphanumeric;<br>- change to ink used for a solid dosage form where the ink is already used on an approved product. Impact of the change depends on effect that ink characteristics may have on printing operation and on |

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| | product appearance, so this may be regarded as major change in some instances.<br>Risk assessment should be used to determine the impact of such changes. If the change impacts product CQAs or product stability, it should be considered major change. |
| Change of imprint by embossing, debossing or engraving on an oral solid dosage product | Risk assessment should be used to determine the impact of such changes. If the change impacts product CQAs or product stability, it should be considered major change. |
| Changes of a validated process that are within ranges that have been validated using a bracketing or matrixing strategy | Validation is typically not performed. |