

associated with one process parameter may influence the ability of other parameters to adequately control product quality. With Example 1, a temperature deviation during the reaction can lead to a greater-than-usual amount of a process impurity and can influence when the reaction should be terminated, and these in turn may impact the ability of the product crystallization to provide adequate control. It may be appropriate to designate temperature and/or reaction time (or endpoint test) critical for this example, and based on the risk assessment some may also choose to identify the crystallization conditions critical as well.

#### **Example 2:**

For a DP tablet manufacturing process, compression parameters, the interaction of excipients and perhaps other factors may interact or independently impact the dissolution and hardness characteristics of the product. A design of experiments (DOE) study may help in understanding which of these factors should be identified as CPPs.

#### **4. Using Risk Assessment**

Risk assessment of parameters should include evaluation of any process parameters impacting product quality, either directly or indirectly. The risk assessment provides the justification to explain why lower risk is associated with the quality-related parameters that are not identified as CPPs. Parameters that have a reduced risk of affecting product quality are sometimes described as Key Process Parameters, in manufacturing of small molecule APIs.

While validation brings focus to the CPPs, all process parameters identified in the manufacturing instructions are typically monitored during preparation of every batch, so it is also expected that parameters not identified as CPPs will be kept within prescribed ranges.

Using risk assessment of process parameters for this purpose is consistent with strategies for selection of CPPs established by industry trade associations. Additional guidance on the use of risk assessments for validation is available.

For new products, a focus of the risk assessment will be on whether there is a direct relationship between the parameter and a CQA. It is recommended that the risk assessment evaluation follow the Co-Development work process, which provides support and training for conducting appropriate risk assessments for selecting CPPs. A decision tree for determining criticality, adapted from the RFT work process, is shown in **Appendix II**.

Examples of risk assessments are provided in **Appendix IV**.

The relationship between parameters and CQAs is generally well-established from a variety of sources. These may include technical reports and memos prepared during and after process development, documented change management information and incident investigations, annual/periodic quality reviews, production manufacturing records and process capability studies.

#### **5. Interrelationship of CPPs with process support systems**

The risk analysis used to help select the CPPs for validation may be influenced by the ability of the equipment and supporting systems to control process variables (e.g. temperature, pressure and agitation). The equipment's capability to control process parameters within defined limits is typically demonstrated by commissioning and verification / qualification of the process equipment. Process Validation depends on the supporting systems – facilities, utilities, equipment and automated controls, measurement/analysis, and process – performing as expected to consistently manufacture a product that