

Alternatively, a critical step may not have any critical process parameters if it can be established that the parameter(s) in question has a NOR that is strictly controlled well-within the PAR.

One way of determining what is a critical process parameter is to begin with the CQAs. Technical experts and engineers from both development and production knowledgeable about the product and the production process should determine the CPP. Quality operations should be involved to verify that the CQA and CPP are properly documented and defensible. A flowchart of the manufacturing process should be made available to all participants. This flowchart should have sufficient detail to readily understand the primary function of each step. Then, each critical product attribute should be evaluated individually to determine what steps may or may not impact that attribute.

Any step or unit operation determined to be critical should be evaluated to determine if it contains one or more critical process parameters. The parameters must have some influence on a CQA to be considered for evaluation as critical. The degree of control over the parameter will determine if it is critical. It is possible to have a critical step that does not contain any critical parameters if control of process parameters is tight. This portion of the analysis requires both knowledge of the process and manufacturing equipment. An example might be a fully automated compression step. The step is critical but complete control over the parameters leads to defined noncritical process parameters. Critical parameters identified during the research and development phase are not necessarily reflective of production scale equipment. The analysis of the process at this level is analogous to a failure modes and effect analysis without estimating frequency of failure or severity of the effect.

Relevant information about any parameters suggested as potentially critical but determined to be non-critical should also be documented.

Example 1-Blending time and tablet lubrication evaluation during R&D

During R&D it is found that the lubricant blending time and the tablet press feed system are critical to tablet hardness. Over-blending of the lubricant leads to soft tablets. R&D conducts a study that defines the NOR limits of the blending step and tablet press feed conditions while still supporting adequate mixing of the lubricant. Blend time and press feed system are critical process parameters.

Defining Ranges for Critical Process Parameters

An understanding of each parameter is necessary before defining a parameter as critical. Parameters may be defined as critical depending on their effect on critical quality attributes, ability to be controlled, and the process design and capability. Process design and process capability are related to the concepts of Edge of Failure (EOF), PAR and NOR.

NOR and PAR values are established during research and development, but may also be further characterized during the manufacturing phase. Some EOF and PAR values may

determine if a variety of ranges or set points have been used. All set points used that resulted in acceptable batches within specifications are suitable for inclusion in the NOR.

If these data are not available, additional development work may be required. However, before such work is performed, it is useful to review the process and conduct a risk assessment to determine which parameters are likely to be most critical. The analysis ensures that the development work is focused correctly. With an adequate understanding of the product and process, the development may be performed on a reduced scale or through sub-lotting of the batch.

Definitions of Fixed, Variable and Dependent Parameters

A variable parameter is one that can be directly adjusted during processing. A fixed parameter is one that cannot be adjusted during processing, instead it is set prior to processing (e.g. mixing blade design, rotator/stator combinations, milling screen size, on/off motor speeds, etc.).

A dependent parameter is one that is the result from the effects of one or more variable and fixed parameters. A dependent parameter cannot be adjusted directly, but it can be changed through changes to other parameters or by making equipment changes. It is helpful during the review of the process to identify parameters that are fixed, variable and dependent.

Example 6-Output or dependent parameter

The pH of a solution is a dependent parameter. The pH itself cannot be adjusted directly like changing the speed of a motor. Instead an amount of acid or base must be added and often the rate of the addition must be controlled. The pH is an output or dependent parameter of the amount and rate of the addition.

Non-Critical Parameters

Those parameters that will have no effect on critical quality attributes are classified as non-critical. These would include parameters that if taken to an extreme might have an effect, but is highly unlikely the extreme would ever be reached. It may be useful to identify those non-critical parameters that, unless otherwise controlled, have the potential to impact the quality of The product. For example, these may be parameters that have a NOR well within the PAR owing to highly sophisticated automated controls. However, if this process were transferred to a facility which lacked this level of control, the parameter may then become critical. These parameters should be monitored and/or verified during validation and routine production, but are not required to be challenged during qualification and validation.

Example 7: Non-critical parameter

Protein will typically denature at temperatures exceeding 70°C. Some protein products will denature or degrade at a lower temperature such as 50°C. The routine processing condition for a protein product is often room temperature or 20-25°C. In the manufacturing environment even without special control it is highly unlikely that the