Summary - Selection of Critical Process Parameters for Validation

Two objective criteria must be met for a process parameter to be considered a potential critical process parameters (CPP):

1. Running the process outside the proven acceptable range (PAR) for the parameter results in a significant risk of producing material of unacceptable quality;

2. The difference in quality is carried through the process to the finished product (intermediate for sale, API or DP) where it results in the product not meeting one or more pre-determined Critical Quality Attributes.

For new processes, CPPs are identified during CoDevelopment. The CPPs are typically identified by Technical Support site personnel, if not previously identified during process development. For many processes, a recommended approach to identifying the CPPs for validation is to begin with identifying the product's CQAs and the process parameters that directly and indirectly impact these CQAs.

A process parameter may affect a CQA in either a univariate (single variable effect) or multivariate manner (multiple variables each having an impact). Some CQAs may have no specifically related process controls or parameters. Assessing the criticality of a process parameter should include consideration of all of these potential situations.

In a given API process, control of a process-related impurity is primarily determined by controlling reaction temperature within the identified PAR and by preventing an extended reaction time. Additionally, the conditions under which the

API is crystallized influence the ability to diminish the presence of this impurity. Reaction conditions (e.g., temperature and duration) and crystallizations conditions (e.g., solvent composition and temperature) should all be evaluated when determining which parameter(s) should be identified as critical.

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.

When evaluating the potential impact of a change (e.g., to the manufacturing instructions, equipment, manufacturing site, product specifications, or addition of a new product to existing equipment), the associated risk analysis of the parameters that impact product quality should be re-examined.

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