2. ***Steps for Identifying CPPs***

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.

A process parameter that impacts a CQA should be assumed to be a CPP unless it is demonstrated that control of the parameter is adequate to minimize the risk of operating outside the proven acceptable operating range for the parameter. Previous experience with similar processes can be used to assess if a particular process control is likely or unlikely to influence product quality.

Steps for selecting CPPs for validation may be summarized as:

I. Identify CQAs and process parameters and controls that impact the CQAs.
II. Establish strength of correlations between parameters/controls and the CQAs.
III. Assess capability of process controls and risk of CQA failure. 4. If the regulatory filing identifies parameters as CPPs, the validation should include those CPPs.

3. ***Interactions of parameters***

A CQA can sometimes be affected by more than one process parameter. In this event, one parameter may often have a greater impact on the CQA than another parameter, or may provide a greater degree of control than another parameter. Deviation from one such parameter may influence the ability of the other parameter to adequately control the associated CQA.

In an API process, it is important to have good knowledge of how process impurities form and the fate of impurities before attempting to determine if process parameters impact product quality. The extent to which subsequent process controls can diminish or remove an impurity is an important component of this knowledge. Formation of a manageable amount of an impurity, for example, may not be a quality problem if a subsequent purification can reduce or remove that amount of the impurity to an acceptable level. Conversely, sometimes subsequent processing has little or no ability to remove a specific impurity, so minimizing or preventing its formation may become critical for the process.

Example 1:

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.

A deviation that affects product quality should be carefully investigated to understand any and all process parameters that played a role in determining the quality outcome. For instance, a deviation

Comparing the Normal Operating Range (NOR) to the PAR is one part of performing a risk assessment of potentially critical process parameters. The comparison will typically reveal one of three general situations:

- The NOR is a significantly smaller range than the PAR (as depicted in Figure 1, where the value of Δ is relatively large). It is typical to conclude such parameters are not critical to product quality if the magnitude of Δ minimizes the risk of exceeding the PAR.

- The NOR is close to one or both limits established by PAR (consider Figure 1 where the value of Δ is relatively small). In these cases, the parameter may be a CPP, unless modification of the ranges can be made to increase the magnitude of Δ by decreasing the NOR and/or increasing the PAR.

- No PAR has been identified or historical information does not provide substantiation of acceptable ranges broader than the NOR. In this event, it may be possible to establish the PAR from historical experience with the process (using knowledge of both routine processing and from deviation investigations). It may be necessary to identify the parameter as a CPP if the NOR approximates the PAR established from historical experience. To conclude that it is not a CPP, further study may be necessary to establish a broader PAR, or constrict the NOR to increase Δ and minimize the risk of deviation outside of the established historical limits.

Figure 1: Interrelationship between NOR and PAR

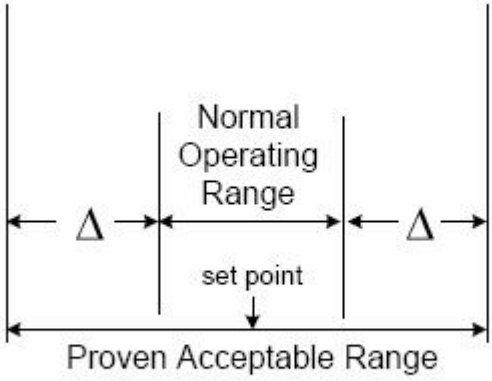

Figure 1: Interrelationship of NOR and PAR

Figures in Appendix IV provide further illustration of the relationship between NOR and PAR.

The Edge of Failure (EOF) for a process parameter may coincide with a PAR limit or be beyond this limit. It is not unusual for an EOF limit to be unknown. While it can be helpful to know the EOF to enhance process understanding, experimentally determining an EOF can often be impractical or difficult in terms of development time and resources and is not necessary.

Determination of overall risk:

The overall risk is referred to a quantitative Risk Priority Number (RPN). The RPN is calculated as follows:

RPN = Severity (S) x Frequency (F)

Thresholds for action (or for determining criticality) based on RPN scoring should be agreed upon by reviewers before performing the risk assessment. A sample of action thresholds based on the above scoring strategy is shown below. Justification of values assigned to Severity and Frequency for each evaluated risk should be provided in risk assessments.

Action Thresholds		
Risk category	**Risk factor (RPN)**	**Interpretation**
Intolerable Region: Unacceptable Level of Risk	40 or greater: Intolerable risk	The risk is so severe that it is not tolerable. Refer to Appendix III (explanation of Figure C) for general approaches for reducing risk .
Acceptable Levels of Risk; mitigation recommended (ALARP region)	>24: Risk is tolerable only if reduction is impractical, or costs of mitigation are disproportionate to improvement	Risk in this region are CPPs and should be evaluated bearing in mind the benefits of accepting the risk and the costs or further reduction. Acceptable risk is established on a case-by-case basis.
Acceptable Risk	24 or lower: Negligible risk	The risk is negligible/not CPP, compared with the risk of other hazards that are accepted. Mitigation not necessary, however for business reasons, management may decide to mitigate.

A qualitative classification for risk scoring (low, medium, high) may be used rather than a quantitative scaling. In this event, thresholds for action should still be defined before performing the risk assessment.

Risk Assessment example #3: Selected controls for tablet compression/coating process

Using the quantitative risk scoring described above for a couple of typical process controls, and a lower RPN threshold (48) for classifying the risk as a CPP than in earlier examples:

Parameter/ control	Acceptable range	Failure mode	Cause	Effect
Press speed	30 – 70 rpm	Out of range speeds (high or low)	Machine speed controlled by operator	Can give non-uniform tablet weights, thicknesses, friability and hardness, impacting product potency and dissolution
Feeder speed	60 – 100 rpm	Out of range (high or low)	Machine speed controlled by operator	Impacts tablet weight. Continuous monitoring of tablet characteristics with adjustments made to insure required product characteristics are met.
Overload setting	Maximum 40 KNewtons (NOR)	Higher	Machine set-up	Maximum force allowed to avoid tooling damage. Potential impact to tablet weight, hardness, thickness, friability
Spray rate	Total 380 – 420 g/min for all guns	Out of range (high)	Spray rate governed by automated controls with limit alarms.	High spray rate may impact tablet appearance and dissolution. Low spray rate extends coating process times but not critical to product quality.
Pan load weight	260 – 340 kg	Out of range (high or low)	Pan load charge established for each pan load based on lot weight.	High load weight may overcome equipment working capacity and process performance. Low load weight may cause non-uniform coating to tablets.

