Guidance Number: 042

Figure 1: Interrelationship between NOR and PAR

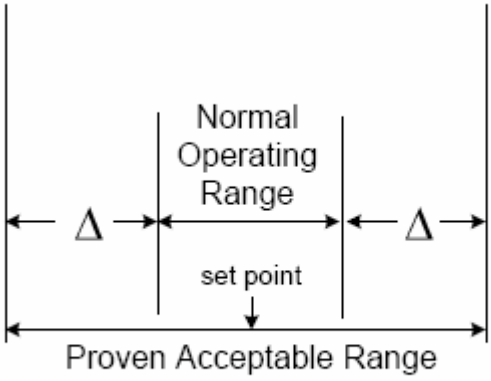


Figure 1: Interrelationship of NOR and PAR

Appendix I: Examples of CQAs and CPPs

Examples of potential Critical Quality Attributes

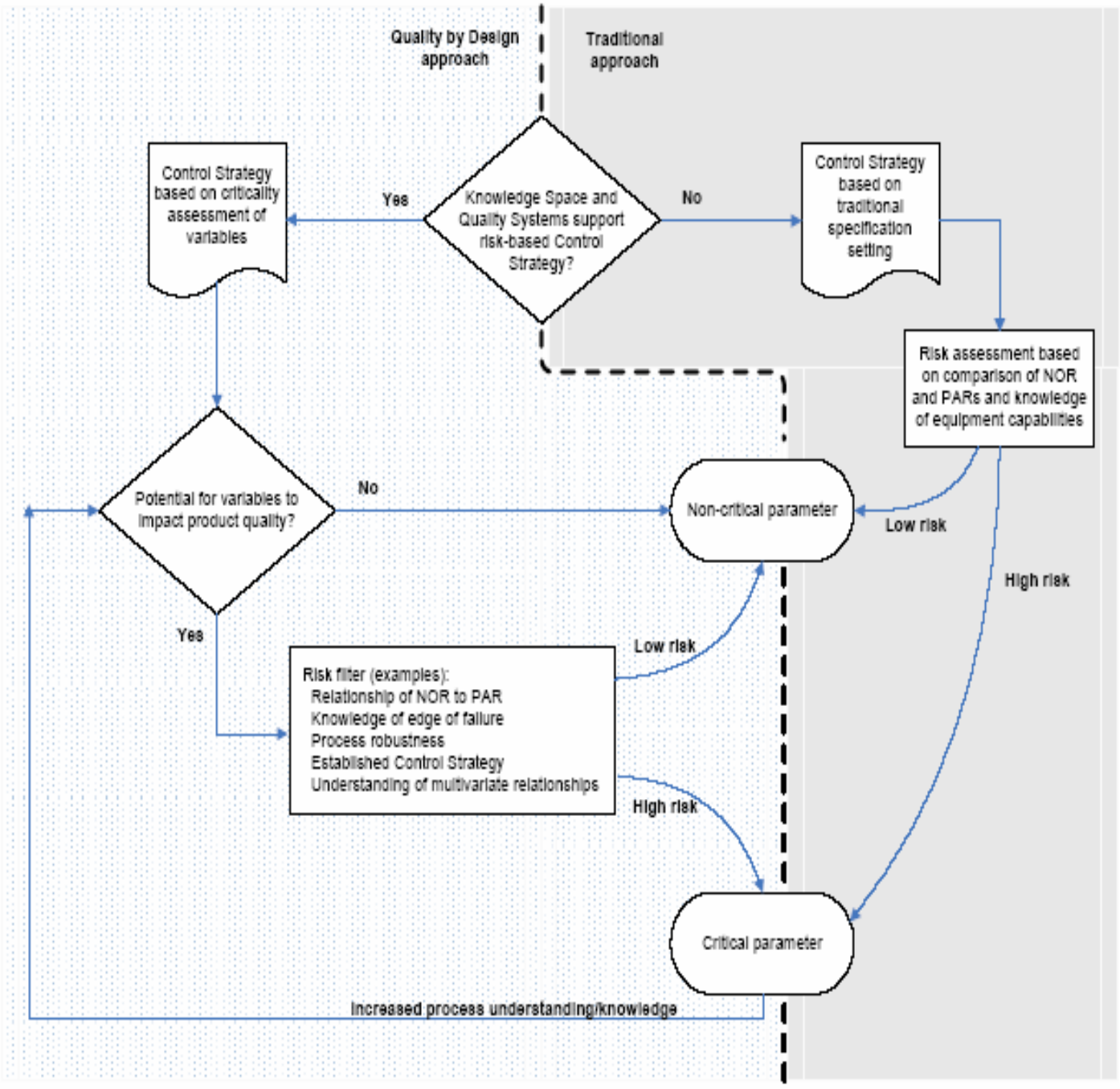
API	Biologic product	Oral Solid Dosage product	Inhalers and Devices
Potency (purity/assay)	Biopotency	Dissolution	Potency
Impurity levels	Protein content	Content uniformity	Homogeneity
Particle size distribution	Aggregates	Tablet hardness/friability	Bulk/tap density
Residual solvent	Host cell protein	Appearance of film coating	Flow properties
Loss on Drying	Endotoxins	Capsule length, tablet thickness	Aerosolizability and spray pattern
	Contaminants		Pouch seal integrity
	Sterility		Bioburden/sterility

Examples of potential Critical Process Parameters

API	Biologic product	Solid Oral Dosage product	Inhalers and Devices
Reaction time	Temperatures	Impeller speed	Relative Humidity of fill environment
Reaction temperature	Hold Time	Air Flow of fluid bed dryer	Temperature of fill environment
pH	pH	Spray rate for film coating	Disc Alignment
Stoichiometry	Culture transfer rate	Blender rotational speed Ribbon blade/mixer speed	Stirring/suspension rate
Agitation speed	Nutrient feed rate	Holding time	Drying time for powder blend
Addition rate	Seeding density	Compression force	Foil tension of blister machine
Distillation temperature	Air sparging rate	Mill speed	Nozzle angle
Drying time	Dissolved oxygen		

Appendix II: Decision tree for Evaluation of Process Parameters

(adapted with modifications from reference 13)



Appendix III: Comparison of NOR and PAR for a potential CPP

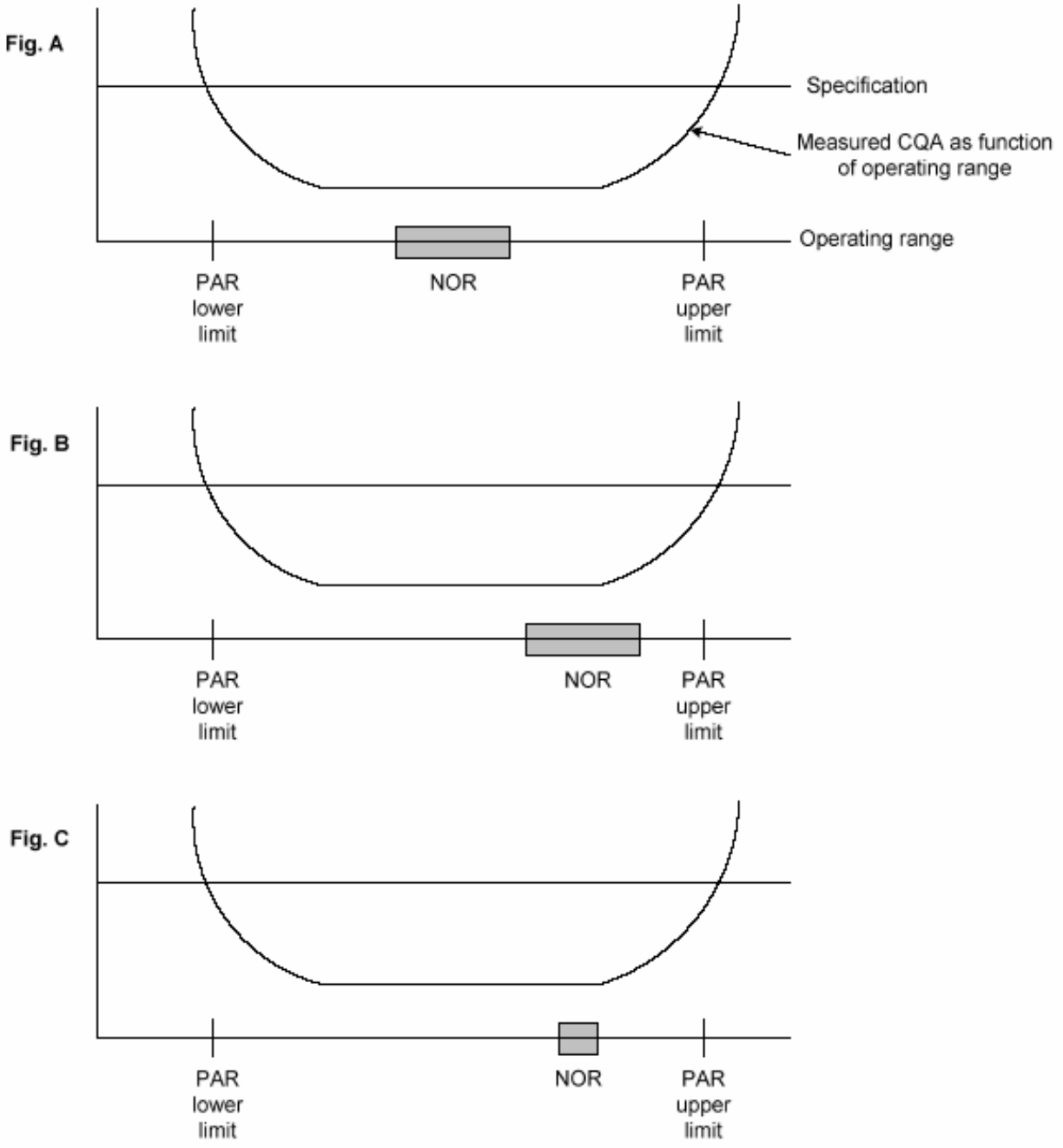


Figure A illustrates NOR values well within the boundaries defined by the PAR. Here it is expected that control of the parameter is easily achieved and from the risk perspective the parameter would usually not be considered critical.

In Figure B, the NOR is near one of the limits defined by the PAR. Here adequate control of the parameter within the acceptable boundaries may pose a higher risk, suggesting that the parameter may be critical.

With Figure C, NOR is once again near the PAR, but as shown here the NOR has been narrowed by improved control of the parameter to lower the risk of deviation outside the PAR. Broadening of the PAR, or narrowing or moving the NOR away from PAR limits, may result in the determination that the parameter is no longer critical. Note however that the NOR cannot be narrowed to a range that is unsupported by the ability to control the equipment within that range.

Appendix IV: Examples of Risk Assessment to evaluate potential CPPs

Actual risk assessment will contain more process controls and parameters than shown in these abbreviated examples. The risk assessment should include discussion of risk controls and actions taken to reduce risk. In these examples it is assumed the parameter/hazard is readily detectible, so detect ability is not included in the scoring.

Example of Definitions of Risk Terms:

Severity (S)	Definition	Interpretation
8	High	Predicted to cause severe impact to quality (product failure to meet specifications)
4	Moderate	Predicted to cause significant impact to quality (likelihood of failing specifications)
2	Low	Predicted to cause minor impact on quality (might fail to meet specifications)
1	None	Predicted to have no impact on quality of product (Quality within specifications)
Frequency (F) (Probability)		
10	High	Problem likely to occur (expected or has occurred multiple times in the past)
7	Moderate	Problem has occurred in the past and can be expected to reoccur if action is not taken to correct or prevent.
3	Low	Problem unlikely to occur but is possible
1	Remote	Highly unlikely to occur: probability of failure occurring is so low that it can be assumed that the failure will not reoccur

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 #1: Selected controls for an API process step

Using the quantitative risk scoring described above for a couple of typical process controls.

Parameter/ control	Acceptable range	Failure mode	Cause	Effect
Reaction temperature	35 – 40 deg C	Low temp	Overcooling	Incomplete reaction, starting material (SM) difficult to remove
		High temp	Insufficient cooling or rapid addition	Exothermic reaction, impurity difficult to remove
Reaction completion (IPC)	NMT 1% remaining SM	>1%	Varied (consult technical reference for process)	SM difficult to remove from product
		≤ 1%	Reaction proceeds as desired	Expected result

Parameter	Severity (S)	Frequency (F)	RPN (= S*F)	Follow-up action	Decision
Reaction temperature (high)	8	7	56	Tighten temp controls to improve margin of safe operations, if possible	CPP
Reaction completion	8	7	56	Treat as CPP if process cannot be made more robust	CPP

Risk Assessment example #2: Bioprocess controls for protein purification chromatography and nanofiltration

Using the quantitative risk scoring described above for a couple of typical process controls,

Parameter/ control	Acceptable range	Failure mode	Cause	Effect
Resin chromatography: conductivity of first buffer wash	27 – 33 µSiemen/cm	Low	Buffer prep. or mixing issues, variability in salts from different suppliers	Low conductivity hampers host cell protein clearance and increases product loss.
Resin chromatography: pH of first buffer wash	6.9 – 7.1	High or low		Out of range pH can allow impurities to elute with product or cause product leaching from resin.
Nanofiltration to remove viral particles: filter inlet pressure	Not above 1.0 bar	> 1.0 bar	Inadequate control of inlet pressure	Filter rupture or integrity failure that may allow bleed-through of viral particles

Parameter	Severity (S)	Frequency (F)	RPN (= S*F)	Follow-up action	Decision
Resin chromatography: conductivity of first buffer wash	2	7	14	Insure conductivity is within range before using buffer.	Not CPP, primary impact on yield
Resin chromatography: pH of buffer	8	1	8	Insure pH in range before use of buffer	Typically not CPP, easy to control before proceeding
Nanofiltration to remove viral particles: filter inlet pressure	8	3	24	If integrity test fails, batch is rejected; refiltration not currently an option.	**May be CPP** if control of pressure is not adequate to sufficiently reduce risk of deviating from PAR

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.

Parameter	Severity (S)	Frequency (F)	RPN (= S*F)	Follow-up action	Decision
Press speed	8	3	24	Perform continuous monitoring, alarms	Not CPP
Feeder speed	2	7	14	Perform continuous monitoring	Not CPP
Overload setting	4	3	12	Verify proper machine set-up	Not CPP
Spray rate total	8	7	56	Rate periodically verified within range by operator	**CPP**
Pan load weight	8	3	24	Adjust parameters for each pan load to insure appropriate process performance.	Not CPP