**Contamination Control Strategy - Process risk assessment guidance**

A significant requirement of Annex 1, and of any CCS is a Process Risk Assessment. There are a number of ways this can be achieved, and [ICH Q9](https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Guideline_Step4_2023_0126_0.pdf) contains a number of tools which may be used to complete the necessary risk assessments.

When performing Process Risk Assessments (PRA), it is important to realise that a single process may be used by several products. Section ix of your CCS should describe your approach to PRA, the methodology you will use, and how you will manage the output of these risk assessments.

One approach which would be acceptable is to use a FMECA (Failure Modes Effects and Criticality Analysis). This is an example of the steps required to effectively perform an FMECA on a manufacturing process.

The scope of the PRA is to establish risks to VIABLE, NON-VIABLE PARTICULATE AND ENDOTOXON / PYROGEN CONTAMINATION ONLY, the purpose of this exercise is to establish if the current process controls are sufficient, identify areas where additional controls may be implemented to reduce the identified risk, and finally, the impact of these planned changes on the risks identified.

After completing the PRA, you will have a list of mitigated process steps which must be used to ensure your Process Validation (media fills) are sufficiently robust and challenge the established processes.

This appendix describes the steps required to perform a PRA using FMECA methodology:

### **Define the Process**

Consider your product profile, and determine how many processes you will need to risk assess to cover all of the products prepared or manufactured. It is likely several products will be prepared using a single process which will be qualified by an Aseptic Process Simulation (APS) or media fill. This may be a good starting point to establish how many processes will require a PRA.

Decide where in the process you will start your PRA, being mindful of the purpose of these assessments. The PRA must consider all elements which contribute to the control of viable, non-viable and endotoxin / pyrogen contamination, so the defined process must start at the first stage which controls these factors.

### **List the Process Steps**

Using appropriate team members who are familiar with the process, list all steps involved in the process under assessment.

### **Risk Assess Steps**

For each step, consider:

* What would the outcome be if that step failed (the hazard)?
* What existing controls are already in place to prevent that step failing?

Based on the above information, using a scoring system, assign each of the following scores:

* Likelihood of failure
* Detectability
* Severity of consequence

Scores for each may be any scale (1-5 to 1-100 for example), do not have to be linear (e.g. 1,2,5,6,7), and could be different for each aspect, but the overall approach should be defined in section ix of your CCS.

### **Evaluate Process Risks**

Once a risk has been assessed, multiply all scores together to determine the overall risk score for each process step. Compare this score with the limits you have defined in section ix of your CCS, depending on the thresholds you have assigned you may take a number of actions:

* Accept risk without mitigation
* Require risk mitigation
* Reject risk

Where the risk is sufficiently controlled (risk score lower than your defined threshold) it may be accepted with no mitigation.

Where risk scores are above the threshold required for mitigation, additional risk-reduction measures should be suggested. There may be a number of different alternative ways of mitigating the risk, record each of them within the risk assessment and re-score based on the assumption they have been implemented. This will indicate which option is the better one in terms of risk management, and which will result in acceptable risk control.

Where a risk score is so high it is rejected, you must consider the suitability of continuing with that process until the risk can be controlled to acceptable levels. Again, mitigation should be considered and re-scored.

Repeat the above with all process steps until all steps have been reviewed and risk scores have been reduced to acceptable levels.

### **Generate Action Plan**

When all risks have been assessed, and mitigation considered for unacceptable risks, use the risk assessment to populate an action plan which will implement all required risk mitigation. These should feed into the Pharmaceutical Quality System (PQS) and may require one or more change controls to implement. As with any change control, there should be an assessment of the success of the change, and there have been no unintended deleterious consequences.

Where changes are made to processes, methods or materials, your change control should also consider the impact on the validation of your existing processes, is your APS (media fill) still valid? Do you need to repeat it before accepting the changes?

### **Review**

In addition to the actions required to control risks to acceptable levels, the risk assessment will also contain a number of risks which have been accepted without mitigation. These risks should be reviewed periodically to assess if any new technology, methods or materials may further reduce risks.

Where changes are made to processes these should also be considered in the context of the accepted risks, with risk assessments repeated where necessary.