Considerations and Steps for Building a Contamination Control Strategy

Controlling Sources of Contaminaton

Mass-produced pharmaceuticals have come far since the industrial manufacturing of synthetic drugs at the end of the 19th century[1] with rapid advancement in technology, process control, and sterility requirements. Yet even as improvements to Pharma develop and stick, **recalls still occur with regularity**[2] and their significant impact on both the manufacturer and consumer are why worldwide regulation of the industry is so enforced. Environmental monitoring (EM) is one facet of the greater picture of current good manufacturing practices (cGMPs) that has been standardized for the safety of human health.

In a typical cleanroom, EM takes the form of monitoring non-viable and viable particles to maintain a reliable state of control in production. Limits per an area's classification or "grade" are defined by both the FDA's *Sterile Drug Products Produced by Aseptic Processing*, and the European Commission's *EU GMP Annex 1 2020 Draft*.

Viable particles are living organisms such as bacteria, molds, and yeasts.

- EU GMP limits found in **Table 7**, Maximum action limits for viable particle contamination.[3]
- FDA cGMP limits found in **Table 1**, Air classifications.[4]

Nonviable particles do not contain a living organism, but act as transportation for viable particles.

- EU GMP limits found in, **Table 6**, Limits for airborne particulate concentration for the monitoring of non-viable contamination.[3]
- FDA cGMP limits found in **Table 1**, Air classifications.[4]

NONVIABLE MONITORING WITH THE AIRNET® II AEROSOL PARTICLE SENSOR (LEFT)
VIABLE MONITORING WITH THE MINICAPT® REMOTE MICROBIAL IMPACTOR (RIGHT)

Past focus was placed on sampling methods for the measurement of potential contamination: particle counters, active air samplers, Petri dishes, and swabs for surface monitoring. Bioburden of bulk product and filter integrity were also tested to increase the detection of microbiological contamination along the production process. This approach has been remodeled to prevent and control potential contamination from reaching the point of no return: the product. Once contamination occurs, there is no cost-effective removal scheme to continue production, making the determination of sources all the more important. This is achieved by:

- Implementing Quality by Design into the manufacturing area.
- Using quality risk management to identify the critical control points (CCPs).

- With the CCPs, identifying the process phases where it is necessary to establish mitigation actions to control the identified risks.

The collective execution of controls is called the contamination control strategy (CCS).

Defining the CCS

So what do regulatory bodies dictate should be included in a CCS? In the document, *EU GMP Annex 1: Manufacture of Sterile Medicinal Products*, you will find the following background:

> **Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications, and the associated methods and frequency of monitoring and control ... A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks associated with contamination. The CCS should be actively updated and should drive continuous improvement of the manufacturing and control methods.[3]**

Note that "critical control points" do not have any associated measurements, and are not an In Process Control (IPC). They are instead process phases in which a risk to be mitigated has been identified.

Finding Root Causes of Contamination

Quality By Design (QbD) and Quality Risk Management (QRM) are both inherently linked to process understanding. In Figure 1, the steps to achieving a full risk evaluation of a process are outlined step by step.

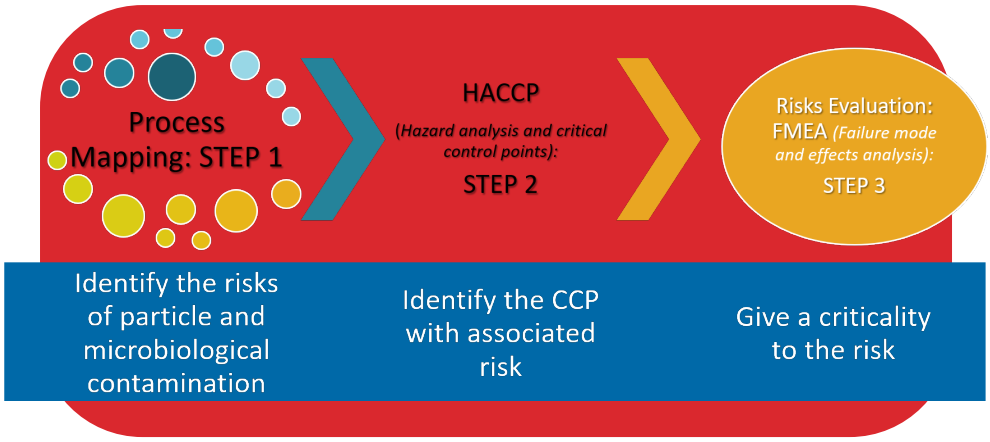

FIGURE 1 The steps to understanding your process

Process mapping allows the risks of particle ingress to be identified. First, a fishbone model is created to document all possible sources of contamination. In **Figure 2**, the root causes are grouped into representative categories (Personnel, Materials, Equipment, Environmental, and Methodology), but your fishbone may need other categories to account for specialized attributes found in your process. There is no exact standard to follow, which is why process understanding is so essential.

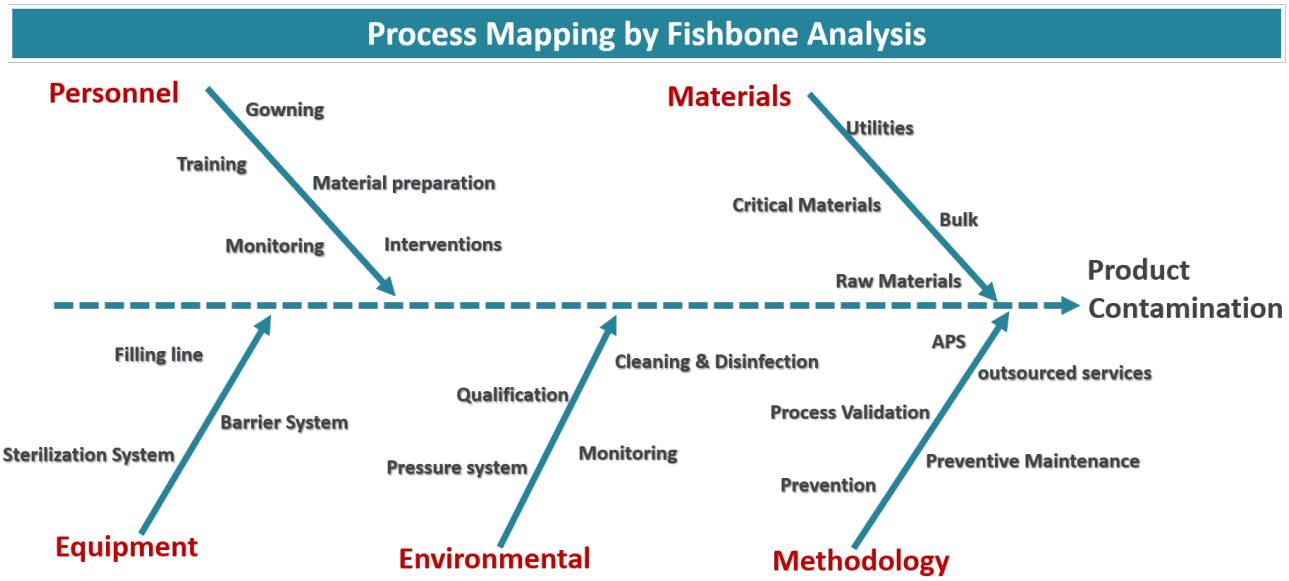

FIGURE 2 Fishbone diagram showcasing all sources of possible particle contamination

Granularity can be added to fishbone diagrams. Take the example of Utilities within the Materials category. Within this aspect of the process, there are multiple steps that may contribute to contamination. A description of the Water for Injection (WFI) phase within the Utilities area could look similar to:

- Production: Downstream of WFI
- Production: After the storage tank
- Upstream of delivery pumps for the loop
- Distribution of the water inside the loop
- Points of use
- Sampling points

Once process mapping is complete, risks to each singular input must be identified. Some inputs may have more than one risk. Continuing with the WFI example, this analysis could look like the following:

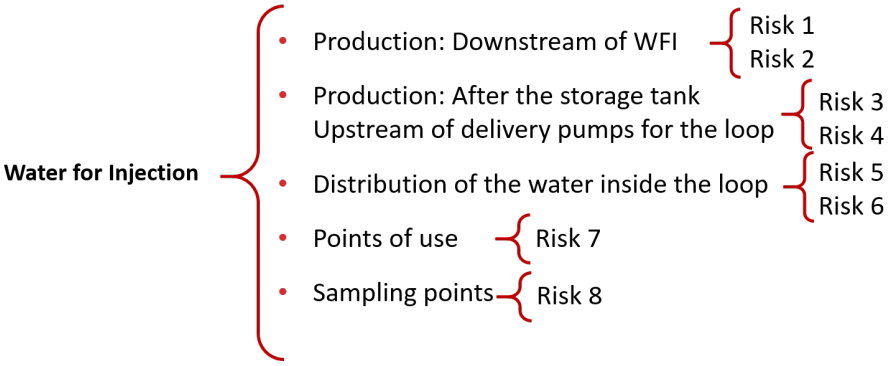

FIGURE 3 Identifying and assigning risks to a process

To determine if risks are critical and in need of control, a decision tree specific to the process is created. Here, questions will be tailored to better assign the label of CCP, which indicates control is required to limit contamination. Again, there is no set map of yes or no questions to use—process understanding is key.

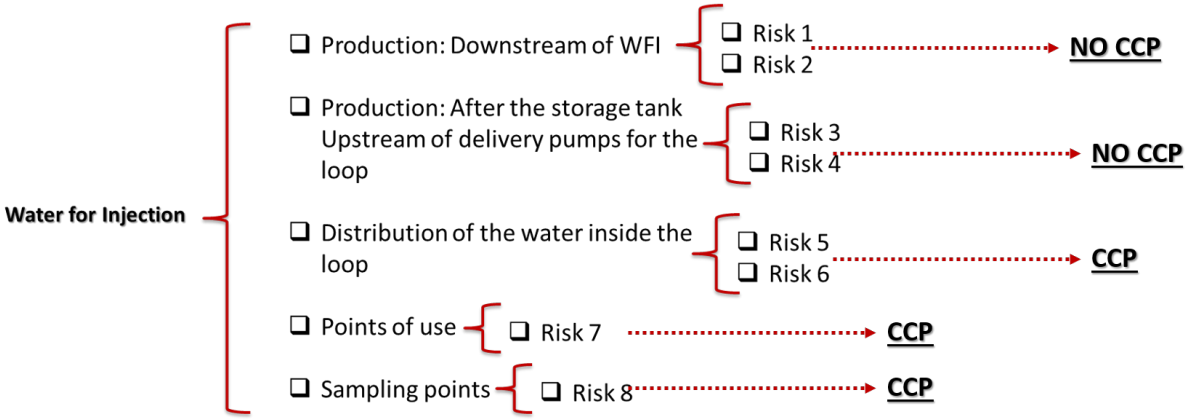

FIGURE 4 Determining whether a risk is critical enough to warrant control

The HACCP approach to identifying risk is qualitative, meaning the risk is identified but not the associated level of criticality and the real impact on the product. To make the risk determination quantitative, the Failure Modes and Effects Analysis (FMEA) approach is used. The FMEA matrix, shown in **Figure 5**, incorporates a cross of three parameters: Severity, Occurrence, and Detectability, and allows the identification of how critical a risk is to the process.

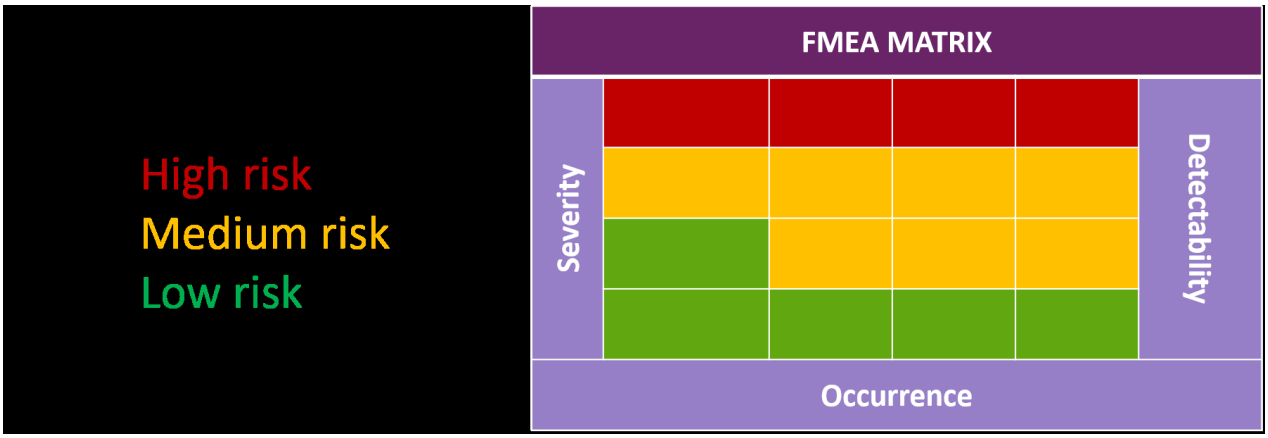

FIGURE 5 FMEA matrix for visualizing risk criticality

From here, a control and mitigation plan can be determined based on the level of assigned criticality. In Figure 6, CCPs have been evaluated and their risk criticality identified.

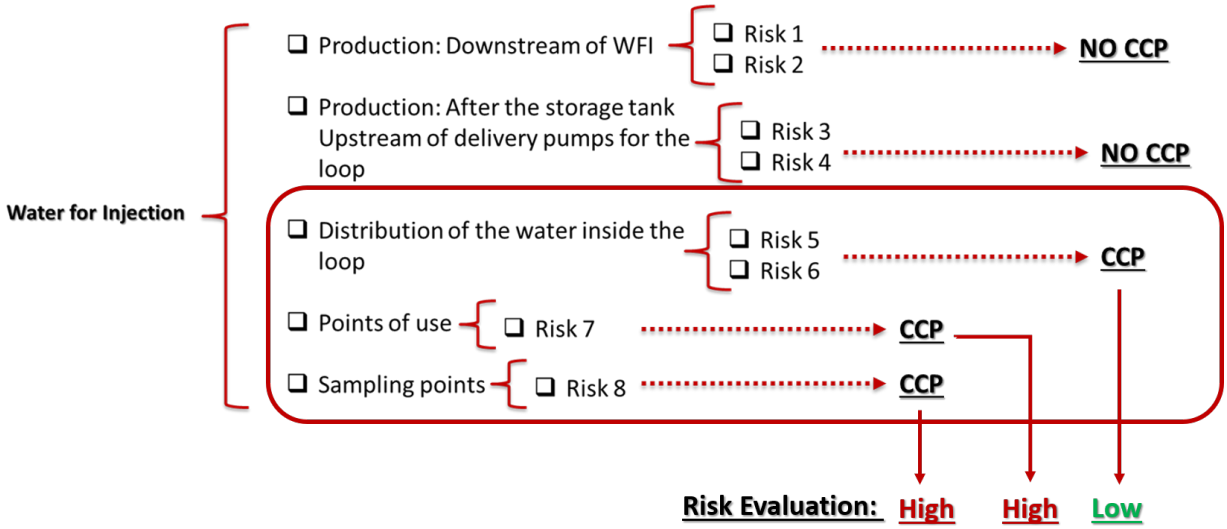

FIGURE 6 High and low risks from CCPs found

Designing the Cleanroom

In order to design a cleanroom according to sterility assurance principles, a risk mitigation plan (Step 4 of **Figure 7**) encompassing set actions and controls must be implemented. This plan could take the form of a redesign, design loop, or a series of valves to reduce contamination. Other possibilities include a system validation or re-validation, and improvements to sampling procedures. Suggested controls to mitigate risk might include increasing or decreasing the microbiological or chemical, and changing the controls set according to the process and points criticality. The impact of the mitigation plan may impact several departments, new and old. As a result, the change control plan definition is necessary to structure the actions to be taken by priority and time required. For new cleanrooms, this intervention takes place in an early phase to avoid a snowball of unfixable issues down the line.

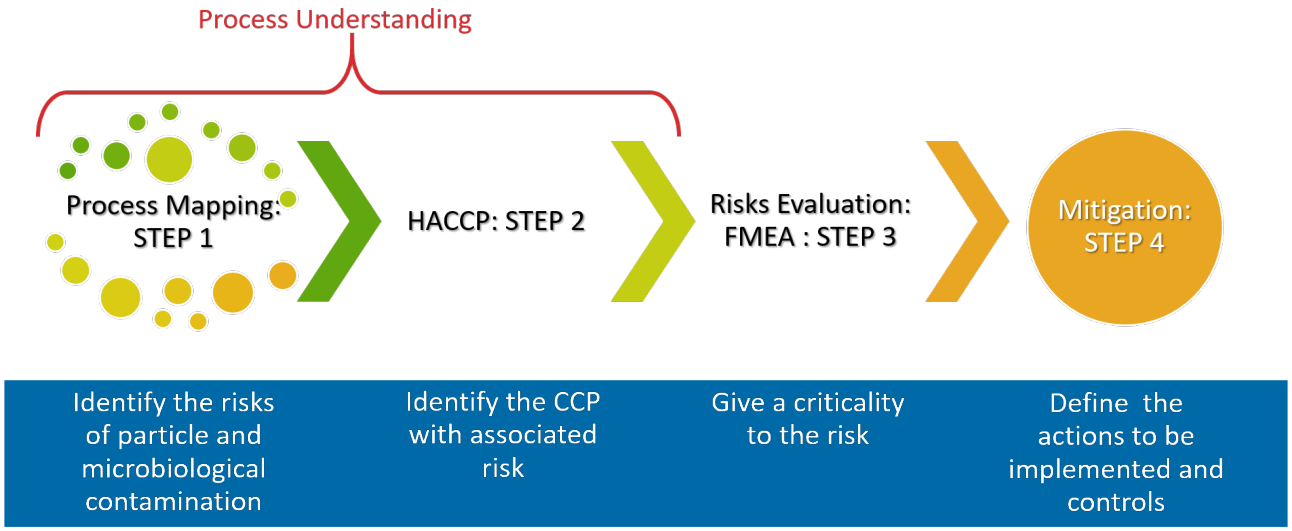

FIGURE 7 The final step: Risk mitigation

Remember that the essential ingredient for contamination control is building a team of experts encompassing quality, production, engineering, and QRM. Use the resources available at your site to build a solid base of process knowledge, and take advantage of the **QRM experts at Particle Measuring Systems** to assist you with the design of your contamination control strategy.

References

1. Daemmrich A, Bowden ME. The top pharmaceuticals that changed the world. *A Rising Drug Industry. Chemical & Engineering News*. June, 20 2005. 83(25).
2. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts. Accessed April 2, 2021.
3. European Commission. EU GMP Annex 1: Manufacture of sterile medicinal products. *Annex 1 Draft*. Published December 2020. https://www.gmp-compliance.org/files/guidemgr/2020_annex1ps_sterile_medicinal_products_en.pdf. Accessed March 30, 2021.
4. Food and Drug Administration. *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*. Published September 2004. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice. Accessed March 30, 2021.

Author

Anna Campanella, PhD

Head of Advisory Team

Anna has vast industry experience which she uses to collaborate and consult with pharmaceutical companies. She is highly skilled in the development and implementation of science-based strategies, principles of contamination monitoring, and methods of controlling and improving the chemical, physical, and microbiological states of various production processes. Anna holds a PhD in Molecular Medicine and is an authority in many areas of pharmaceutical manufacturing, such as QA & QC processes, validation of chemical and microbiological methods and the validation of sterile production processes. Additionally, she maintains expert-level knowledge of the microbiological aspects of aseptic production processes.

Editor: Briana Krueger, Technical Writer, Particle Measuring Systems

Check out the full webinar from these presenters **here**.

Looking to comply with your local pharmaceutical regulations? **Contact us** for world-class expertise in GMP requirements.