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Life Sciences

Specifying Non-Viable Particle Monitoring for Aseptic Processing

Aseptic Processing and Continuous NVP Monitoring

Historically, vaccine production has accounted for a large portion of aseptic production. Recent years have seen increased focus on new biologic therapies, most of which are administered via injection or IV. Major pharmaceutical companies are investing to drive the development and release of these new biologics. Most of these will be manufactured with aseptic processing[1].

Continuous non-viable particle monitoring (NVP), when properly configured, provides useful information on changes in the aseptic environment with minute-by-minute updates of count populations and trends, which catch contamination events and thereby identify and quantify risks (i.e. a non-zero result)[1].

Both the FDA and EU specifically reference continuous monitoring of NVP during aseptic processing for the purpose of real time event detection.

Key Considerations when Implementing an NVP System

Determine the risk of contamination events to define monitoring locations

Traditionally, fill operations are monitored at three locations: (1) where sterile containers enter Grade A, (2) at the point of filling, and (3) where open and filled containers are exposed prior to capping. This is sufficient for small, compact filling operations. However the following potential risks should also be considered to determine if additional monitoring locations are needed:

- **Points of human entry into the Grade A area.** For example, loading stoppers, cleaning up broken vials, maintenance doors, etc.

Figure 1. NVP monitored Hopper inside clear isolation barrier

- **Interference with unidirectional flow.** Deviation from SOPs regarding configuring/stowing systems prior to sterile product exposure can be a risk. Some systems have equipment that can be above the sterile product during pre-production activities, or when reconfiguring the line.
- **Moving robotics.** Failed bearings or seals can generate particles. Air turbulence from moving robotics can transport these particles to the sterile product.
- **Reconfigurable lines.** Equipment or access doors/ports which are not positioned incorrectly for the specified process, can provide an access point to the sterile product for particles.

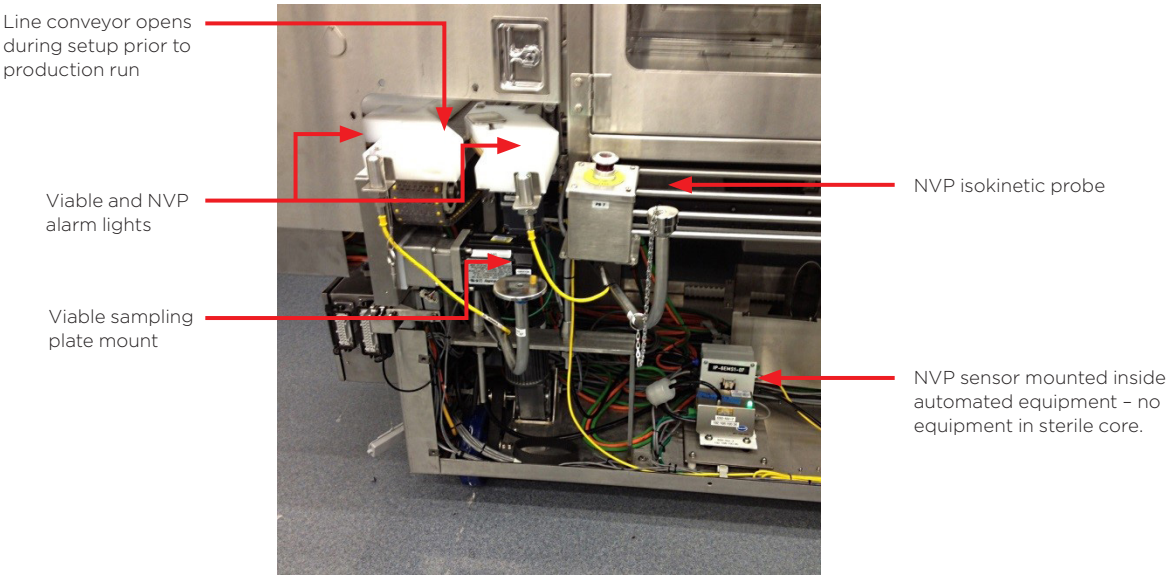

Figure 2. Sampling at point of line configuration

- **Particles from packaging components.** If components break or spill when being loaded into the operation, particles can be generated that may enter the sterile product.
- **Power or equipment failures**. In the momentary absence of airflow, additional monitored points may be needed to verify sterile product is not exposed to contamination during these events. (Note: NVP systems can serve the role of validating that environmental control was not lost during these events as it is relatively easy and affordable to ensure continuous power for the NVP system.)

Understand the workflow

It is important to carefully review the media fill study and subsequent workflow to help identify the required monitoring process steps and required report contents. Most aseptic processes are batch processing workflows, which can have many steps. For example, when NVP monitoring in a liquid fill operation, some, or all, of the following workflow steps may be employed:

- **Line configuration.** No monitoring is necessary during this step.
- **Line cleaning/sterilizing**

  The air particle counters should not ingest liquid cleaning agents during this process. Airflow through the sensors should be stopped and the isokinetic sample probes capped or otherwise protected from collecting caustic cleaning agents such as acetic acid or bleach, which can contaminate or damage the optics in the particle sensors.

- **Particle sensor verification (typically called “zero counting”)**

  After the environment is sterilized, the particle sensors should be tested with absolute purge filters, or while the environment is at rest. This ensures that any remaining liquid vapor, or particles collected in the isokinetic probes during line configuration, are cleared from the sensors, thus ensuring spurious counts are not included in test data. Operators can monitor the particle counts until they reach zero, which should occur within a few minutes. (Note: Most modern aseptic processing areas will produce zero particles at 0.5 micron when they are at rest.)

- **Environment “At Rest” testing**

  This is a defined length sample period (e.g. 36 minutes), prior to sterile product exposure, with the particle counters sampling. Alarms are active using limits set at the lower limits of the “At Rest” specification for the environment. The purpose is to verify the environment meets specifications prior to sterile product exposure. This test verifies that the environment is producing the cleanest air possible. If alarms occur, automatic retest or supervisor approval may be required prior to exposing sterile product and beginning the batch process.

- **Batch monitoring “In Operation”**

  This is the period of sterile product exposure to the environment during production activities. Alarm limits are set to detect contamination events as discussed earlier in this article, which means alarm levels are set below the “In Operation” limits of ISO 14644 for 0.5 micron particles. Advanced NVP systems can automatically label data collected during this period with the Batch ID to facilitate generation of batch reports for product release. Alarm acknowledgments during this period can capture “alarm reasons” by the operators to facilitate root cause investigations.

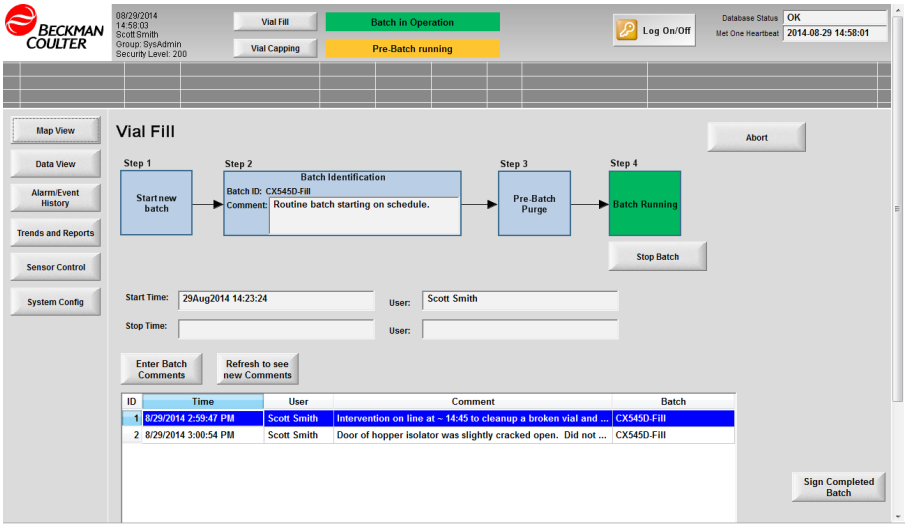

Figure 3. Batch workflow built into monitoring software

- **Batch pause/intervention**

  Some NVP systems enable a pause in batch data collection during line interventions. If the line is stopped, for example to clean up broken vials, and sterile product is covered or otherwise protected, then the particle counters would continue sampling for QA purposes, but alarms can be disabled and the count records excluded from the batch release report—but only until the batch processing is resumed. This is only true if sterile product is not exposed during the intervention (i.e. exposed/damaged containers disposed.) It is well understood that a human intervention can generate higher-than-normal particle levels and exposed product should be discarded. The SOP for interventions, any remedial sterilization/cleaning, and the associated risk to product, should be well defined during the media fill study.

- **Batch completion**

  When the batch is complete, the NVP system can automatically generate the batch data report, with batch alarms, for review and approval.

Determine who will control and review the monitoring process

In the past, when NVP monitoring of the aseptic process was primarily a manual task, it was usually performed by QA or Microbiology staff operating in the aseptic area with the production staff.

In modern aseptic environments using automated NVP monitoring, most of the monitoring process is controlled by computer. This reduces the chances of monitoring errors and/or eliminates the need for QA or Microbiology staff in the aseptic area during sterile product exposure. Monitoring can now be controlled remotely from outside the aseptic area, or it can be accomplished by Production staff using a simple, error-free, single-button process that controls the particle counters and defines the workflow.

Reducing people in the aseptic area is one of the key advantages of automated NVP monitoring systems. Just as isolators and RABS reduce or eliminate people from Grade A environments, automated NVP monitoring reduces the need for people in the Grade B environment. In some environments, a single operator in Grade B can support a large fill/finish operation. Supervision of the process is done from a control room, which monitors all equipment and processes.

Therefore, most modern NVP automated monitoring systems utilize "client and server" systems, with multiple client interfaces for different responsibilities, such as performing monitoring, supervising monitoring, acknowledging alarms, or reviewing and approving batch results. The main system software resides on a server (or VM) somewhere on the network. Client systems should be considered for the following responsibilities:

- **Operator.** This is the person in the Grade B aseptic area who will start/stop monitoring, enter the batch ID, and perform interventions.

Figure 4. Operator workstation in Grade B

- **Alarm acknowledgment.** This may be the operator in the Grade B area, or it may be a supervisor or microbiology professional in an office or control room. Alarm notifications can be announced via computer clients, lights/buzzers in Grade B, or e-mail and text messages.

- **Reviewer and/or Approver of monitoring results.** This is usually performed by Supervisors. Once the product lot/batch is completed, the batch reports must be reviewed, investigated and approved. Supervisors may also wish to monitor the process in real time if alarms have occurred.

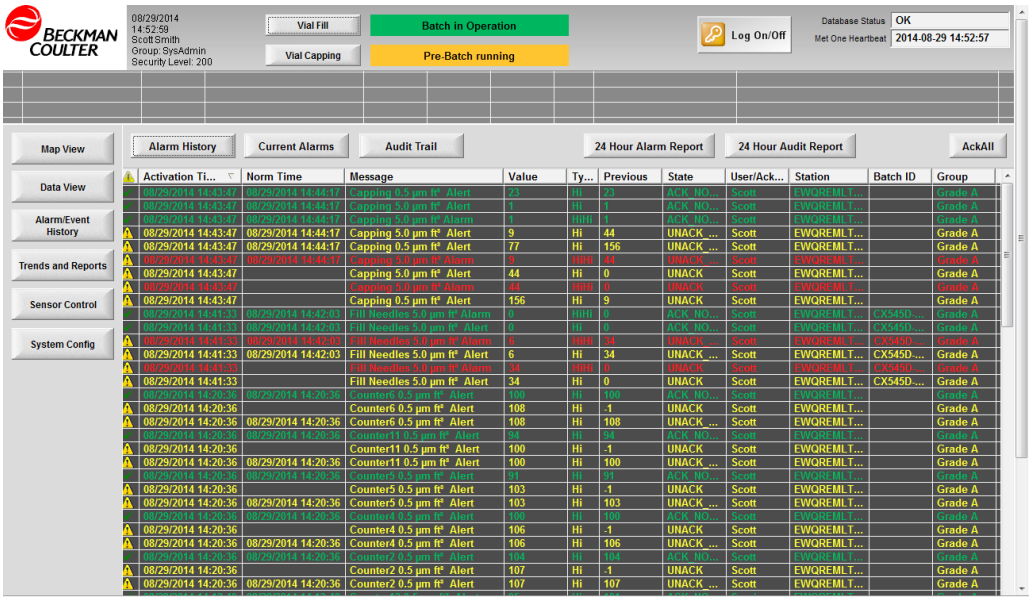

Figure 5. Supervisor alarm review screen in Internet Explorer

Client computers or software will be needed for each of these tasks. Each organization operates a little differently, so the number of clients/people involved will vary.

Define the audit "customers" and requirements

There is always the potential for government regulatory audits of the process and monitoring data. Usually, multiple legal entities will audit the process, and each has slightly different requirements.

Customers who purchase the sterile product often have unique audit requirements based on their internal QA standards. If new customers are involved, it is wise to check their unique requirements when designing a monitoring system.

Most aseptic manufacturers have internal auditors and requirements that attempt to harmonize the various regulatory and customer demands. If the company requirements have not been updated in recent years, check them against the latest regulatory updates and new customer requirements:

- **FDA:** 2004 Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing
- **EU:** 2009 GMP Volume 4, Annex 11 – Manufacture of Sterile Medicinal Products
- **ISO 14644:** Cleanrooms and Associated Controlled Environments. Note: new approved version as of November 2014

The NVP monitoring system will have to meet the demands of all auditors. There are two primary areas of concern:

1. **Reports:** The monitoring reports must include all the required information: measurement data, alarm events, alarm reasons, persons performing each action, reviewer and approver signatures, etc. This data must be available for any requested batch in a reasonable period of time (usually 30 minutes to a couple of hours.)

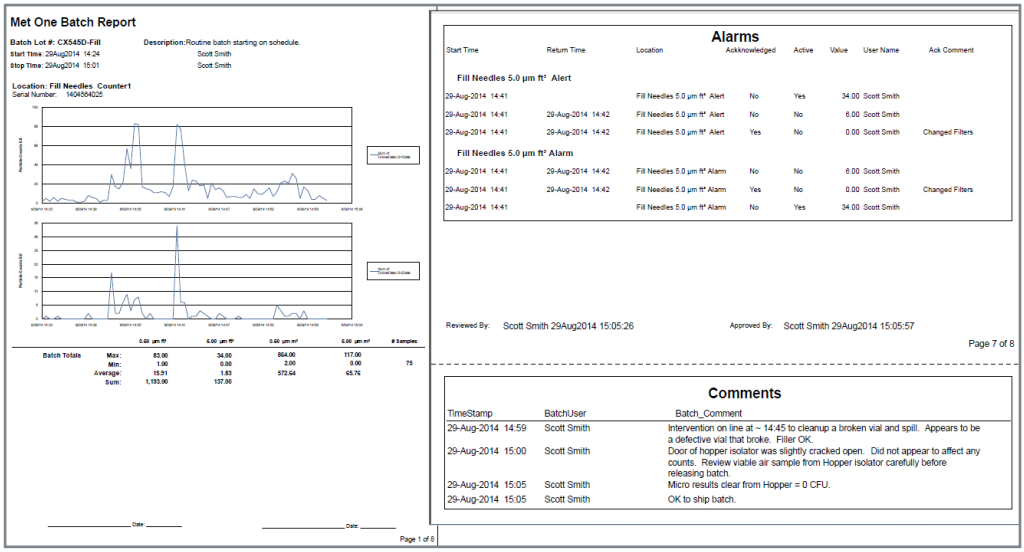

Figure 6. Sample pages from batch release report

2. **Monitoring System:** The monitoring system itself is often audited. Auditors want to review alarm limits and rationale for those limits, the locations monitored, when monitoring is performed, who performs monitoring, audit trail data, data security & system access controls, validation documentation for the system, etc.

Meeting auditor demands can be time consuming; make sure that reports can be quickly and easily generated from a secure database.

Additional needs

It is helpful if the NVP system allows periodic review of data over an extended period of time. Long-term reports can help you ensure that alarm limits are appropriate, reflect improvements in cleanliness levels, and can show repeat occurrences of the same alarm reasons, allowing potential process improvements to improve particle control. The monitoring system should facilitate long-term data mining for continuous improvement efforts.

Summary

It is best practice to consider the requirements for a non-viable particle monitoring system early in the design of your workflow and facility. NVP monitoring is an essential part of a modern isolated, automated, aseptic environment, and not something to be "bolted on" as an afterthought. Automated systems require additional time to implement and validate.

The key to implementing a successful automated monitoring system is found in correctly analyzing the aseptic workflow, identifying risks, and defining the appropriate system requirements. A User Requirements Specification is the first step. Hopefully this article will help you get started.

References

1. Excerpts from Modern Trends in Non-Viable Particle Monitoring during Aseptic Processing: https://www.beckman.com/resources/reading-material/application-notes/modern-trends-in-non-viable-particle-monitoring

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