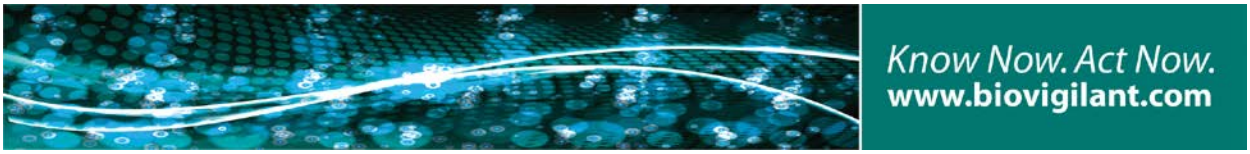

Applications Concept:

Use of an IMD-A® System to Support On-Site Assessments

Major benefits:

- Quickly perform a cleanroom assessment, immediately identifying areas of concern
- Ability to assess identified risks in the environment and in operator activities, in real-time, using Instantaneous Microbial Detection™
- Better quantification of risks through enhanced detection of the failure mode utilizing the FMEA concept

Introduction

For pharmaceutical manufacturing, it is important to understand cleanroom environments' microbial content and dynamics so that manufacturing operations can be performed with minimal risk. This is reflected in the need to generate rationales for environmental monitoring (EM) sample site selection, to review and understand the impact of specific activities within that cleanroom, and to perform proactive risk assessment on the product manufacture or process itself.

Traditionally, microbial EM (i.e. growth-based detection) has been resource intensive from a personnel and consumables standpoint. In addition, the time required to collect and incubate samples further complicates the assessment of risk.

With personnel, consumables, and time resources at a premium, the opportunity is great for a real-time microbial assessment tool to support critical manufacturing/process decisions up-front in a rapid and quality-driven manner. Azbil BioVigilant's IMD-A system can be used as such a tool, and can mean the difference between spending too much time waiting for results, and making fast, quality-driven decisions to support manufacturing goals.

IMD-A Systems: Ideal Risk Assessment Tools

Azbil BioVigilant's IMD-A systems instantaneously detect and report the presence of airborne microbes and inert particles, continuously and in real-time, using an optically-based system that requires no culturing, staining or reagents. Both the IMD-A 300 (sample flow of 1.15 lpm) and IMD-A 350 (sample flow of 28.3 lpm) instruments are 21 CFR Part 11 compliant and validated to USP<1223> and EP 5.1.6 guidance.[A]

IMD-A system features include[B]:

- Instantaneous detection of microbes and inert particles
- Simultaneous detection of particle number, size and biologic status
- Reporting of real-time results with the PharmaMaster® software interface
- Video camera and synchronized data playback functionality
- Marker function enabling activity tracking and display in data files and reports

IMD-A systems display results in real-time using the IMD-A PharmaMaster software (Figure 1). The display options include a graph that plots counts for biologics, particles ≥ 0.5 µm, and particles ≥ 5 µm every second while the air is sampled, as well as updating total and average counts for each particle type so changes in contamination levels are easily noted.

In addition, each IMD-A system is supplied with a small video camera that can be used to record and display activity in the room during sampling. The software features a playback function that allows a review of videos for completed samples as they were collected, replayed in synchrony with the recorded data.

[A] Azbil BioVigilant, USP<1223> and EP 5.1.6 Validation Testing of IMD-A 300/350 Systems, LI-007.
[B] Azbil BioVigilant, Product Specifications: IMD-A Series, LI-005.

BioVigilant® Instantaneous Microbial Detection

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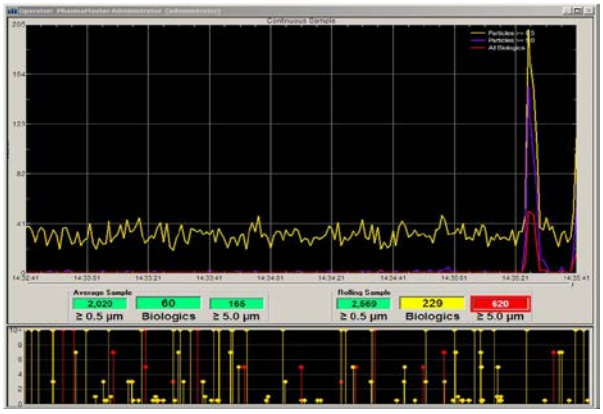


Figure 1: IMD-A System's PharmaMaster software interface.

Sample Site Selection

Environmental sampling sites in a cleanroom are typically determined through a combination of grid-based and risk-based approaches. Both of these approaches may be driven by a large dataset of EM samples collected under static room conditions. While a grid-based approach may be unnecessarily complex, a risk-based approach can skew site selection based upon perceived risk being emphasized over empirical data. In this case, unexpected sources of risk may go under-sampled, such as:

- Leaks around HEPA filters
- Seals around conduits (electrical panels, compressed gas lines, fire sprinkler heads
- Positive pressure from interstitial areas

Additionally, periodic reassessment and justification of site selection are typically required, which can be a time-consuming process. Using a traditional paradigm, reassessment of these areas could take days or weeks, while manufacturing activities are hampered or being performed at-risk.

Dynamic Modeling of Cleanroom Activities

Once sample sites have been selected in a static mode, the next step is to understand the dynamic interaction of personnel and equipment within the cleanroom. The retrospective nature and lack of temporal resolution in traditional, growth-based EM methods make these interactions challenging to model.

The use of Instantaneous Microbial Detection, however, can simplify the modeling process. By giving real-time information to the operator on whether their actions impact the microbial attributes of the environment, specific activities (e.g. manual line intervention) can be refined and adjusted on- or off-line to support requirements of the manufacturing process. Additionally, the IMD-A system can model operator interactions with the process, providing real-time data feedback in a validation or protocol setting.

FMEA: Quantifying the Qualitative

Most aspects of pharmaceutical manufacturing impart some level of risk to quality which is seldom possible to completely eliminate. However, risk can be analyzed and ranked for specific activities within a process. Quantitative evaluations of risk using a tool such as the IMD-A system can greatly enhance and simplify review of specific process steps. Additionally, quantitative analysis allows for risk ranking, assuring that resources are properly allocated to review and reduce high priority risks first. The Failure Mode Effects Analysis, or FMEA, is a risk assessment tool which has been used effectively in the pharmaceutical industry for decades.

Using the FMEA to Detect the True Failure Mode

The FMEA process was developed originally for systematic review of a product or process, the evaluation of risk to product or process quality, and optimization of the overall design. The outputs of such an evaluation are dependent upon the data used. While all risk cannot be completely eliminated, it can be assessed and quantified to enable management of said risk. Because of this, accurate assessment of risk is vital to risk management.

The FMEA approach breaks down a process into a series of steps, looking critically at all possible failure modes of a specific step, various causes that could lead to that specific failure mode, and the effects of each failure. Once the primary causes are determined, an assessment is made as to the relative Occurrence, Severity, and Detection rates of each failure mode cause. Each of these metrics is assigned a numerical value, typically on a scale of 1 to 5.

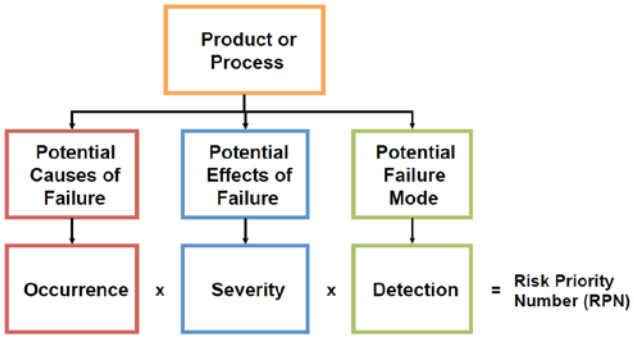


Figure 1: How primary causes, effects, and failure modes relate to the Occurrence, Severity, and Detection of a failure mode within that product or process.

At the end of the valuation, the metrics are multiplied across each failure mode cause, giving an overall Risk Priority Number, or RPN. The various failure mode causes are then ranked according to RPN values from highest risk to lowest.

This chart is valuable in determining which process steps may cause the greatest risk to a process. However, when reviewing processes with associated microbial attributes, the Detection metric becomes a limiting factor in determining risk priority numbers. In particular, microbial monitoring (e.g. environmental, personnel, product, etc.) often leads to an "all-or-nothing" evaluation of risk– the act of detection, using traditional growth-based methods within a cleanroom, may actually constitute a failure mode.

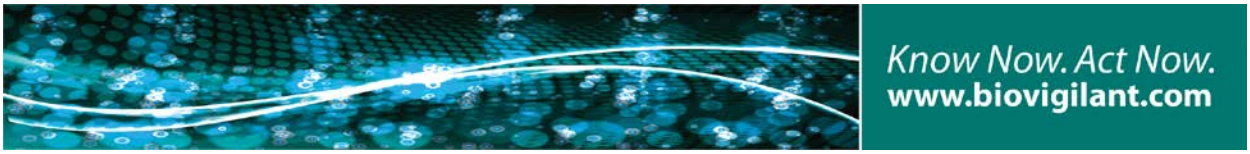
Due to the microbial nature of pharmaceutical processes (very low microbial counts, Poisson distributions, etc.), the sensitivity required for reliable detection of the failure mode may not always be available. For example, cleanroom environments routinely yield zero counts using traditional, episodic microbiological sampling methods, so the issue of failure mode detection is not one of deviation from a baseline level of counts, but rather attempting to determine the probability of an environmental sample yielding non-zero results.

Function	Potential Failure Mode	Potential Effects of Failure	Potential Causes of Failure	Current Process Control	Occurence	Severity	Detection	RPN	Risk
enter gowning room, don gown	contaminated gowns	contamination allowed into cleanroom	gown supplier: inadequate cleaning or sterilization of gowns	supplier audited routinely for conformance to best practice standards	2	5	4	40	High
	incorrect gowning technique	contamination allowed into cleanroom	procedure not validated	quality system requires validation of cleanroom materials. Compliance to USP 1116.	1	5	4	20	Medium
			validation inadequate	compliance to USP 1116	1	5	4	20	Medium
			operator error	training demonstrated to be effective	3	5	4	60	High

Table 1: FMEA using traditional EM methods.

Function	Potential Failure Mode	Potential Effects of Failure	Potential Causes of Failure	Current Process Control	Occurence	Severity	Detection	RPN	Risk
enter gowning room, don gown	contaminated gowns	contamination allowed into cleanroom	gown supplier: inadequate cleaning or sterilization of gowns	supplier audited routinely for conformance to best practice standards	2	5	1	10	Low
	incorrect gowning technique	contamination allowed into cleanroom	procedure not validated	quality system requires validation of cleanroom materials. Compliance to USP 1116.	1	5	1	5	Low
			validation inadequate	compliance to USP 1116	1	5	1	5	Low
			operator error	training demonstrated to be effective	3	5	1	15	Low

Table 2: FMEA using IMD-A system.



Furthermore, as traditional methods are retrospective, the Detection metric may drive a higher Risk Priority Number than is inherently appropriate if detection could occur more swiftly. However, with the use of more sensitive methods such as with the IMD-A system[c], evaluations of cleanroom activities achieve an enhanced quantification of risk. The IMD-A system provides the sensitivity necessary to 'quantify the qualitative,' so that mitigation efforts can be placed accurately on the risk priorities. Furthermore, the detection occurs in real time, allowing an assessment team to make timely decisions about the relative risk of a process – immediately after a risk-assessment meeting, a process can be modeled, and instant feedback can be attained.

[c] The IMD-A system is validated to the standards of USP <1223> and EP 5.1.6, demonstrating equivalent or better results as compared to existing microbial methods, as described in fact sheet LI-007.

Risk Assessment Support

Azbil BioVigilant's Field Applications Scientists can provide the tools and knowledge to help support your on-site risk analysis. Given specific assessment goals, a one-week on-site review of potential risk sources can give you the quantification and data necessary to make important decisions moving forward, all in real time, without having to wait for growth of a microorganism.

Examples of how Azbil BioVigilant can support your internal Risk Assessment team include:

- Real-time (continuous or episodic) static review of cleanrooms, identifying areas where potential for risk may occur
- Real-time risk assessment of dynamic activities in cleanrooms
- FMEA support of the combined evaluation of static and dynamic reviews to understand the true risks in your environment

Please contact an Azbil BioVigilant sales executive or field application scientist to learn more.

LI019 April 17, 2013

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Instantaneous Microbial Detection

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