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Risk Mitigation in Sterile Manufacturing

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INTRODUCTION

Risk in sterile pharmaceutical manufacturing environments is pervasive, requiring unflagging diligence, well-understood aseptic manufacturing processes and controls, as well as a robust quality systems management to mitigate contamination and other risks across operations. Quality excursions in sterile manufacturing take myriad forms — from glass particles in suspension to microbial contamination introduced during filling operations, there is ample opportunity for humans and the process equipment they operate to introduce contaminants in process. The best risk mitigation strategies start with preparation. In this Special Report, Pharmaceutical Manufacturing's editors have selected three articles that will serve operators well, that is, those looking to better understand how to effectively manage and eliminate risk inherent to sterile manufacturing environments.

Minimizing Aseptic Contamination Risk
Utilizing an "Advanced Aseptic" Technique

Contamination events for aseptic manufacturing have led to product recalls, and even the complete shutdown of manufacturing plants to remediate the issues. This has caused companies real economic and reputational damage. But, fundamentally, the reason why contamination must be avoided at all costs is the potential to harm patients. If a case of contamination is not picked up before the filled product leaves the facility, the risks to patients are obvious.

In recent years, there have been numerous high profile recalls and facility shutdowns after the discovery of contaminated products. Even reading through the FDA's list of product withdrawals there are multiple examples of contamination ranging from glass fragments and other visible particles in vials, to products that caused immunogenic reactions. The severity of contamination risk was highlighted in 2012 when formulations for spinal steroid injections led to hundreds of people becoming infected with fungal meningitis — and caused multiple deaths.[1] Many of these could have been avoided had better manufacturing and control procedures been in place.

Perhaps the biggest challenge to aseptic parenteral filling is the avoidance of microbial contamination. The number one source of microbial ingress into a filling facility is the human operators running the process. If contact between operator and product can be minimized, or even eliminated, then a major potential hazard is instantly reduced, if not removed.

Traditional filling processes offer many opportunities for microbes to enter the filling line. The primary container and closure components have to be cleaned and sterilized ahead of use, but are then exposed to the atmosphere as they rotate on the filling line or stopper bowl. This provides plenty of chances for particulates and other contaminants to be deposited on or in the otherwise sterile components.

Human operators within the filling suite still pose the biggest risk in a traditional filling. They will be physically monitoring the line, straightening vials on the turntable and dislodging stoppers that may have become stuck. This physical contact provides an opportunity for microbe or pyrogen ingress, and even the fact that there are people within the filling suite, breathing and moving around, adds the potential for adventitious contamination.

LEVERAGING ADVANCED ASEPTIC MANUFACTURING TO MINIMIZE CONTAMINATION RISK

An advanced aseptic filling process that leverages blow/fill/seal, or BFS, technology has the potential to reduce these risks. The container is made in situ, and filled in a virtually closed process, with the container being sealed before it leaves the class A/ISO 4.8 environment. This technique has been in common use for the manufacturing of sterile products for decades, and is well established in the filling of parenterals in Europe, South America

and Asia. However, surprisingly, in the United States traditional filling techniques for parenterals are essentially exclusive to traditional filling, despite the significant and documented benefits of BFS filling in maintaining product sterility.

BFS has been designated as an "advanced aseptic" technique by regulators. The FDA has established requirements that will render a technique advanced aseptic.[2] Essentially, it is a technique where operators dressed in normal cleanroom garments do not — and cannot — interact with open containers of products or exposed surfaces that come into contact with the product. The advanced aseptic environment of BFS is automated and controlled, with rapid product processing, and the critical control parameters are set and monitored. Other equipment that can be deemed advanced aseptic includes restricted access barrier systems and isolators.

BFS is able to meet advanced aseptic demands because the in situ manufacturing, filling and sealing of the container requires no human intervention, and the line is remotely operated and controlled. In addition, continuous monitoring of parameters, such as the viable and non-viable air in the fill zone adds a further layer of security. In all, its features greatly reduce the potential for microbial and foreign particulate contamination to the product. The FDA deems the design of the equipment, process and operational controls to render it advanced aseptic, with further evidence provided by test results from numerous microbial challenge experiments that were designed to push performance to the limit.

SYSTEM DESIGN

At the heart of the advanced aseptic technology of BFS is the automation and control. The equipment design is rooted in the principles of Quality by Design. The filling process takes place in an ISO 4.8, or Class A, environment, and it takes less than 15 seconds from the start of the container molding process to the final seal being applied to the container. Both the pathway that brings the plastic used to make the container and the pathway by which the product is introduced are virtually closed, with no operator intervention required. A further advantage is the additional level of safety afforded by the high heat and pressure used to melt and process the plastic resin, which inactivates any residual or adventitious microbes or endotoxins that might be present in the plastic.

To make the container, virgin plastic pellets are fed into an extruder through a vacuum line, where the pellets will undergo a phase change with high temperatures and pressures (typically 180 C and 200 atm). The plastic is extruded into parisons, which are long plastic tubes, into a space that meets ISO 4.8 viable air standards, where the maximum number of 0.5**µ**m particles per cubic meter is 3,520, and the maximum for 5.0**µ**m particles is 20. The primary container is shaped via brass and steel 2 stage mold. In the first stage, the mold closes around the parisons and a vacuum is pulled to create the container body. The top of the container is still open and is now ready for filling. Fill nozzles are then activated to fill the container with drug product. Once this is complete, the second stage of the mold closes and seals the product. Again, this entire automated process takes place in an ISO 4.8, or Class A space in the matter of seconds.

Control of the quality of the airspace around the nozzle is maintained and monitored, for both non-viable and viable air. Should the permitted particulate levels be exceeded, the filling machine will automatically shut down to prevent the container and product from being exposed to potential contamination risks. And, as the whole process takes just 15 seconds from start to finish, any risk from exposure to the atmosphere is minimized as the time the container is open is so short.

The fact that the product pathway is also closed in BFS provides further surety of safety. In a traditional filling line, components and equipment are cleaned and sterilized ahead of time and then stored before being assembled and aseptically connected, after which they sit open to the atmosphere within the filling suite. In contrast, in a BFS line all the cleaning and sterilization is done in situ, and thus the product is never exposed to equipment that has been open to the atmosphere or operators assembling it after it has been sterilized.

The ISO 4.8 space that surrounds the filling nozzle is not exposed to human operators. In the unlikely event that an operator does have to enter the closed filling area, the run is stopped and a full re-clean and sterilization procedure will be run, prior to restart. This is much less impactful than in the case of a traditional filling line, as only minimal amounts of product are ever going to be exposed, and the containers simply do not exist until they are extruded.

MICROBIAL CHALLENGE TESTING

It is clear on a qualitative level that vials filled using BFS are inherently much less likely to be contaminated by microbes or pyrogens. However, at the heart of the advanced aseptic designations is the microbial challenge data that supports this designation. Companies such as Advanced Liquid Packaging (now part of Catalent) ran numerous tests, in which various parts of the filling process were exposed to extreme microbial insults.

In order to run these tests, a specific microbial challenge facility was designed with completely dedicated HVAC and exhaust systems, to ensure unplanned contamination was not allowed in, and none able to escape. Microbial loads could therefore be carefully measured, the room safely fogged, and equipment with known amounts of contamination introduced. Several such challenge tests were carried out to form the basis of the advanced aseptic nature of BFS. The three most referenced tests are on the impact of an extreme microbial challenge on the equipment surfaces, the virgin plastic pellets used to make the containers, and the air within the room.

The first of these tests is the equipment surfaces and components test. All of the BFS surfaces were coated with varying levels of up to 108 spore suspension of Bacillus subtilis.[3] The filling process was then run under normal conditions. Even though the surfaces were loaded with microbial contamination, the only surface that created a media failure was the fill nozzle that comes in direct contact with the product. This proves that even if the equipment itself is extremely contaminated and you control the fill nozzles, the final product remains safe.

The challenge test on the raw plastic pellets involved using the loading of up to 108 B. subtilis spore suspension being fed into the extruder.[4]The combination of the heat and pressures utilized in the process created a 10–3 reduction in bioburden. Even though the microbial contamination was far greater than typical resin values, the data provides the benchmark for the critical control parameters for the plastic resin. In addition, this process offers an additional barrier to microbial contamination based on the extreme heat and pressure needed to convert the plastic from a solid to molten liquid.

Finally, the airborne challenge study.[5] The microbial challenge facility was fogged with 102 to 108 of an aerosolized suspension of B. subtilis, with aerosolization continuing throughout the test. Numerous filling runs were carried out under different microbial load conditions, including the activity of the HEPA air shower in the ISO 4.8 space. The tests showed that the contamination fraction was reduced to 10–3, a substantial reduction from the levels that had been introduced. This was directly proportional to the applied microbial load, as was the number of contamination incidents. Clearly, the high levels of B. subtilis introduced are significantly higher than those that are ever likely to be present in the real

world, and these results allowed operating and environmental conditions under which the BFS equipment can automatically be guaranteed to meet the sterility assurance level demanded of products that are terminally sterilized, which is set at 10–6.

Now imagine carrying out similar tests in a traditional filling line. Everything within the filling suite — from equipment to consumables — would be covered with microbial contamination if the room were aerosolized with a 107 spore suspension. Virtually every single vial of product would be contaminated — in contrast to those tests leveraging the advanced aseptic process of BFS. Fundamentally, BFS drastically reduces the risk of contamination, which is at the heart of its advanced aseptic designation.

Traditional glass vial filling operations continue to have challenges with aseptic manufacturing that cultivate into contamination issues and product recalls that are leading to drug shortages. It is clear that implementation of BFS to fill parenteral products would reduce the risk inherent in the traditional aseptic filling process by eliminating variables and increasing automation. This could potentially enhance patient safety and product availability due to the decreased risk of contamination. The adage 'Because that's how we've always done it' is not good manufacturing practice, especially when there are alternatives that are safer and more reliable.

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Quality: Make a Pre-Emptive Strike

Don't wait for a significant issue to reveal weaknesses in your Quality Assurance processes.

Too many pharma companies have learned the hard way that the quality and compliance environment is getting much tougher. The cost of recalls or remedial actions to fix manufacturing and quality assurance deficiencies can run into hundreds of millions of dollars, and companies that suffer them typically make strenuous efforts to improve their processes and prevent recurrence.

Some of the companies that recently experienced major quality issues thought that they were performing well before problems hit, because they relied on vaguely defined and inconsistently measured quality KPIs. For example, one plant was reporting right-first-time rates of above 95 percent, while actually experiencing more than 300 deviations per 1,000 batches — a metric that was not tracked or reported.

So what if your organization has yet to experience a high profile failure? Or even a minor one? Leading companies are constantly testing, evaluating and evolving their quality capabilities in detection and management. It is that relentless improvement that keeps them one step ahead of potentially damaging problems.

But in the absence of a large-scale issue or explicit instructions from regulators, how do organizations select where to focus the improvement efforts? Quality vanguards make use of a range of diagnostic techniques to build a detailed picture of the strengths and limitations of their processes, organization and culture. Then they make prioritized and targeted interventions to close gaps to best practice.

DIAGNOSING QUALITY PERFORMANCE GAPS

To prevent quality and compliance issues, quality vanguards assess the inputs into their quality processes as well as the outputs, using internal, external and cross-industry benchmarks to compare their own current processes with the best available (see box on next page for an example tool).

They also make smarter use of quality metrics, which should be tracked at local and functional levels. All companies take action when lagging quality indicators (e.g., customer complaints, recalls) reveal an issue. Some pharma companies conduct leading indicator analyses (e.g., number of deviations per batch, share of overdue CAPAs, right first time, CTQ trends) at the aggregate level as well, to identify the early signs of potential issues. But it is very rare for any pharma company to analyze leading indicators constantly and at a granular level for individual products and value chain steps — analyses that provide the true insights into potential issues.

One powerful way to reveal such systemic issues is the use of risk "heat maps," which help assess quality performance across functional processes (e.g., sourcing, formulation and/or sub-steps, QC, packaging, maintenance, distribution), risk occurrence (e.g., observations per audit, number of customer complaints), operational maturity (e.g., right-first-time rates, capability of critical processes) and quality system maturity (e.g., CAPA cycle time, frequency of recurring deviations) at the site or even product level. Such maps can quickly uncover areas of high risk or significant opportunities to boost quality performance.

Quality decision making and governance is another area where weaknesses can hide. Decision making and governance policies need to be transparent so that everyone in the organization, regardless of function, understands their quality goals and targets, is incentivized appropriately to achieve them, and knows immediately who is responsible for quality-related decisions. Without such clarity, companies risk compromising quality objectives in their desire to meet other targets, like output, for example.

Ineffective communication and execution processes between global and local levels can limit a company's ability to react quickly to the early risk indicators and preempt potential quality and compliance issues. Post-mortem analysis of recent failure or near-failure cases is one of the most effective tools to identify potential areas of weakness in governance and decision-making processes.

The final critical element in any organization's assessment of its own quality performance is culture. The effectiveness of everyday decisions often depends on how well and clearly the company communicates the type and size of risks it is prepared to take, how decisions are weighed and whether all employees feel accountable for quality performance. Employees must feel comfortable escalating concerns around actual or potential quality issues to management. Managers must be willing to seek out different perspectives in order to inform their decisions, and teams must be willing to operate in close cooperation, while still being prepared to point out issues and challenge current practices.

PRIORITIZING, PLANNING AND DELIVERING

The harder any company looks at itself, the more faults it will find. Once companies start to scrutinize their quality processes, they are often overwhelmed by hundreds of different improvement opportunities. Vigorous prioritization is the key step that allows companies to move from diagnosis to rapid and significant performance improvement. That, in turn, requires an explicit understanding of, and alignment on, the organization's appetite for risks of different kinds.

"Zero tolerance" of any risk does not help meaningful prioritization or effective decision making. Instead, companies must differentiate between issues that have impact on patient safety or product efficacy, and those that affect other goals, like manufacturing cost or delivery performance, and they must set clear targets for each. Such an approach gives the organization a clear picture of its most important quality risks, allowing more efficient resource deployment.

Prioritized countermeasures or process changes don't have to be stand-alone initiatives requiring separate resources and management. Quality improvement initiatives often work best when integrated with Lean and continuous improvement or organizational capability building efforts.

BENCHMARK YOUR QUALITY ONLINE

Quality benchmarking tools are available online. The McKinsey IQ-scan tool, for example, is a fast and easy-to-use, self-administered assessment available free-of-charge to registered users. The tool, which takes around 15 minutes to complete, allows companies to compare their quality practices to best-in-class across four dimensions: quality strategy & KPIs, functional quality processes, quality organization & governance, and quality risk culture.

One large global pharmaceutical manufacturer recently applied many of the techniques described above to uncover and rectify some important weaknesses in its quality organization. The company had a strong track record of quality performance, but its leaders were unsettled by several "near misses" internally, and a series of big failures elsewhere in the industry. They were determined to ensure that the same thing did not happen to them.

An intensive diagnostic process gave management much to be happy about. It revealed good processes and a strong compliance culture across the organization. But it also identified some blind spots and hidden risks "camouflaged" by current quality measurements and governance. These included, among others, inconsistencies in the interpretation and reporting of quality KPIs and little visibility into supplier and vendor performance. Poor coordination between the central quality function and site-level organizations was also hampering standardization, implementation of global initiatives, and the free flow of best practices across the organization.

In addition, overall risk strategy was not well understood, which meant that "risk-appetite" was being determined locally. This affected decision making, made it hard for sites to prioritize the quality improvement initiatives that mattered most and led to inconsistent risk levels across the network. Finally, some site-level quality managers, while they were executing existing processes very well, lacked the skills they needed to develop and implement new ones.

In response to these findings, the company's quality function started working with its existing Lean improvement teams to develop a simplified and streamlined set of quality KPIs and a new reporting structure focusing on a few leading indicators, while its supplier management group focused on revising its approach to risk assessment and communication with vendors. The company also enhanced its capability-building program to improve the problem-solving skills of its mid-level management at the sites, and it made important changes to the way quality performance and risk issues are communicated across the organization.

The same diagnostic approach can be equally useful when things do go wrong, helping companies to identify the root causes of quality issues, rather than just treating the symptoms.

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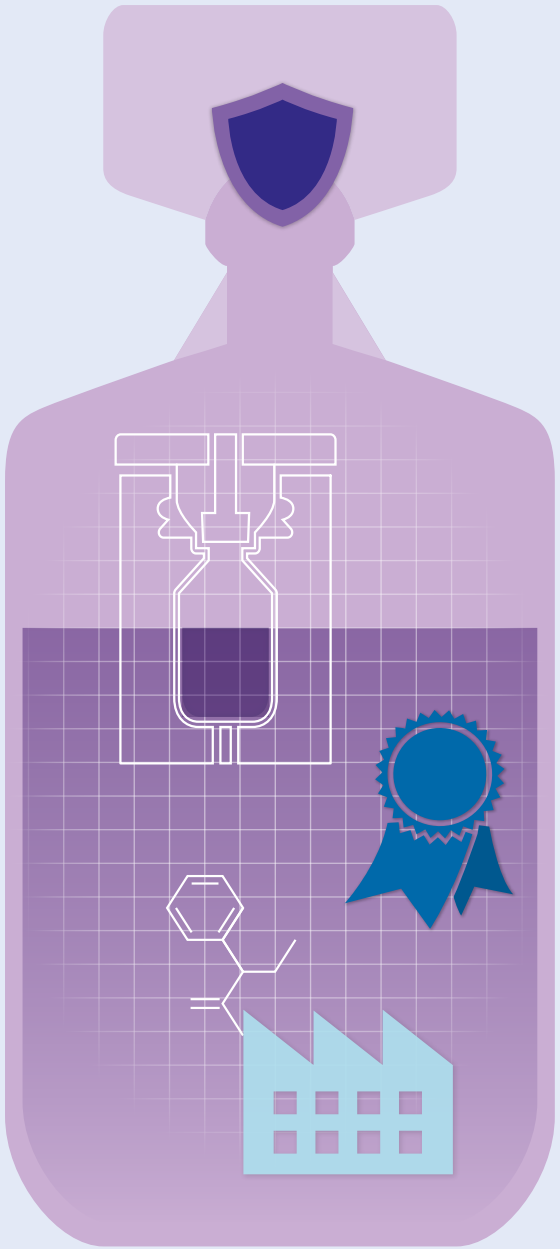

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Putting Particulates on the Map

Contamination mapping isn't exactly cartography, but it can be an effective troubleshooting tool.

BY PAUL THOMAS

Many drug facilities have fallen afoul of FDA regulators over cleanroom contamination. A cottage industry of consultants and solutions providers thrives on helping manufacturers avoid such a fate.

Often the problem is one of negligence. In a Warning Letter sent to one manufacturer a few years ago, FDA stated: "The absence of sterility failures and adverse reporting trends do not indicate to us that sterility assurance has been attained. Sterility assurance is achieved by showing the controls and procedures implemented to prevent microbial contamination." In other words, contamination control should be a proactive exercise. The Agency continued, "We recommend that you continually evaluate your facility on an overall basis to determine cGMP compliance."

There are basic tools that manufacturers can use to establish better contamination control — among them, contamination mapping of a facility or its sterile areas, says Philip J. Austin, Ph.D., director of research of Acorn Industries Inc. (Livonia, Mich.), a consulting, training, and engineering firm specializing in contamination control. (The firm was founded by Austin's father, Philip R. "Doc" Austin, S.E., who has consulted and lectured on contamination issues for some 40 years.)

Contamination mapping is a bit of a misnomer, the younger Austin says. Maps aren't always used, and there are no clearly defined practices.

Some manufacturers actually do use facility maps, upon which they plot contaminant readings and establish "hot zones" in cleanrooms and other locations. And some might go so far as to draw computer-generated maps with color gradients illustrating levels of particulates in various locations. More often, however, says Austin, the "maps" are spreadsheets or tables presenting contamination data from specified locations, which are then referenced against a layout of the facility.

One of the reasons there's not more consistency in how mapping is done is that most manufacturers would rather not talk about it, Austin says. (Recently two facilities turned down our requests to be interviewed about their mapping activities.) "Most of the time we're called in a crisis," Austin says. "There's been a problem at the facility, the FDA has asked for CAPA, given the manufacturer a year to do it, and 11 months have already gone by."

Done right, mapping can be a useful diagnostic tool, Austin says, something that goes beyond mere compliance. Many

manufacturers map certain particles (eg, bacteria) out of protocol, Austin says, but "they're not really mapping." Rather, they're doing the minimum to ensure compliance for whatever cleanroom standard they must meet.

He offers up some advice for those who would map:

Set your objectives. Clearly define your reason for mapping and what you hope to get out of it. Some considerations:

- Compliance and/or control? Are you mapping because you have to, want to, or both?
- Aerosol and/or surface particles? Mapping usually concerns airborne particles, but there are reasons to examine both, Austin says.
- Viable and/or non-viable particles? "Each company must decide what it is they're worried about," he says.
- "At rest" and/or "operational"? Baseline data and mapping is usually done at rest, Austin says, since operators are not present and readings will be consistent (and the manufacturer is more likely to obtain favorable results). "Operational" data can vary dramatically depending on level of workers' activity.

Have a plan. Once you've defined what particles you're looking for, what work areas you want to monitor, and what activities pose the most risk, and so on, establish clear monitoring procedures accordingly, Austin says.

Make mapping systematic and proactive. "Smart companies are doing it as part of a routine," Austin says. They say, "This is something we need to do to control our processes and troubleshoot potential problems."

Make use of new testing and monitoring technologies available. Anything that cuts down on the two weeks or so it takes to receive bacterial results, for example, is helpful. "While waiting for a test result, you may have been running for 14 days with a contamination issue," Austin says. "If the tests show a problem, then what are you going to do?" It goes without saying that more timely data will make maps more current and relevant.

Make sure data is meaningful. "Some manufacturers do continuous monitoring and mapping, but they usually stick [the test plate or sensor] in the corner of the room . . . it makes you feel good, but the data's not that important." One good practice, he says, is to monitor near critical work areas, particularly where product is exposed. This will provide the most meaningful contamination data.

Resolve issues immediately. "If you find a problem, you have to deal with it." Smart manufacturers know that any contamination issue ignored will come back to haunt them.

Go with the pros. Contamination is a complex issue which is not well understood by those most often assigned the task of contamination control, Austin says. "There is no formal college training for the discipline. There are a variety of issues to consider, and every facility and manufacturing process is different. For mapping and contamination control in general, it makes sense to defer to those who do it for a living."

ADDITIONAL RESOURCES

Jonathan Arnold, VP and GM of Sterile Technologies at Catalent, discusses new applications for BFS at Interphex 2012.
http://www.pharmamanufacturing.com/multimedia/2012/003.html

Aseptic BFS vs. Traditional Aseptic Processing: An Overview
http://www.pharmamanufacturing.com/articles/2009/093.html

Drug Delivery and QbD: A Collision of Lifecycles, by Bikash Chatterjee
http://www.pharmamanufacturing.com/articles/2008/055.html

Solving Tech Transfer Challenges for Complex Pharmaceutical Products
http://www.catalent.com/index.php/thinking/supply-chain/solving-tech-transfer-challenges/solving-tech-transfer-challenges

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