Media fill simulations

Aseptic processing is a complex yet key part of biopharmaceutical manufacturing. Anne Connors, Regional Marketing Manager, BioMonitoring, **Merck Millipore** and Scott Sutton, **Microbiology Network**, outline the regulatory requirements for aseptic process simulation and look at some industry trends based on a recent survey

Aseptic processing, the technique used to ensure sterile drugs are packaged in sterile containers, is one of the most important steps in biopharmaceutical manufacturing, because of the risk that contamination poses to patient safety. Aseptic process simulation, also known as a media fill trial, estimates the contamination risk of an aseptic production process by using sterile culture media in place of the product constituents. Process simulations vary depending on the particulars of the process and the type of product to be filled, such as liquid or solid dosage forms.

The use of media fill trials for aseptic process simulations is not a new concept. The goal of a media fill is to demonstrate that the manufacturer can follow the routine aseptic production process using sterile media without contamination. However, drug manufacturers and regulatory bodies are not only concerned with the media fill results, but also with ensuring a quality approach to study design and proper risk analysis (FDA 2004). A successful media fill study should never be used to justify aseptic processing practices that pose unnecessary contamination risks.

Regulatory agencies hold manufacturers to very high standards for aseptic processing. The current regulatory requirements for media fills are encapsulated in two major guidance documents: *FDA Aseptic Guide (FDA 2004)*[1] and the *PIC/S Recommendation on the Validation of Aseptic Processes (PIC/S 2011)*[2].

The study design

The most critical attribute of a media fill trial is that it imitates the routine production process as closely as possible. Any element that could potentially affect the sterility assurance of the process needs to be part of the study design. For this reason, every study should include a protocol with defined interventions, all of which need to be practised during the

media fill. Specifically, every study design should incorporate:

- Factors associated with the longest permitted run on the processing line that can pose contamination risk (e.g. operator fatigue)
- Representative number, type, and complexity of normal interventions that occur with each run, as well as non-routine interventions and events (e.g. maintenance, stoppages, equipment adjustments)
  - Define allowable interventions
  - Define grades of interventions
  - Practise all interventions during media runs
- Lyophilisation, when applicable
- Aseptic assembly of equipment (e.g. at start-up, during processing)
- Number of personnel and their activities.

Three consecutive, successful simulations should be conducted to initially qualify the process. Each process should be confirmed with an additional process simulation study twice a year, unless there is a significant change in the product, process or facility, in which case revalidation may be required; this should be determined by the company's change control procedures. All personnel qualified to enter the aseptic processing room should participate in at least one media fill per year.

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The study design should incorporate 'worst case' conditions, which typically involve the largest container with the widest mouth or small ampoules running at high speed with frequent jamming. Media fill trials should also be conducted at different times on different days of the week to incorporate as much variability as possible. Although it is frequently impractical, the best approach is to exactly mimic a full production run. If the production run is less than 3,000 units, then the actual size of the production run should be simulated. For production runs greater than 3,000 units, the simulation can be scaled back. Finally, each media fill should evaluate one line speed, which must be justified to the regulatory agency.

It is clear that inclusion of multiple interventions and potential situations can lead to a large and involved media fill design. To this end, several approaches have been suggested to employ a risk approach to minimise the complexity of the task, for example, see Sandle 2012[3].

There has been some controversy over the past few years regarding the inclusion of anaerobic analysis in aseptic process simulation. In an aerobic environment, there should be no real concern because true anaerobes cannot survive. However, if the opportunity for an anaerobic condition does exist (e.g. a nitrogen overlay), then an anaerobic analysis should be incorporated into the study design.

Media considerations: Aerobic media is typically used in a media fill trial. In this case, standard practice is to use Soybean-Casein Digest Broth (SCDB), also known as Trypticase Soy Broth (TSB). However, anaerobic media might be considered in special circumstances where the media fill needs to be conducted in a closed system under anaerobic conditions. Regardless of the type of media used, each unit must be filled with enough media to contact all inner surfaces and growth promotion of the media must be demonstrated. A certificate of analysis from the vendor is not adequate provision for growth promotion.

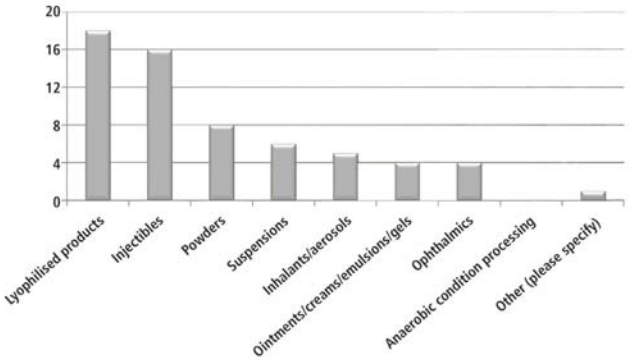
Incubation conditions: The incubation temperature should be suitable for the recovery of bioburden and environmental isolates. Currently, regulatory expectations are that two temperatures will be used with media-filled containers – the initial incubation at 20–25°C for 7 days, and then at 30–35°C for 7 days. The reasoning for this procedure is to allow fungi an opportunity to grow before the plates are overwhelmed by bacterial growth. However, at the low numbers of colony forming units (CFU) recovered in cleanrooms, this does not seem a major concern. A recent study has demonstrated that there seems little advantage to this sequence.[4]

The incubation is to take place in the sample containers to be used for the finished dosage form. The media is to be removed from these containers after incubation for reading if the containers interfere with the determination of microbial growth in the media.

Analysis of media fill: All filled units must be incubated and reconciled. The conditions under which vials are rejected should be clearly defined ahead of time and should be signed off by the quality assurance team, who are ultimately responsible for media fill analysis and sign-off.

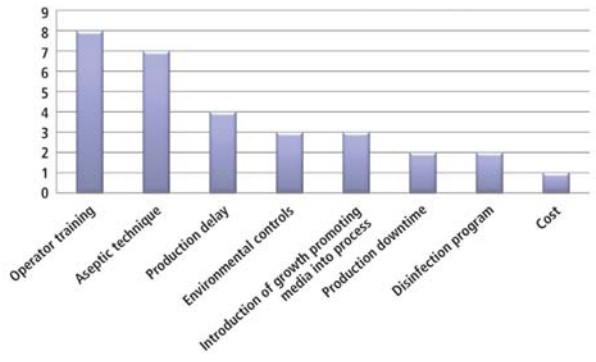
The target for a media fill trial is zero growth. The industry is well past the time when a certain number of positive units in a media fill would have been acceptable from a regulatory perspective. All units from the media fill are incubated; those that would be invalid in a product run (damaged vial, position in run, proximity to a major intervention, etc.) should be identified in the process simulation protocol and the results treated appropriately (see below).

Figure 1 Survey question: does your facility produce or fill any of the following products?*



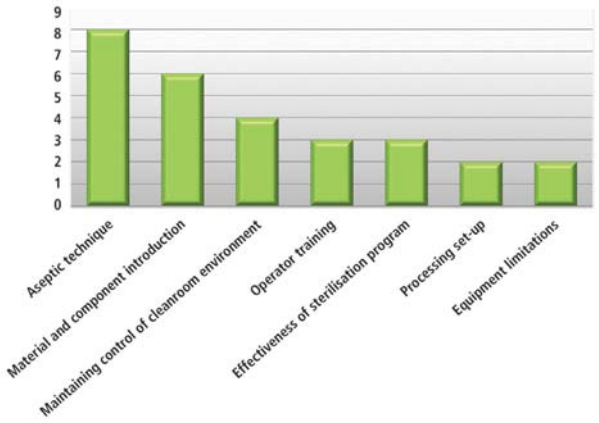
Note: Respondents could choose more than one answer. (Other products: drug-eluting devices, media)

Figure 2 Survey question: what are your primary concerns when validating a process simulation?*



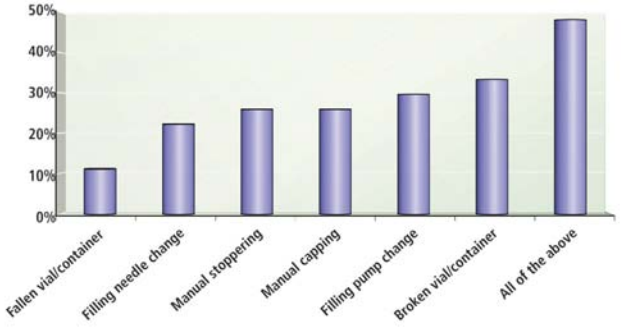
*Data presented represents top two ranking selections out of eight

Figure 3 Survey question: what are your primary concerns in regards to contamination control when performing routine process simulations?*



*Data presented represents top two ranking selections out of seven

Figure 4 Survey question: what are typical planned interventions during an aseptic process simulation?



Any growth of micro-organisms in a valid media fill vial is cause for great concern and must be viewed as a failure subject to full investigation. This investigation must also assess the impact on any relevant commercial runs between the last successful media fill and the current test failure.

Industry practice and trends

To help gain some insight on industry practices and trends in aseptic processing simulations (media fills), Merck Millipore conducted a blind survey in August 2013 through *American Pharmaceutical Review*. The following survey results include 59 qualified respondents who perform aseptic simulations, with a balanced representation from manufacturing and validation (63%) and quality control (37%).

Figure 1 includes the types of products represented by these respondents. While traditional processing technology is being used within the majority of facilities represented, other technologies, including isolator technology and other barrier systems such as RABS, are also well represented.

The areas of most concern among respondents with respect to validating a routine process simulation are operator training and aseptic technique; notably, cost is the least concern (see Figure 2). This finding suggests that the majority of respondents understand the importance of study design – and that a quality approach to study design outweighs the cost.

After the process has been validated and approved, the major concerns associated with performing routine process simulations include aseptic techniques and material and component introduction (see Figure 3).

The majority of respondents indicated that the FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing (2004) is the guidance document most closely adhered to at their facility.

Interventions are an inevitable part of process simulation. About 50% of respondents perform all of the typical planned interventions during their media fill trials (see Figure 4). In addition to planned interventions, some situations may arise where corrective intervention would need to be performed. Sixty percent of respondents indicated that corrective interventions would be added to the next simulation; 37% were unsure.

Since the outbreak of 'mad cow' disease, there is a great deal of focus within the industry on eliminating the introduction of Transmissible Spongiform Encephalopathy (TSE) and Bovine Spongiform Encephalopathy (BSE) into aseptic facilities.

Despite the fact that media manufacturers take care in sourcing the raw materials, 70–80% of all respondents still remain somewhat or very concerned about the risk of these specific contaminants, especially when their products are distributed to the European Union.

When it comes to selecting growth media, respondents indicated that quality documentation, ease of use and compliance with ISO 11133, which is focused on the production and qualification of prepared media, are the most important criteria. When selecting environmental equipment and consumables (i.e. air samples, contact plates), the most important criteria include the accuracy of the instrumentation, ease of use, compliance with regulatory standards, and the availability of validation documentation.

In summary, the goal of a media fill trial is to demonstrate that a manufacturer can follow the routine aseptic production process using sterile media in place of a drug product without resulting in contamination. However, a successful media fill should never be used to justify aseptic processing practices that pose unnecessary contamination risks. Therefore, regulatory bodies advocate a quality approach to study design and proper risk analysis when validating an aseptic production process.

The survey results suggest industry alignment on a few key topics when it comes to validating aseptic processing. Respondents align on the use of regulatory guidance and agree that safety and quality documentation are critical factors when choosing or qualifying a new media vendor. Additionally, respondents show greater concern over ensuring that quality is built into the process than cost control, and the risk to the product and process always comes before cost and time commitments.

REFERENCES

1. FDA. 2004. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
2. Pharmaceutical Inspection Convention Co-operation Scheme (PIC/S). Recommendation on the Validation of Aseptic Processes (Revision 6; 2011)
3. Sandle, T., *et al.* 2012. *J. of Validation Technology* **18**:70–78.
4. Sandle, T. 2014. *Int. J. Pharm. Compounding*. **18**(3):242–247.

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