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Advanced Sterilization

FDA Official Warns Manufacturers of Common Problems Found in Aseptic Operations

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Sterile drug manufacturing is a high-risk operation and to manage these risks, drug manufacturers need to "tightly control" a multitude of variables to ensure processes remain in a state of control, asserted Brooke Higgins, a senior policy advisor for global compliance in the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER).

Higgins outlined some of the consequences that can occur when these variables are not controlled, including warning letters or Form 483 reports, and discussed some inspection trends and common problems investigators are seeing in auditing aseptic manufacturing facilities at the International Society for Pharmaceutical Engineering's (ISPE) 2023 Aseptic Convenience in North Bethesda, MD on 6 March.

Her remarks focused on problems seen in media fill operations, sterility testing and environmental monitoring.

"Aseptic processes carry along with them a high level of risk, there are numerous steps to produce a product … When I think of aseptic processing, I immediately think high risk," Higgins said.

A host of variables need to be considered in ensuring the sterility of the final products, including the design of the cleanroom, disinfection procedures and practices, the media fill procedures and responding to deviations and environmental control trends.

Poor root cause investigations

Higgins recounted the details of one warning letter sent to a company following repeated media fill failures resulting from contamination of product vials.

The company failed to arrive at the root cause of product contamination. These media fill failures involved a large number of turbid vials found during the product's incubation. The investigation found that the contamination emanated from the presence of pseudomonas aeruginosa or gram-negative rods found in the cooling water of the mandrel, the hose used in the blow/fill/seal (BFS) equipment to produce sterile drug products. Higgins said the presence of gram-negative rods should be "very rare" in an aseptic operation and in media fills.

The firm responded by repairing the water leak in the mandrel and cleaned the outer surface of the BFS bowl, and then proceeded to perform a single media fill to requalify the line.

"One media fill is not sufficient to fulfil the requalification," Higgins said. Rather, the firm needed to perform a comprehensive CAPA followed by three consecutive runs in order to requalify that line.

"The presence of highly pathogenic microbes can present high-risk mutations and can be fatal to patient. Their presence needs to be urgently and efficiently remediated."

A subsequent root cause investigation concluded that the contamination emanated from a design flaw in some of BFS machinery, and not from the water leak.

Investigating media fill failures

Another problem is when firms fail to do any sort of remediation for failed media fills. In one case, a firm "had numerous turbid vials" but failed to investigate. The drug in question was produced in an aseptic filling cabinet.

"Imagine a media fill failure with maybe a half of the vials turbid and not a single corrective action was implemented. Even if you are not able to pinpoint the exact root cause it is essential to identify areas for improvement. Without this there is no assurance that you can prevent recurrence of failures," Higgins said.

Inconclusive sterility tests

Another trend are lax investigations into failed sterility testing results. In one case, a firm decided that a positive sterility test where a microbe was identified was the result of the fact that the microbiologist conducting the test was sick and failed to conduct a more comprehensive investigation.

A healthy analyst subsequently conducted the test, and the batch passed, so the firm invalidated the failing sterility results and released the batch. Yet the microbe was never identified. The firm was also told to have procedures in place to prevent sick employees from performing test in the sterility room.

Inadequate environmental monitoring programs

Some firms are not adequately conducting environmental monitoring of their aseptic processing areas. In one case involving an aseptic filing in a closed restricted access barrier system (RABS), the firm was isolating thousands of microbes in the aseptic processing room but rarely identifying them

In one year, the firm identified one microbe in an ISO 7 area, which was identified through the use of the firm's photo library.

She asked the audience to raise their hands on whether they could identify a microbe down to the species level based on a visual inspection. No hands were raised.

The warning letter told the firms that it lacked the vital information to ensure their aseptic operations were in a state of control.

RABS and isolators

In her final remarks, Higgins urged manufacturers to adopt closed barrier systems, such as isolators and RABS to eliminate human intervention in the cleanroom, noting that human presence in the cleanroom is a major source of contamination.

"We are still setting up sterile aseptic processing lines and these lines are from the 1990s … These older antiquated lines are not what we should be seeing here. These will continue to b he most common cause of non-sterility," Higgins said.

She added she is "hoping to see the continued drive to improve and increase the separation of the operator form the fill line and even eliminate personnel from sterile drug production altogether. This will profoundly cut down the risk of contamination."

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