Preventing and Controlling Contamination From Entering Cleanrooms

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Introduction

Maintaining microbial control in the pharmaceutical cleanroom environment is not only a regulatory requirement and expectation, but is absolutely critical to prevent contamination of the final drug product. Recently, expectation of cleanroom microbial control has evolved to include environmental monitoring of material handling artifacts. This trend places a new burden to evaluate material and understand the steps that need to be taken to avoid the contamination of finished drug products. Currently, implementing an effective contamination control procedure in material handling artifacts significantly reduces the risk of microbicidal cross contamination caused by transfer of contaminated materials through the artifact. Artifact and cleanroom design, decontamination method, disinfectant chemistry selection, and material preparation must be evaluated as part of the contamination control procedure development.

"It is critical to adequately control material (e.g., in process supplies, equipment, utensils) as it is transferred from lower to higher classified areas to prevent the influx of contaminants. For example, written procedures should address how materials are to be introduced into the process area, what protective components should be included, and what high level material and cleanroom conditions remain unconcealed. In this regard, organs should be disposed of according to appropriate procedures or, when in need of critical areas, rendered sterile by an aseptic method."

FDA Guidance for Industry 2006, Page 11

Cleanroom Design

The pharmaceutical cleanroom facility is designed to minimize contamination of the environment. The asptic processing area, or most critical zone and highest environmental classification, is at the center of the cleanroom. Air pressure differentials separate each room classification level, ensuring appropriate air flow and protection of the asptic processing area. Ceiling and floor conditions prevent the uncontrolled microbial control of the environment and all surfaces within. Access is limited and controlled in order to minimize contamination of the environment by the largest source of microbial contamination — operators personnel. Contamination from operations personnel is managed through use of gowning rooms, attire, conduct and procedures.

The next highest risk of contamination to the cleanroom environment is from materials brought into the cleanroom. Only materials essential to the operations should be permitted, including process equipment, raw materials, tools, carts, etc. Materials brought into the cleanroom should be identified for entry into the cleanroom if at all possible. However, much like personnel gowning and operational procedures help to control the source of contamination, procedures and materials must be developed for transferring materials into the cleanroom in the event they cannot be sterilized.

Contamination Prevention and Control

Possible sources of microbial contamination in the cleanroom include improper facility design, operations personnel entering and working within the cleanroom, and transfer of equipment into the cleanroom. Personal entering the cleanroom pose the greatest microbial risk to the environment. However, it is not always feasible to evaluate material and conduct procedures that may reduce microbial contamination. Following are general recommendations to control microbial contamination through cleanroom decontamination and proper transfer of material.

Selecting a Decontamination Chemistry

Specific considerations must be evaluated when selecting a disinfectant for cleanroom decontamination for treating equipment through the material handling artifact. The environmental conditions in the room area should be reviewed and the chemistry with the appropriate microbial efficacy should be implemented. There needs to be a balance between the chemistry efficacy, toxicity and suitable compatibility with the materials treated.

When selecting a disinfectant for use in a pharmaceutical manufacturing area, the following points should be considered:

1. The number and types of microorganisms to be controlled;
2. The spectrum of activity of commonly available disinfectants;
3. The chemical or bactericide;
4. The disinfectant or sanitizer supported by the EPA registrations;
5. The concentration, application method and contact time of the disinfectant;
6. The nature of the surface material being disinfected and its compatibility with the disinfectant;
7. The amount of organic compounds on the surfaces that may increase a disinfectant's effectiveness;
8. The possible need to maintain a residual bactericidal activity of the disinfectant on the surface;
9. The corrosion potential of disinfectants to equipment with associated application;
10. Safety considerations for operations applying the disinfectant;
11. The compatibility of the disinfectant with cleaning agents and other disinfectants;
12. The planned disinfectant rotation;
13. The steps that need to be taken to avoid the contamination of pharmaceutical products by a disinfectant.

Sanitizers, Disinfectants and Sporicides

Materials and equipment in the artifact should be decontaminated using:

• Reproducible and effective application techniques (spray sporicide, followed by strip alcohol)
• Application methods (spray coverage, mechanical wiper);
• Validated working times;
• Proven sanitizers/disinfecants/sporicides types;
• Airlock procedures (including personal training, approved equipment)

Efficiency Data Alcoholks

The following table includes a summary of microbial efficacy for 70% ethanol and 70% isopropanol:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>70% Ethanol</th>
<th>70% Isopropanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. subtilis</td>
<td>30 sec</td>
<td>60 sec</td>
</tr>
<tr>
<td>C. albicans</td>
<td>30 sec</td>
<td>30 sec</td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>30 sec</td>
<td>60 sec</td>
</tr>
<tr>
<td>S. typhi</td>
<td>30 sec</td>
<td>60 sec</td>
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<tr>
<td>Fungi</td>
<td>60 sec</td>
<td>60 sec</td>
</tr>
</tbody>
</table>

Efficiency Data Sporicides

A series of six kill studies were conducted to compare microbial efficacy of Sporicider® RTU Sporicide, 5.25% sodium hypochlorite, 0.525% sodium hypochlorite and 4% hydrogen peroxide. Recommended test organisms were Bacillus subtilis and Aspergillus niger. The result at 3 different time points are shown in the following graph:

References

10. STERIS Life Sciences Notebook 6851, pp. 72-71 to 80.

Equipment Preparation

Special consideration must be taken when preparing equipment for entry into the cleanroom. Items may be double wrapped and gamma irradiation sterilized, if available. Sterilization is not feasible if equipment can be contaminated when passing the materials into a more strict room classification. The outer wrapping can also be manually disinfected (spraying or wiping) with a sporicide in the material handling artifact.

Additional measures at other areas of concern, such as wheels on carts and mobile equipment, should be addressed by spraying a sporicide followed by a neutralizer, so these areas can cause a great trend of preventing microbial contamination to the cleanroom.