Issue
What alternative methods exist to replace formaldehyde fogging of clean rooms?

Introduction:
Alternatives to formaldehyde fogging include the use of liquid sanitizers or fogging with an alternate chemical sterilant such as chlorine dioxide, vapor-phase hydrogen peroxide, or atomized peroxyacetic acid-hydrogen peroxide. For biological facilities where viral contamination is a concern, it may be a regulatory expectation to decontaminate via fogging with some frequency. The switch from one disinfectant to another involves both laboratory and facility studies. The laboratory validation should include surveying the bioburden of the facility and determining the environmental isolate that is least susceptible to the agent. The efficacy of the agent should then be tested against the least susceptible organism on representative surface materials found in the facility. The required reduction of bioburden should be proven in the laboratory with the least susceptible organism on the surface that allows for the greatest number of survivors.

Studies should then be conducted under actual conditions of use via surface monitoring of the facility both before and after application. To qualify a new fumigant it may not be necessary to include biological indicators in the facility studies if distribution of the chemical can be shown by physical means.

The International Agency for Research on Cancer classified formaldehyde as carcinogenic to humans in June of 2004. It is therefore prohibited to use formaldehyde in new fogging applications. However, since many GMP facilities currently use formaldehyde to fog clean rooms on a periodic basis, there is a need for information on the options that exist to replace it. Facilities are encouraged to actively pursue alternative sanitization methods. Feasibility studies should be completed to determine the business impacts and EHS implications of changing to a different sanitizer. If the feasibility study indicates that formaldehyde use must continue, facilities should evaluate modification of the application process to minimize amounts of formaldehyde used, the airborne concentration of formaldehyde gas, and total exposure times.

A common use of formaldehyde at GMP some facilities is to sanitize clean rooms following maintenance shutdowns. Other facilities have more established frequencies of use during routine operations that vary from daily to monthly. This good practice bulletin will discuss the options available to replace formaldehyde, some regulatory requirements for sanitization of clean rooms, and validation considerations for switching sanitizers Definitions .

Disinfectant -Substance that destroys most forms of microorganisms on inanimate objects but not necessarily spores.

Fogging -Use of a chemical, typically a sterilant, in a gaseous or vaporous state to destroy microorganisms in a facility. Also known as fumigation.

Sanitizer -Substance that significantly reduces the bacterial population on inanimate objects.

Disadvantages

– Requires specialized equipment that may be costly to purchase and validate
– Requires control over temperature and humidity
– Corrodes heavy metals
– Does not penetrate like a gas
- Absorption/de-absorption issues
- Oxidizing agent that may have fire safety implications

Validation Requirements

Whether a liquid, gas, or vapor is chosen, a new sanitizer must be qualified according to Aseptic Area Environmental Control. The qualification should include an assessment of the number and types of microorganisms to be controlled. This could be determined either through historical review of environmental monitoring data or a special study. Once the types of microorganisms typically found in the facility are known, laboratory studies should be conducted to determine the environmental isolate that is the least susceptible to the chosen sanitizer.

For a liquid application, these studies typically involve inoculating a suspension of each test isolate into the use dilution of the sanitizer at expiration. After a set time period, the solutions are either neutralized or filtered to stop microbiocidal properties of the sanitizer and the number of survivors determined. It is critical to validate the neutralization or membrane filtration step to ensure organisms surviving at the endpoint will be recovered.

The isolate with the highest survival rate is assumed the least susceptible to the chosen sanitizer. Official methods for qualifying chemicals as sanitizers, disinfectants, or sterilants are available from the AOAC or European standards committee.

Although the user need not repeat these tests, they may be useful guides in designing laboratory studies.

For a fogging agent, lab studies are performed in a glove box or other suitable environment that allows exposure of inoculated carriers to the chemical for a set time period followed by prompt aeration, removal, or segregation to halt microbiocidal activity. The isolate showing the highest number of survivors following exposure to the chemical at the actual use concentration and environmental conditions is considered the least susceptible to the fumigant.

The organisms selected for screening should include representatives identified during environmental monitoring that offer the greatest resistance to the chemical; for example Gram (+) spore formers, fungal spores, viruses, etc. Additional organisms with limited susceptibility to the agent may also be included to show the relative resistance of the facility bioburden in comparison to those discussed in the literature as being difficult to destroy by the chosen agent.

The method used to apply a sanitizer and the type of surface being sanitized can have an effect on survivability of target microorganisms, so it is prudent to evaluate these variables in the lab prior to facility studies. This can be accomplished by inoculating representative carriers of the materials found in the facility with the least susceptible

