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Mini Review

Disinfectant Validation - Regulations and compliance

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Abstract

Disinfectant uses in Pharma Industry: Disinfectants are used to keep aseptic conditions and improve product quality by reducing the proliferation of various microbial ecosystems (bacteria, fugus, yeast, and mould) in clean areas. Patient safety is always considered at risk during the manufacturing of medications.

Why Validation is must: Validation is the determination of the degree of validity of a measuring disinfectant efficiency and the range of microbial load log reduction on each contact surface in the clean zone.

Conclusion: Before doing any clean area task, especially sterile function handling, it is necessary to select disinfectants with specific varieties of microbial cultures as per pharmacopoeia and environmental isolates.

Keywords: *Disinfectant Validation; Microbial Ecosystems*

As part of any pharmaceutical manufacturing area accreditation, a documented and approved disinfection procedure must be developed, verified, and implemented. This industry receives a lot of regulatory attention because it is such a crucial part of any industrial facility's maintenance strategy.

Figure 1

The US FDA, MHRA (Medicines and Healthcare Products Regulatory Agency), HPRA (Health Products Regulatory Authority), and CFDA (China Food and Drug Administration) and others, routinely make observations on disinfectant validation studies and disinfectant methods.

"Each company must have a systematic programme managing the qualification, use, and disposal of disinfectants," according to the US FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing (Aseptic Processing Guide September 2004) [1]. The current United States Pharmacopeia, Chapter <1072> [2], provides some recommendations on disinfectant selection, use, and qualification. Without a doubt, pharmaceutical businesses must demonstrate that their room decontamination systems achieve and maintain the required levels of contamination control. This article will discuss considerations and best practise for verifying disinfectants used in medicine manufacturing settings.

It's crucial to note that disinfectant validation is a three-part process. These components are:

- Disinfectant qualification (*in vitro*),
- *In situ* qualification,
- Environmental monitoring with trending during routine operation activities.

Studies that are conducted in a laboratory or artificial setting are known as *in vitro* (Latin means "in glass") [3]. Because a variety of factors might influence disinfection effectiveness in real-world situations, it's critical to undertake *in vitro* tests to show that a product is intrinsically effective against a certain organism under well-defined settings like concentration and contact time. Most countries require *in vitro* testing in order to register and market a disinfectant or sporicidal product. The product labelling reflects the precise organisms (ATCC strains) used in these experiments, as well as the testing circumstances (temperature, concentration, contact time, as main factors). The testing required for product registration, on the other hand, frequently does not suit the needs of pharmaceutical companies who must meet regulatory requirements.

Disinfectant validation should be viewed as a form of process validation and is a much more in depth and extended process. It is often site or facility specific. In summary: "Disinfectant validation is the documented verification and implementation of procedures that have been shown to consistently control the range and levels of micro-organisms that may be encountered on the surfaces in a facility" [4].

What regulatory is expecting from industry

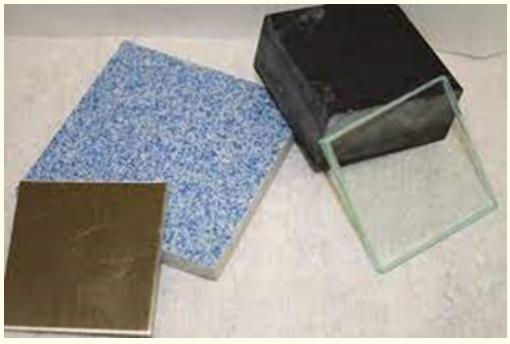

Figure 2

Effectiveness of disinfectants on construction materials that are being used for actual manufacturing surfaces (e.g. epoxy flooring, glass, PVC, aluminium, panel surface etc.), should demonstrate effectiveness against environmental isolates, and demonstrating effectiveness when applied in accordance with the validation protocol or pharmacopeia, such as use dilution, contact time, prepared-solution expiration dating, soil load, application techniques used and so on.

For a variety of reasons, including disinfectant reactivity, porosity, and other factors, the state and composition of the surface might have a negative impact on disinfection performance [5]. Letter of Warning dated April 23, 2019: "You failed to demonstrate that your cleaning and disinfection practices are adequate to remove contaminants from equipment you use to manufacture your (b)(4) drug products. Your determination of the adequacy of your cleaning and disinfection process is limited to a visual examination of the surfaces to detect any contaminants" [6].

Environmental isolates are particularly interesting because they were isolated from the manufacturing environment, implying that they are being brought into the facility on a regular basis and so may constitute a risk to the product. Environmental isolates have been expected to be included in validation studies by pharmaceutical companies since the early 1990s.

"Characterization of recovered microorganisms provides vital information for the environmental monitoring program. Environmental isolates often correlate with the contaminants found in a media fill or product sterility testing failure, and the overall environmental picture provides valuable information for an investigation" [1].

Specific details for disinfectant preparation (e.g. use-dilution concentration, water quality, water temperature, sterilization method etc.), requires wet contact time for the surface, application devices and instructions (mopping instructions and room area), and expiry dates for both the use-dilution and the opened source container of disinfectant or sporicidal should all be included in SOPs.

FDA Warning Letter October 31, 2008, "However your response to our FDA-483 is inadequate because the following were not addressed: Effectiveness of _____ solution at the dilution used, and 2) effectiveness of _____ throughout the shelf life (up to the expiry date)".

In vitro testing

During investigation a variety of prospective disinfectants or sporicidal treatments *in vitro*, it's a good idea to start with suspension experiments. In its most basic form, a suspension study is exposing a known inoculum of a certain organism to a known of disinfectant or sporicidal, for example, for a set amount of time. This form of evaluation provides a quick indication of whether a product and/or set of application conditions (i.e. water quality, temperature, use dilution, contact time) are efficient against a specific organism or group of organisms. Following the completion of the suspension trials, a comparison of the efficacy of various products should allow for the selection of a small number of highly effective products that can then be subjected to more rigorous testing, including coupon studies.

Coupon trials have been the subject of a number of recent FDA Warning Letters. Regulators are particularly concerned that the MOC selection and condition do not accurately reflect both the real MOC and the state of such materials in production regions. "All surfaces used in essential processing and manufacturing areas were not assessed," according to a recent FDA warning letter. (January 29, 2013 FDA Warning Letter) "On about 15 distinct hard surfaces (e.g. Aluminium) found in classified areas used to manufacture sterile products, there is no examination of the effectiveness of cleaning and chemical agents used to suppress microbial populations" (November 1, 2013; GMP Trends).

Figure 3

Aside from the MOC and the state of the coupons, choosing which environmental isolates to test is important. Organisms most commonly isolated from manufacturing surfaces and personnel (e.g. Gram-positive and Gram-negative bacteria), organisms known to show resistance to decontamination or other harsh conditions (e.g. spore-formers, mould), and organisms introduced into the area via known vectors, such as raw materials, water samples, personal monitoring, environmental monitoring, should all be included in the selection. If a facility is freshly operating and a large body of isolates has yet to be developed, a broad spectrum of organisms acquired from ATCC, for example, may be considered.

Regulators will examine additional parts of the *in vitro* study, such as log reduction targets and results, recovery and neutralisation tests, and controls, in addition to MOC and isolate selection. "Your disinfectant qualification for (b)(4) and (b)(4) bi-spore disinfectants documented that the log reduction criteria (Bacteria 4, Fungi 3) was not met when tested with numerous organisms in a range of surfaces," according to a recent FDA Warning Letter. (October 7, 2011 FDA Warning Letter). "There is no guarantee that the disinfectant is effective against mould because it failed to fulfil your established recovery rate acceptance threshold in the "Disinfectant Validation and Efficacy Research by the Surface Test Method" study in December 2001" (May 24, 2007 FDA Warning letter).

In situ testing

Figure 4

In situ (Latin meaning "on site" or "in position) [7] testing shows that the disinfection or sporicidal agent, in combination with the facilities and personnel' preparation and application methods, is successful at maintaining the environmental bacteria levels deemed required for the target product's production. The disinfection program's effectiveness is proved by analysing environmental monitoring data over time and during "worst-case" remedial events. Many companies, for example, may compare environmental data before and after a preventative maintenance shutdown, when the room is more likely to indicate relatively high levels of environmental pollution. As evidenced by regulatory feedback, "There is a lack of written procedures assigning responsibility, providing cleaning schedules, and describing in sufficient detail the method, equipment, and materials to be used for sanitation," [8] it is critical that the procedures used to decontaminate the area during the *in-situ* evaluation reflect the written SOPs. Your company, in particular, lacks established and approved procedures for cleaning and disinfecting equipment and materials" (FDA 483, 11 June 2013). Clearly, the individuals who are assigned to carry out these tasks must get adequate training and supervision. The most common FDA 483 observations are failure to have and/or follow written processes, difficulties with cleaning, sanitization, and maintenance, and failure to offer enough training.

"To demonstrate the efficacy of a disinfectant within a pharmaceutical manufacturing environment, it may be necessary to conduct the following tests...a statistical comparison of the frequency of isolation and the numbers of microorganisms isolated before and after the implementation of a new disinfectant," according to USP chapter <1072>. "The efficiency of these sanitization techniques should be judged by their ability to assure that potential contaminants are adequately removed from surfaces (i.e. via acquiring samples before and after sanitization)," according to the FDA Aseptic Processing Guide from 2004. It goes without saying that evaluating surfaces in order to compare contamination levels before and after sanitization or disinfectant treatment is a requirement for proving disinfectant effectiveness.

Acceptance criteria (Disinfectants efficacy test):

- For contact time establishment there should be minimum 5 log reduction for vegetative bacteria/yeast and 3 log reduction for bacteria spore/fungi (Mold) with a control disinfectant and sanitizing agents.
- For surface coupons studies there should be minimum 3 log reduction for vegetative bacteria/yeast and 2 log reduction for bacteria spore/fungi (Mold) with a control disinfectant application.
- The 2-day hold time study disinfectant in use studies for established contact time should show 5 log reduction for vegetative bacteria/ yeast and 3 log reduction for bacterial spore/fungi (Mold) with a control disinfectant and sanitizing agents stored.
- There should not be any microbial growth in store disinfectant to establish with selected hold time period.

Environmental monitoring and trending

Figure 5

Environmental monitoring techniques, such as frequency, location, and number of samples per sampling interval, should be based on the most up-to-date guideline documents and a scientific justification that is appropriate for the product being created [9]. However, a single day's worth of environmental monitoring data is only a snapshot in time, and it can't provide much helpful information about an industrial area's state of control on its own. The effectiveness of a holistic pollution management programme is further validated by ongoing environmental monitoring with data trends. Any organisms found should be identified to the species level and kept for use in future *in vitro* experiments. Data should be checked on a regular basis to look for undesirable trends; once a month is a good starting point. In addition, criteria for detecting a negative trend must be specified.

Summary

In vitro studies demonstrate how effective the disinfectant or sporicidal agent is under highly controlled conditions; *in situ* evaluations demonstrate how effective the disinfectant or sporicidal agent is under actual use conditions (typically conducted in a worst-case scenario); and routine environmental monitoring with trending and assessment of negative trends are all part of disinfectant validation. While there is no single regulatory or advisory document that serves as a blueprint for developing a disinfectant validation study, there are a number of documents and references, such as FDA 483 observations and Warning Letters that both highlight pitfalls and provide valuable insight into study design.

Conclusion

Before doing any clean area task, especially sterile function handling, it is necessary to select disinfectants with specific varieties of microbial cultures as per pharmacopoeia and environmental isolates.

Bibliography

1. "Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice" (2004).
2. USP <1072>, disinfectants and antiseptics, volume 42. USP (2019).
3. "*In vitro* - Wikipedia".
4. "Disinfectant validation - European Pharmaceutical Review".
5. "Efficacy | Disinfection & Sterilization Guidelines | Guidelines Library | Infection Control | CDC".
6. "Laboratoires Clarins - 568157 - 04/23/2019 | FDA".
7. "*In situ* - Wikipedia".
8. "CFR - Code of Federal Regulations Title 21".
9. Dr. Tarun Chugh and Dr. Apar Dholakia. "Environmental Monitoring in Aseptic Processing Area, Dec 2020 - Jan 2021 Edition by Pharma Machines - Issue" (2021).

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