Disinfectant Efficacy: How Can We Make It Effective?

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Microorganisms are ubiquitous and their numbers as well as their diversity is beyond comprehension. According to the review article by Gibbons and Gilbert (2015), the largest global survey of microbial diversity to date, carried out by the Earth Microbiome Project (http:// www.earthmicrobiome.org/), revealed the existence of 5.6 million Operational Taxonomic Units (OTUs) (97% similarity at the V4 region of the 16S gene; not including singleton OTUs) in the first 15,000 samples, which set a new lower-bound on the number of bacterial and archaeal phylotypes on Earth. In addition, as sampling efforts increase, the number of novel phylotypes discovered continues to rise beyond prior estimates, and far beyond estimates for multicellular organismal diversity.[1] This gives us an idea about the complexity, resilience and evolutionary capability of the microbial world. It is important to keep this view of the microbial world in perspective when we are considering activities such as cleaning, sanitization, disinfection and sterilization. In other words, removal or killing of microorganisms to keep our product and patient safe. In this article, the topic of disinfection and sanitization will mainly be covered and considered as a chemical agent. It will also be covered from the standpoint of their application being on environmental surfaces.

It is important to understand the definitions of these terminologies of microbial reduction or killing. According to USPa disinfectant is a chemical or physical agent that destroys or removes the vegetative forms of harmful microorganisms when applied to a surface.[2] CDC describes disinfection as a process that eliminates many or all pathogenic microorganisms, except bacterial spores, on inanimate objects. Disinfectants are antimicrobials applied only to inanimate objects.[3] According to US EPA, disinfectants are used on nonliving surfaces and objects to destroy or irreversibly inactivate infectious fungi and bacteria but not necessarily their spores. The EPA has divided disinfectant products into mainly two major types:[4]

A. hospital type disinfectants are critical to infection control and are used on-medical and dental instruments, floors, toilet seats and other surfaces;
B. general use disinfectants are the major source of products in-households, swimming pools and water purifiers.

USP<1072> describes Sanitizers as an agent for reducing, on inanimate surfaces, the number of all forms of microbial life including fungi, viruses and bacteria. According to the CDC, a sanitizer is an agent that reduces the number of bacterial contaminants to safe levels as judged by public health requirements. Commonly used with substances applied to inanimate objects. Similarly, according to the EPA, Sanitizers are used to reduce, but not necessarily

codes or regulations. EPA also further delineated sanitizers between those designed for food contact and non-food contact.

It is important to understand the EPA's definition of these terminologies as in the United States, chemical germicides formulated as sanitizers, disinfectants, or sterilants are regulated in interstate commerce by the Antimicrobials Division, Office of Pesticides Program, EPA, under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1947, as amended. Under FIFRA, any substance or mixture of substances intended to prevent, destroy, repel, or mitigate any pest (including microorganisms but excluding those in or on living humans or animals) must be registered before sale or distribution. To obtain a registration, a manufacturer must submit specific data about the safety and effectiveness of each product. For example, EPA requires manufacturers of sanitizers, disinfectants, or chemical sterilants to test formulations by using accepted methods for microbiocidal activity, stability, and toxicity to animals and humans. The manufacturers submit these data to EPA along with proposed labeling. If the EPA concludes the product can be used without causing "unreasonable adverse effects," then the product and its labeling are registered, and the manufacturer can sell and distribute the product in the United States. FIFRA also requires users of products to follow explicitly the labeling directions on each product (this is mainly applicable for healthcare workers utilizing the product).

It is also important to note that in general, EPA regulates disinfectants and sterilants used on environmental surfaces, and not those used on critical or semi-critical medical devices; the latter are regulated by FDA. Within the definition of the disinfectant and sanitizer, the words harmful/pathogenic/infectious are used because EPA has divided antimicrobial products into two categories based on the type of microbial pest against which the product works:

A. non-public health products and
B. public health products.

Disinfectants and Sanitizers as well as Sporicides fall under the category of public health products and are intended to control microorganisms infectious to humans in any inanimate environment.

Product performance guidelines are outlined by EPA in Product Performance Test Guidelines OCSPP 810.2300 (sanitization) and OCSPP 810.2200 (disinfection). Even though it might not be enough to choose the product intended to use as a disinfectant in a drug/ device manufacturing environment, it is key to understand these test requirements and acceptance criteria as they involve the differences in the microbial load reduction criteria between a sanitizer and a disinfectant, the microbial types and concentration used in the test, the contact time, the type of sanitizer and disinfectant (e.g. non-halide products, water soluble powders, liquids, spray, towelettes) used, surface types against which the tests were performed etc.

It is important to verify this information against the product and its claims selected for use in the manufacturing facility as USP<1072> clearly states that when selecting a disinfectant for use in a pharmaceutical manufacturing area the following points should be considered among others: the spectrum of activity of commercially available disinfectants, the disinfectant or sanitizer supported by the EPA registrations, the concentration, application method, contact time of the disinfectant, the nature of the surface material being disinfected and its compatibility with the disinfectant, and the amount of organic compounds on the surface that may inactivate a disinfectant. All these factors will play a key role in not only the primary selection of a disinfectant but also in the design of your facility's Disinfectant Efficacy (DE) study, which is required to be more appropriate for the manufacturing environment as the EPA registration requirements do not address how disinfectants are used in the pharmaceutical, biotechnological, and medical device industries, however, the EPA categorizes Disinfectants, Sanitizers and Sporicides as public health products and are intended to control microorganisms infectious to humans in any inanimate environment.

According to USP<1072>, to demonstrate the efficacy of a disinfectant within a pharmaceutical manufacturing environment, it may be deemed necessary to conduct the following tests:

1. Use-dilution tests (screening disinfectants for their efficacy at various concentrations and contact times against a wide range of standard test organisms and environmental isolates);
2. Surface challenge tests (using standard test microorganisms and microorganisms that are typically environmental isolates, applying disinfectants to surfaces at the selected use concentration with a specified contact time and determining the log reduction of the challenge microorganisms) and
3. A statistical comparison of the frequency of isolation and numbers of microorganisms isolated prior to and after the implementation of a new disinfectant.

It is well known in the industry that DE studies are not only labor intensive, but they are expensive as well. In order to leverage value added information and apply them in routine cleaning and disinfection practices it important to

Before carrying out a DE study it is important that a cross functional team is created inviting members with different expertise to adequately design the study. At a minimum a SME from the department of engineering, manufacturing and microbiology should be included, respectively.

Points to Consider

• **Selection of Chemical Agents:** This is one of the most important factors and multiple things should be considered during the selection of the chemical agents:

A. The type of the chemical and its mode of action;
B. its compatibility with the surfaces on which they are going to be applied;
C. its compatibility with other chemicals;
D. safety concerns and the PPE requirements;
E. the reliability of the supplier and their business continuity plan for uninterrupted supply.

It is important to keep in perspective that the selected chemical is tied to the manufacturer of the chemical, if the manufacturer or the formulation of the chemical changes, a new DE study might be warranted. The last but not the least item is to thoroughly review all the manufacturers information (direction of preparation, use and storage, safety concern, claims and their associated data) for the selected chemical agent. It would be beneficial if the disinfectant has a biofilm claim. Additional items to consider with the selection of the chemical agent is the quality of the water that will be used to dilute the chemical; the pH range of the chemical solution as well as the temperature range. It is very important to keep into perspective that pH plays a very critical role in the efficacy of disinfectants[3,5] and must be considered during the DE study as well as during routine use of the chemicals for facility disinfection. As a matter of fact, the pH can be used as an indicator to understand the quality and stability of the prepared disinfectant, especially for chlorine-based disinfection.

• **Selection of Challenge Organisms:** The panel of microorganisms selected for the DE study plays a very critical role in assessing the efficacy of the disinfectant. Apart from using standard AOAC challenge organisms, the value is in using typical environmental/facility isolates. If not all, some information on the performance of standard AOAC challenge organisms can be obtained from the studies performed by the manufacturer for the purpose of the EPA registration of the product.[6] Moreover, as we know that microorganisms differ from one another not only at the species level but also at the "strain" level. This difference is also attributed against the efficacy of antimicrobials. From a best practice one word it will be prudent to use a combination of AOAC and in-house isolates as challenge microorganisms. A rationale should be used and documented for the selection of the microorganisms for the efficacy study. For in-house isolates it is not only important to have a laboratory procedure for sound preparation, maintenance and storage of microbial cultures but it is also important to ensure that culture are always maintained and used within five passages to mitigate genetic and phenotypic variations so that they could still be considered environmental isolates as within each subculture there is a potential for variation. A good time to create the in-house isolates library is during the initial survey of the facility areas (i.e. microorganisms isolated prior to implementation of the new disinfectant). Therefore, performing the initial survey of the locations is an important task and indirectly adds to the efficacy of the disinfectants.

• **Selection of Surface Types:** During the initial survey of the facility areas, it is important to determine all the surface types on which the chemical agents will be applied. Include all those surface types to the DE study. In the past many companies have received regulatory agency citations during inspections for not including all surface types in their DE study on which the facility disinfectants are routinely applied. A couple of important things to consider during surface selection:

A. the compatibility of the surfaces with the chosen chemical agent and this is performed preliminary in parallel with the selection of the chemical agent. Today most of this information can be obtained from the manufacturer of the chemical agent;
B. the contour of the surface type that should be used in the study. Should study be performed on completely new surfaces or should be performed on surfaces mimicking those to be used? The coupon materials representing the surface type should be prepared accordingly; and
C. decision should be made to consider whether to include any soil in the study.

If the facility does not have a separate cleaning step, it would be prudent to use a soil in the DE study as it is well known that the efficacy of disinfectants is impacted by the amount of soil load present on surfaces. Usually, a 5% serum is used in the study to simulate soil conditions to determine the efficacy of the chemical agent.

• **Selection of Contact Time:** This is the single most important factor which influences the effectiveness of the

A. the type, characteristics and concentration of the chemical agent;
B. the type and concentration of the microorganism;
C. the type of surfaces on which the microorganisms are present;
D. the type and concentration of soil present; if the chemical agent is going to be applied on a biofilm as organisms hidden within biofilms are not only difficult to reach but the biofilm state of cells is more resistant than their planktonic counterparts.

Unfortunately, this single most important factor which determines the efficacy of a disinfectant is not only difficult to adequately determine but also it is difficult to enforce and achieve during routine applications.

The most common way of achieving the contact time during routine application is to ensure that the surface is kept visibly wet for the full contact time indicated on the product label or as determined by the DE study. The contact time, also known as the wet time, is the time that the disinfectant needs to stay wet on a surface in order to ensure efficacy. Contact times for disinfectants range from fifteen seconds to ten minutes, the maximum time allowed by the EPA.[7] Disinfecting products usually include directions that instruct users to ensure that the surface is visibly wet for the contact time. For the drug/devices manufacturing facility the contact time/wet time is determined by the DE study, however, it will be important to understand how the DE study is conducted to determine the contact time and if it is aligned with how the agent will be used for routine application (discussed below). This practice does have its challenges though. Keeping a surface visibly wet can be difficult for disinfectants that require a long contact time, such as ten minutes. Under some conditions, such as high temperatures and low humidity, it can also be difficult even for disinfectants with contact times as short as three or four minutes to stay wet. It is particularly challenging for disinfectants with high alcohol content, which evaporate quickly. If the disinfectant does dry on the surface before the contact time is reached, label instructions usually require reapplication to ensure that the contact or wet time is met.

EPA regulations require data to support disinfecting claims. Data requirements are not specific or consistent around the requirement to keep the surface visibly wet for the full contact time and are also dependent on the microorganism against which a claim is obtained. For example: The EPA Standard Operating Procedure for germicidal (disinfectant) sprays does not specify whether the carrier containing the microorganism under testing must remain wet for the duration of the contact time. The EPA Standard Operating Procedure for towelettes or wipes requires that wiped carriers are left in covered petri dishes for the duration of the contact time. Although it does not specify whether the carrier surface should remain visibly wet for the duration of the contact time, the closed environment created by covering the petri dish reduces drying. Therefore, it is important that the DE study is conducted in a way that it is aligned with how the chemical agent will be routinely applied in the facility. The contact time must be data driven, realistic and achievable for the chemical agent to be effective.

Another example is with the sanitization of the gloves. It is important to conduct the DE study in a way that it is aligned with how the sanitizer will be applied on the gloves so that the contact time is realistic and achievable.

• **Selection of Correct Neutralizer:** Appropriate neutralizer should be included in the study to inactivate the disinfectants. Neutralizer should be included in either the diluent or microbiological media used for the microbial enumeration or both. In addition to this it is also important to incorporate the appropriate neutralizer in the microbiological media used for routine surface monitoring.

• **Selection of Laboratory:** Selection of a laboratory plays a very important role in the execution of a successful DE study to generate meaningful data as the experiments are technique oriented, labor intensive and lengthy. If the study is conducted in-house it is key to select the right laboratory personnel to execute the activities. If outsourced, it is important to select a laboratory, which has proven and adequate capability, knowledge and expertise in the area of DE. Selecting a vendor based solely on cost may not be a good idea for a DE study as it might become more costly in the long run due to inconsistent data, data inaccuracies and method execution issues. In addition, these studies will be reviewed during agency inspection and audits and thus important from both quality and compliance standpoint. The cleaning and disinfection program and environmental monitoring is not only important for products that are aseptically filled but also for non-sterile and terminally sterilized product. It is of immense importance for terminally sterilized products that are approved for parametric release.

As per USP<1072>, Issues associated with the successful imple- mentation of cleaning and disinfection program are the development of written procedures, staff training, decision on disinfectant rotation, institution and enforcement of application methods and contact times, environmental monitoring to demonstrate efficacy and personnel safety. Staff training plays a very critical role in the implementation and effectiveness of the cleaning and disinfection program post DE study. The staff should have basic training in microbiology, understand the importance of contact times, expiration dates, importance of water quality in the preparation of the disinfectants, standard training for cleaning and

procedures. Material Safety Data Sheets (MSDS) for all the disinfectants used in a manufacturing area should be available to personnel handling these agents. Appropriate safety equipment such as face shields, safety glasses, gloves and uniforms must be issued to personnel handling the disinfectant and personnel must be trained in the proper use of this equipment.

Conclusion

An effective cleaning and disinfection program is required for controlled environments used in the manufacturing of medicinal products to prevent microbial contamination and deliver quality products thus enhancing patient safety. Selection of suitable chemical agents for the purpose of cleaning and disinfection is a challenging task. All appropriate due diligence should be performed before execution of the DE study as already being mentioned DE studies are not only expensive but also requires sound technical capabilities so that meaningful data could be generated. It is important to note that DE studies are performed under controlled laboratory conditions within defined parameters, which are different from the dynamic conditions of the manufacturing environment. Thus, along with performing the study adequately, the data should be interpreted so that the information can be leveraged during routine cleaning and disinfection of the facility. Environmental monitoring data and the recovered microorganisms should be reviewed to determine the state of effectiveness of the disinfectants and if required the most frequently isolated microorganisms from an EM program periodically must be subjected to use-dilution testing.

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