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ADVANCING DEVELOPMENT AND MANUFACTURING

Prevention of Microbial Contamination

A holistic approach to establishing robust control measures.

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A recent bestseller tackled the question of why an entire nation can be compelled to help one or a few people in life-threatening situations (e.g., Chilean miners), but will do little to help millions who are at equal or greater risk (e.g., tsunami victims) (1). This concept may be irrational, but it is an accurate portrayal of the difficulty in working toward abstract goals based on concepts or proportions that are near impossible to grasp. Saving one nearby person is far easier to conceptualize than saving millions who are suffering in a distant land. In situations such as these, the tendency is to turn away because we cannot visualize how to effect change in something that we do not understand. This phenomenon also plays a role in environmental control of drug-manufacturing spaces. We are asking personnel to exercise a great deal of caution and follow rigid protocols designed to prevent contamination of the drug by invisible entities that number in the millions. To put it simply, those who work in crucial manufacturing areas have an innate tendency to underestimate the impact they have on controlling a large complex system, nevermind what subsequent effect that may have on public health, which really can be the outcome of poor manufacturing control as evidenced by recent influenza vaccine shortages and product recalls (2,3).

Effective management of drug-manufacturing areas requires a holistic approach based on identifying and monitoring those components that play the most critical roles: facility (design and conditions), personnel (training and management), and microbial control programs (products and application). A holistic, multidisciplinary approach relies heavily on metrics to address and understand the behaviors of complex systems.

Facility design

Figure 1: Water damaged wall covered with mold. (FIGURE 1: PHOTO BY JIM POLARINE)

The best defense is a good offense, especially when there are millions of dollars and the public health at stake—not hyperbole when talking about vaccines and other biotechnology derived drugs. In these cases, where terminal sterilization is typically not an option, a strong offensive position begins with a robust facility design that insulates the drug and packaging components from sources of contamination. This design must include adequate barriers (e.g., interlocking doors, clear zone demarcation), enough HVAC capacity to handle seasonal fluctuations in temperature and humidity, water control (e.g., placement of drains and water-for-injection drops), cleanable design features (e.g., smooth coving, limited obstructions), and the selection of chemical and moisture resistant materials of construction (e.g., 316L stainless steel, epoxy or polymeric flooring) to name but a few considerations. When budget, time, and expertise is unlimited, design and construction of a drugmanufacturing facility optimized to prevent product contamination can be easily achieved. However, in a less-than-optimized environment, the design and facility condition are often contributing factors to microbial excursions, and in some cases, product contamination.

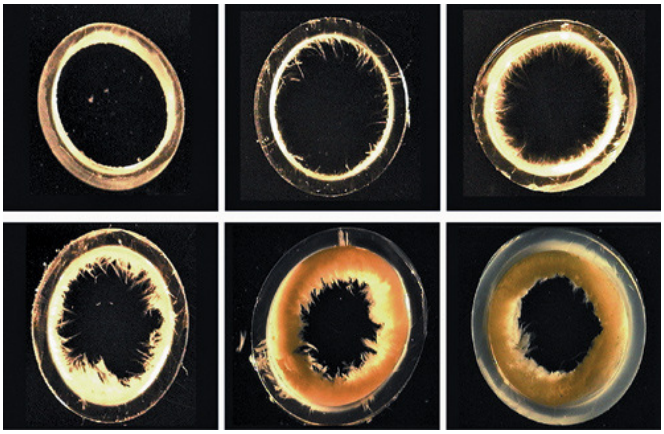

Figure 2: Biofilm formation in pipes. (FIGURE 2: ADAPTED WITH PERMISSION FROM MONTANA STATE U. CENTER FOR BIOFILM ENGINEERING)

Even stainless steel may suffer the effects of chemical exposure, or overexposure, resulting in rust. Rust and pitting present challenges to effective microbial control in two ways: by providing shelter to microorganisms and residue, and by inhibiting cleaning and decontamination agents from reaching microbes to achieve adequate contact time. Stainless steel is not the only surface that can be damaged. Epoxy and polymeric floors can suffer significant damage from high foot traffic or the force of moving heavy equipment—and are not immune to the effects of significant chemical exposure. Both scenarios may lead to pooling water and associated microbial control problems, such as mold and *Bacillus* proliferation. Significant water damage to the structure can lead to endemic problems with molds and *Bacillus* (see Figure 1). Drainage issues can result in biofilm formation (see Figure 2), which cause significant, recurring problems with *Bacillus* and other bacteria due to increased resistance to antimicrobial chemistries demonstrated by biofilms (4).

Another necessity of good design is the inclusion of sufficient barriers to isolate the drug manufacturing process. Older facilities or facilities that were not originally designed for this purpose may not have an ideal barrier design. The warehouse or component staging areas, for example, may not be ideally located to prevent egress of undesirable particulate. It may not be possible to establish one-way traffic because of structural limitations. In both cases, contamination control is more problematic and, consequently, the drugmanufacturing process is more difficult to manage.

The most common approach to microbial control problems due to facility design flaws or damage is to increase the use of chemical antimicrobial products by concentration, frequency, or both. Extremely aggressive chemical agents, such as acidified bleach, may also be used on a short-term basis. While these measures may result in immediate improvements in environmental monitoring data, in the long run, this approach may lead to even more damage and, thus, less ability to control the environment in the future. The best solution to establish a high degree of control is to repair or retrofit the facility as required, which, although costly, is perhaps less expensive than the alternative of chasing root causes of microbial excursions or product contamination and rejection.

Personnel compliance

In addition to microbial efficacy, the question of the role that disinfectant and cleaning agent residues play in environmental

The personnel who work in asepticmanufacturing areas continue to represent the greatest threat to drug production. Human beings are prodigious bioreactors; by some accounts, 90% of the cells on the human body are microbiological in nature (5). Furthermore, even with the most robust training programs, cleanroom personnel do not always adhere to good aseptic practices, generally through thoughtlessness alone. Willful deviations from standard operating procedures may intend to mitigate the risk of failing environmental monitoring data. Spraying sterile isopropyl alcohol on gloved hands or Tyvek suits immediately prior to plating, for example, may reduce the risk of failing results, but is never condoned. Other deviations from standard operating procedures and aseptic practices are more difficult to categorize. During a training event, an operator spoke of adding unapproved household dish detergent to the validated disinfectant solution used in the classified cleanroom in order to produce more foam, which was essential to good cleaning, they believed—a fallacy that can be dispelled through training. Though the intention was noble, the behavior was still not compliant with cGMP practices and, at the very least, placed management in a poor regulatory situation. In a worst-case scenario, it may have compromised the performance of the disinfectants putting the drug at risk.

There are hundreds of ways that an aseptic environment can be compromised through the well-meaning efforts of insufficiently trained and monitored personnel. The key to reducing operating risk is to incorporate a solid cGMP platform in the training program. This platform should draw on the evolving history of drug production, incorporating real-world examples of the damage that adulterated drugs represent to human health. Everyone knows someone who uses pharmaceuticals at least periodically and understanding what the risk of poor production control represents to a friend, loved one, or to oneself helps to personalize the message and drive more thoughtful behavior. Basic training in microbiology, antimicrobial chemistry, and cleaning techniques can ensure greater compliance by establishing a solid rationale for why certain products and conditions are used. In other words, through education, a large complex system that requires the control of millions of invisible objects can be scaled to a level that the cleanroom operator can understand and embrace. And once training is delivered, it must be reinforced through frequent management interaction. However, as operation management spends more time away from the manufacturing floor, there is less opportunity to observe behavior and a chance that oversight of problems may occur.

control has become a more urgent concern (see Figure 3). Most

Enviromental controldisinfectants and cleaning agents contain ingredients that are nonvolatile. In many cases, these are inert substances;

however, the impact of these residues should be evaluated with regard to subsequent cleaning and environmental monitoring activities. The evaluation is performed to ensure that cleaning solution residues do not negatively impact environmental sampling or testing. (11). In short, it is prudent to incorporate a strategy into your cleanroom contamination control procedures. This strategy should identify the frequency in which cleaning and microbial control takes place varies from site to site, in part because of differences in facility design and production needs. However, there are guidance documents and best practices that should be incorporated into the cleaning and microbial control strategy (6, 7).

Cleaning is a cGMP requirement. The environment must be controlled to prevent particulate and microbial contamination of the drug, packaging components, and product contact surfaces. The manner in which products, application methods, and finishing agent, frequency of rinsing and specific application procedures. Further, if a rinsing agent other than purified water is used (e.g., isopropyl alcohol that leaves no residue), is to be used, then the nature of the residues being introduced must be considered. Frequency of application needs to be assessed on the basis of "risk versus reward." Introduction of water or other rinsing agents too frequently, especially immediately following disinfection, may lead to further microbial control challenges through dilution of the disinfectant before sufficient contact time is achieved for optimum performance. Environmental monitoring data must demonstrate a state of sufficient control to prevent adulteration of product in an environment where the facility operates.

There are also practices that are not universally applied or sometimes well-understood. One such practice is disinfectant/sporicide rotation. The term itself has undergone change over the past decade or so. In the past, rotation implied alternating use of two broad-spectrum disinfectants of similar chemistry (e.g., two phenols or two quats). By rotating two different formulations with similar active ingredients and different chemical or physical properties (e.g., pH, alkalinity), one might address a broader spectrum of microorganisms (e.g., bacteria, fungi, viruses), while minimizing the development of problematic residues that may occur from the interaction of two different, and potentially incompatible chemical species. At this time, the above type of rotation is still prevalent as evidenced by recent FDA 483 observations, "The firm failed to follow written procedures for cleaning and disinfection of Class 10,000 rooms, in that, production personnel do not alternate cleaning and disinfection agents for sinks and flat surfaces, as dictated in SOP..." (8). However, as the need to control more resistant organisms, such as fungal spores and bacterial endospores, becomes greater, rotation programs are often refined to include the use of a sporicide. This model of alternating routine disinfectants, or one routine disinfectant, with a sporicidal agent, is fast becoming a regulatory preference, and is noted in various regulatory and advisory documents, including *USP* <1072> "Disinfectants and Antiseptics," in *USP* 32 –*NF* 27: "It is prudent to augment the daily use of a bactericidal disinfectant with weekly (or monthly) use of a sporicidal agent. The daily application of sporicidal agents is not generally favored because of their tendency to corrode equipment and because of the potential safety issues with chronic operator exposure. Other disinfection rotation schemes may be supported on the basis of a review of the historical environmental monitoring data."

Selection of disinfectants and sporicides should be made based upon scientific evidence of efficacy against the target spectrum of organisms, as well as other important considerations, such as substrate compatibility and operator safety. Sources that provide information on the mechanisms by which different chemical entities work against the structures of various microorganisms are too numerous to count and can certainly aid in the selection of disinfectants and sporicides (9). However, scientifically-based references and conventional wisdom used to select these products does not alleviate drug manufacturers of the requirement to validate disinfectants, sporicides, and even isopropyl alcohol for use in facilities under actual use conditions against environmental isolates. According to FDA, "Disinfectant agents used to sanitize surfaces in the aseptic processing areas (APA) have not been adequately qualified to assure that they provide the intended microbial decontamination when used in the manner as specified in the standard operating procedures as follows: a. The qualification study only evaluated stainless steel and not other surfaces in the APA such as glass, plastic and epoxy painted surfaces. b. The qualification study used a longer exposure time to the sanitizing agent then that time specified in the cleaning SOPs. c. The qualification study immersed the test surface in the disinfectant for ... Instead of wiping the surface as specified in the SOPs" (10).

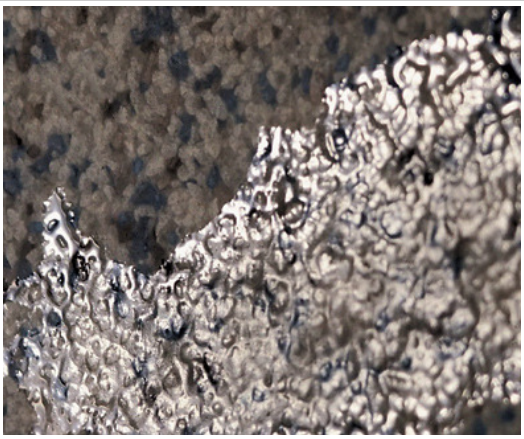

Figure 3: Disinfectant residue on epoxy flooring. (FIGURES 3 & 4: STERIS CORPORATION)

Figure 4: Disinfectant residue on vinyl flooring.

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