Critical Cleaning Bulletin

Disinfectant Selection and Rotation

Background:
Back in the late 1980's, a few regional FDA inspection offices were citing "failure to use more than one disinfectant agent" to treat environmental surfaces. Recently the 1997 and newly revised 2002 EU cGMPs also called for the use of more than one agent for Grade A/B areas. Although the FDA's concern back in the 80's and 90's was using a sufficient range of agents in order to provide the required spectrum of kill, a large number of firms responded by using quat based and phenolic disinfectants on alternating weeks or months, a practice commonly called "rotation". This was primarily the result of disinfectant vendors suggestions and internal concerns over the possibility of developing resistant organisms to only one chemical agent. Most of these same firms were also still using bleach or glutaraldehyde to control bacterial spores and molds on a once per week, or once per month or as-needed basis.

The result of alternating cationic(+) quats and anionic(-) phenolics without thorough rinsing between is a reaction that actually can deactivate disinfectant active ingredients and creates residues. Most of the "rotating" firms reported the buildup of these discoloring residues. In response, a different practice was promoted by one supplier: alternating the same or compatible active ingredients but formulated in different pH solutions. Thus, organisms would be exposed to a very different pH challenge from time to time, alternating by pH. A widely utilized approach of this type was alternating between daily use of a low pH phenolic and an alkaline phenolic on a monthly or quarterly rotation.

As previously discussed, the EU and US FDA have an expectation that more than one agent is used for microbial control. The term "rotation" is often used, adapted from misconceptions and industry practices. For firms who choose to "rotate" disinfectant agents, there are numerous options to use more than one type of active ingredient in a compatible rotation or in ways that do not reduce biocidal efficacy or create residue problems. For example, Quats are excellent cleaning and general purpose agents and are compatible with bleach, iodophors, peroxygen and glutaraldehydes, alternated for higher level kill. If a firm does a careful rinsing/removal step between rotated agents compatibility is less an issue. The real question is, "do I really need to rotate agents to prevent the development of resistant organisms?"

Resistant Organisms- Reality or Myth?
There are large numbers of references related to microorganisms developing resistance to antibiotics and biocides. When large numbers of organisms receive sublethal exposure over extended time, survivors can select for resistant characteristics, shifting the population to adapt and develop resistance to the chemical agent through genetic selection and modification. While primarily a problem related to antibiotics in living systems, problems in water systems, cooling towers, and even in disinfectant containers and solutions have also been reported after misapplication or misuse of agents. (References are attached)

Generally however, the conditions leading to resistant strains are absent from the pharmaceutical /medical device critical environment. Bacterial populations are very small, survivors are few if any, due to the overkill concentrations built into the proper use of the agents. The concentrations applied are proven to completely deactivate 10^5 bacteria in the prescribed time. Typical bioburden is several orders of magnitude lower (5-100 CFU per RODAC plate). An approved agent from a reputable vendor will be effective against the intended organisms when used as directed.

A recent article in Controlled Environments by Scott Sutton provides an excellent review and discussion of this issue. In "Disinfectant Rotation- A Microbiologist's View" the author makes a similar, compelling argument that genetic microbial adaptation is not a risk in the pharmaceutical clean room. *"The need for the rotation of disinfectants in a pharmaceutical cleanroom sanitization program is not supportable from a scientific basis"*. The article was in response to a previous article by a technical manager from STERIS, a supplier of disinfectants. The text of both articles is attached.

As this article points out, for most disinfectants, the issue is not *developing* resistant strains but the known fact most agents have known organisms with *inherent* resistance due to the chemical nature of the active ingredient. Some examples: with only a few exceptions, quaternary ammonium actives will not kill tuberculosis causing mycobacteria. Phenolics will not deactivate some viruses at normal bactericidal concentrations. Alcohol, phenolics, quats and iodophors will not kill gram positive Bacillus or Clostridia spores. The agents that do act as chemical sterilants or that have killing affect on bacterial spores have their own practical limitations regarding corrosiveness, toxicity, irritation, odor, and cost.

A Rational Approach

CANI's recommended practice is also discussed in this article by Sutton. *"We, in fact, are not discussing rotating disinfectants at all. Rather we are urging the routine use of an effective disinfectant with the periodic use of a sporicide [39, 40]."* It also mentioned by Sartane in her article. The best reason to alternate agents is not to prevent developed genetic resistance but to achieve predictable, consistent microbial control that is practical, achievable and verifiable. By using a high level spore control agent on a periodic but infrequent basis, in conjunction with routine daily use of a good general purpose disinfectant, firms can achieve the needed full spectrum of microbial control, periodically shift the chemical exposure to the few remaining organisms and not have to pay the high cost of attempting to "chemically sterilize" as a routine. Generally three agents can be employed in an effective control program:

1. quat, phenolic, or general disinfectant for floors walls and non-critical equipment,
2. alcohol as stand alone cleaning agent for near-product contact or critical surfaces, or as a second step for removing disinfectant residues; alcohol will evaporate at room temperature and leave no or low residue.
3. An agent to control bacterial spores that get past the gowning, pass through barrier. This can be bleach or other hypochlorous acid source, chlorine dioxide, glutaraldehyde or peroxygen/peracetic acid/peroxide solutions. The chosen spore control agent can be scheduled on a set frequency or utilized on an "as-needed' basis in response to monitoring. Selection of a high level agent is a separate topic covered in another bulletin.

This approach uses multiple agents with different actives, modes of action and chemistry and satisfies the regulatory requirements and concerns about using multiple disinfectants in a rational way.

 Contact: Steve Weitzel

Sample disinfection protocols and products:

To meet microbial control and cGMP requirements, several options are available depending on the current practices, prior track record or preferred type of chemistry. The following table is a brief summary.

Chemical Program I., Phenolic based, is the current choice for many drug facilities. Given environmental restrictions on phenolics in some areas and alternate approach is needed.

Program II. Provides the same control without phenolics and without use of second routine agent. A more complete guide to facility environmental control is available.

Typical Protocol for Grade A-C	**I. Phenolic Based**	**II. CANI Program**
1.A. General Disinfectant	low pH Phenolic Disinfectant (compares to LpHse)	CANI HI-CON 256 NPD
1.B. Alternating Disinfectant	Alkaline Disinfectant (compares to Vesphene IIse)	
2. Critical Surfaces Primary residue removal or second step	70% IPA	XTRAclean 70% IPA
3. Spore Control	Bleach solution Spor-Klenz, Others	CP-722 Minncare Actril
Discussion:	Proven type of chemistry and program at numerous pharma facilities. Compatible with most spore control agents.	Better cleaning and residue removal than phenolics, safer neutral pH, reduced waste disposal,

Phenolic Rotation vs. CANI Comparison

Vesphene and LpHse are “phenolic” disinfectants, meaning the active ingredients are derivatives of phenol. LpHse is a “Low pH” acidic agent used at ½ oz. per gallon water, Vesphene is an alkaline or high pH agent used at 1 oz/gal. The phenolic disinfectants were first developed for hospitals because they can kill 10^5 TB mycobacteria. The LpHse is a very good disinfectant with extensive lab testing against numerous organisms. Vesphene is not as effective and not at all cost effective. Vesphene costs twice as much as LpH to use. It is only used because of a common but mistaken practice of “rotation” which biopharmaceutical contamination microbiologists and other experts have debunked as shown in this technical bulletin. You would be better off using LpHse alone for general use combined with a sporicidal agent on a weekly or monthly frequency.

That is our recommendation for the CANI HI-CON 256 NPD, a neutral pH quaternary ammonium base disinfectant. It is used at 1/2oz. per gallon for routine daily use. A second agent that controls bacterial spores can be used periodically or in response to environmental monitoring. We have chlorine based and peroxygen based agents that will control spore forms. We also can supply presterilized alcohol for low residue surfaces. CANI HI-CON 256 as part of a program for facility microbial control will control environmental micro counts the same or better than the phenolic program. I will also send a detailed comparison table for quick reference.

Sanitization-minimum contact time required to work.

Like LpHse, HI-CON 256 NPD is used at 10 minutes contact time and has an extensive list of tested efficacy on a wide array of microorganisms in the 10 minute time frame. HI-CON 256 will keep all vegetative forms of bacteria under control and will completely kill 5 logs with the exception of TB which is not an issue in manufacturing areas. It also has extensive virucidal claims.

Environmental friendliness

Among other typical selection criteria are several other reasons that phenolic agents are being replaced. Many waste disposal districts have placed restrictions on phenolic discharge. The waste disposal and environmental issues with phenolics require a very strong reason to keep them when agents like HI-CON 256 can do the same job without the issues. The benefit of TB kill does not apply, there are frequent applications of sporicide which control it even if it did.

Toxicity, Effect/Safety of Users or employees

Disposal-does it go down the drain or special tanks?

HI-CON is a neutral pH agent. *LpHse is an acid, pH 1.0 at use dilution*. This is a lower pH than many closed CIP acid cycles which are considered hazardous. Although both agents can be safely mixed, applied and disposed of when used as directed there are fewer practical issues with the neutral pH not only with waste disposal but with exposure in the workplace. The MSDS and label information provide detailed information on safety and disposal issues. The CANI HI-CON residuals can go down the drain without going to a neutralization tank as with LpH.

Slip resistance or build up on floor.

Both types of agents have nonvolatile ingredients that will leave trace residues when left unrinsed to dry. These residues generally do not pose an aesthetic or particulate generating issue but it is recommended for both types of agents that a monthly to quarterly periodic purified water rinse or mild detergent cleaning be done if residue become a concern. The slip/safety issues for the two types of agents are similar. When properly applied and maintained, floors treated with HI-CON do not have increased slip hazard vs. wet floors without HI-CON.

CANI Product Descriptions:

HI-CON 256 NPD: Multipurpose Neutral pH Germicidal Detergent

The preferred disinfectant for general use in cosmetic, drug and device facilities and for animal infection control. At 1:256 dilution, effective against a broad spectrum of Gram negative and Gram positive bacteria, fungi and viruses such as Rabies, and HIV-1.(Extensive test results are included in the Product Data brochure.) The tests were done in the presence of hard water (400 ppm as $CaCO_3$) and 5% organic serum. *No perfume or dyes.*

CP-722: 12% Liquid Hypochlorite Sanitizer

Rapid, economical sanitation from a proven chemistry. Can be used in industrial, processing and animal facilities applied by spray, immersion or in clean-in-place (C.I.P)

Minncare: Disinfectant Sporicide concentrate

Peractic acid and hydrogen peroxide based. Used at 1:100 dilution as a high level disinfectant

Actril: Ready-to-Use Disinfectant Sporicide

Peractic acid and hydrogen peroxide based. Compares to Spor-Klenz RTU

XTRAclean, XTRAClean 2, XTRAclean WFI: 70% Isopropyl alcohol solutions

Pre-sterilized, double bagged alcohol solutions for residue removal in critical areas.

The following is the text of the article published in the July 2005 Controlled Environments Magazine.

Disinfectant Rotation - A Microbiologist's View, Scott V.W. Sutton, PH.D, Controlled Environments, July 2005

I HAVE MODERATED THE PMFLIST, an email discussion list on the Internet dedicated to topics of interest to microbiologists in the pharmaceutical and personal care industries; a list that has been active since 1996 (http: //www.microbiol.org/pmflist_info.htm). I mention this only because in that time I have had the opportunity to develop a perspective on issues that interest the working microbiologist. Occasionally, the odd topic will really catch fire in the discussion group. This happened recently in response to an interesting article that appeared in the March 2005 issue of A2C2 Magazine [1] dealing with the advisability of disinfectant rotation. In this thoughtful article, the author argued for the need to "rotate" a disinfectant with a sporicide. The interest in this topic initially came as a surprise to me, as I had thought the issue long since resolved in the pharmaceutical and personal care industries.

As the discussion continued on the PMFList, the points of contention became more clear. A great deal of discussion revolved around the concept that a microorganism could become resistant to a disinfectant. Here is where the first bit of clarification is required. A microorganism will not become resistant to much of anything. It either is or it is not affected by the compound. Within a very large population of microorganisms, there is a chance (normally a chance of approximately 10-6) that a cell within the population will have a mutation at a specific gene. This might provide some competitive advantage under some environments, perhaps survival in the presence of an elevated level of a chemical. The mutation that promotes survival under these conditions could, over the course of a few generations, become the dominant genotype in that population. This is, of course, assuming that the challenge is not too great. For example, it does not matter how acidotolerant a particular mutant is, growth in 6N hydrochloric acid is just plain unlikely—the conditions are too inhospitable to life.

Can a low level of exposure to biocides select variants in a population that are more tolerant than the previous dominant type? Can low level exposure select "resistant" microorganisms? Absolutely The phenomenon of biocide resistance is well known and has been extensively reviewed in the literature [2-5]. Extensive work on the mechanism of action allowing previously susceptible microorganisms to survive elevated levels of the biocide have highlighted efflux pumps as a major contributor to the biocide resistance [6,7], as well as physiological adaptation [8].

The next question is one of significance. Is this phenomenon of any consequence to the pharmaceutical cleanroom sanitization program? Well, that is what I hope to answer in this short essay.

The Development of Resistance in Bacterial Populations

Genetic Resistance

The literature provides many examples of microorganisms able to survive in disinfectants. This can be either in laboratory experiments using an increasing level of biocide to select variants in the population, or by examination of biocidal solutions for the presence of resistant microorganisms. The gram-negative bacilli are the most frequent isolates from this type of evaluation [9-15]. This may be due to a combination of causes including alterations in outer membrane permeability due to changes in porin diameters [16-19]. In addition, it is not clear that the outer-membrane mediated resistance is in fact due to selection of a mutant genotype from the population, or rather phenotypic adaptation, as this trait has been reported to be rapidly lost once the selective pressure is removed.

The other type of experiment performed to demonstrate development of genetic resistance is one in which a laboratory researcher takes a microorganism in culture and exposes it to increasing levels of biocides, selecting resistance variants at each stage. There is one such set of experiments of particular relevance to the pharmaceutical microbiologist that we will examine in some detail as an example.

In 1992, Conner and Eckman published a study purporting to show the need for rotation of a low pH phenolic and a high pH phenolic to prevent the generation of resistant Pseudomonas aeruginosa [20]. This study was a repetitive zone of inhibition design, where an alkaline (pH 10.4) and an acidic (pH 2.6) phenolic disinfectant

were placed in paper discs at the center of a bacterial lawn. As the lawn grew to visible turbidity, the disinfectant diffusing out from the disc created a concentration gradient. Conner and Eckman then picked colonies that grew closest to the disc, therefore in the highest concentration of disinfect in the diffusion gradient, for the next cycle. Four treatments were used: water; high pH phenolic; low pH phenolic; and alternating (rotating) the two phenolics. The challenge was over 40 cycles of picking a “resistant” colony, creating a lawn using this new isolate, and then looking for another “resistant” colony from the first variant.

What the authors found was that the alkaline phenolic treatment eventually resulted in a variant of P. aeruginosa that produced no zone of inhibition around the alkaline phenolic-impregnated disc, while the low pH phenolic and the “rotated” phenolics had measurable zones at the end of 40 cycles. One plausible explanation for these results is that the alkaline phenolic is a poor disinfectant. However, Conner and Eckman concluded that these data demonstrated the need for rotating disinfectants. They provided no explanation for the fact that the low pH phenolic seemed to be as effective as the “rotated” phenolics at preventing “resistance” from developing.

They continued this work in a further study published in 1993 [21] and 1994 [22] where an adherent P. aeruginosa biofilm was formed on a stainless steel coupon and then subjected to repeated cycles of disinfection (by dipping the coupon in the use dilution) and reinocculation. Survivors were determined by sampling with replicate organism detection and counting (RODAC) plates. The authors showed that no treatment eliminated the established biofilm, but the rotation provided a statistically significant decrease in the numbers of colony forming unit (CFU) than in either the high or the low pH treatment. Unfortunately, the difficulty with using biofilms in this type of study is that the biofilm itself can adapt to different environments [23, 24]. This well-studied phenomenon confounds interpretation of the data. In addition, there was no attempt by the authors to determine the sampling efficacy of RODAC plates on biofilm generated under the various conditions. Given the well-documented inefficiency of this sampling method [25, 26] and the variations in biofilm structure [27-31] interpretation of the study becomes a bit more difficult.

Unfortunately, there is a dearth of other articles in the literature demonstrating the need to rotate disinfectants. Given what we know about population variability, the infrequent rate of favorable genetic mutations, and the mechanism of action of many of these biocides, it seems that the probable scenario for selection of a resistant variant would require exposure of an extremely large number of cells (in excess of 1,000,000 CFU) to a low level of the toxic chemical. It is not surprising that this has not been reported in the literature from a pharmaceutical manufacturing cleanroom facility. In fact, this has not been reported even for hospital situations where both the levels of microorganisms are much higher and the potential for recognition of the event is more likely [32, 33]. Put simply, selection of mutants that are resistant to in-use levels of disinfectants has not been shown to happen in cleanroom settings. Literature reports of resistance to in-use levels are restricted to descriptions of the survival of specific microorganisms in contaminated solutions [9, 14, 34].

Physiological Adaptation

While we have discussed genetic adaptation, there is another mechanism for resistance. In the previous section we touched on biofilms. A biofilm is a complex community of microorganisms suspended in a polysaccharide glycocalyx. The extracellular structure provides a foundation, nutrients for some members of the community, and also physical protection from chemical treatment as it impedes the diffusion of chemicals to the cells in the interior. The ability of biofilm to withstand large levels of disinfectants is well established [35-37]. This does not, however, speak to the need to rotate disinfectants, as the biofilm will provide protection against whichever chemical treatment you attempt, as shown earlier by Conner and Eckman.

There is one other aspect of this discussion I should mention. In the aforementioned article [1], the author correctly separated the disinfection of vegetative cells from the need to provide sporicidal activity to eliminate spores of bacteria and fungi. Although there are clear differences among different bacterial species in their sensitivities to disinfectants and these differences can result in persistent bacterial load under some conditions, these differences pale beside the resistance of spores to environmental insult. The spore form is naturally more resistant to chemical treatments and harsher agents must be used to combat these organisms. This is the basis of the common industrial practice of alternating the daily use of a disinfectant with the periodic use of a sporicide in a manufacturing facility’s sanitization program. The obvious approach to this problem might seem to be the exclusive use of the sporicide. However, as the author points out, the consistent use of common sporicides (frequently, strong oxidizing agents) will result in corrosion of equipment in a relatively short period of time and pose safety issues for the technicians applying them to the cleanroom. It is far preferable to use the gentler disinfectant for as much of the time as possible, reserving the sporicide for periodic cleaning, response to an event, e.g. power failure, catastrophic excess of action levels, or bringing a facility back on-line after a shut-down.

On the Need for Clarity in Terms

A final aspect of this discussion is the semantics of the subject matter. A real problem is the use of the term "resistance." This term originated in the clinical microbiology arena where the inhibition of bacterial growth provides a true measure of the efficacy of a particular chemical agent against that bacterial species. This measure has little meaning in disinfectancy where the true test is the ability of the agent to kill bacteria, not prevent them from growing. So we start off with the wrong test. From this poor beginning we then argue that a slight but measurable increase in the ability of the organism to grow in low levels of the chemical agent is proof of resistance, ignoring the fact that the dilution of the agent in a facility may be thousands of times more concentrated than the concentration used in the study [38]. Finally we ignore the basic mechanism of action of disinfectants, incorrectly applying the model of antibiotic resistance (where a mutant develops resistance to a "magic bullet" by altering the specific target of the antibiotic) to the mode of action of disinfectants (most of which act at a basic chemistry level: completely disrupting the cell membrane or fundamentally altering entire classes of cell components). A resistance that can be measured only in the lab, not in the field, is of little practical concern.

A second problem is the term used to describe the pharmaceutical practice. Given our current understanding, describing what we do as "disinfectant rotation" is grossly inaccurate. We, in fact, are not discussing rotating disinfectants at all. Rather we are urging the routine use of an effective disinfectant with the periodic use of a sporicide [39, 40]. Block [41] defines a disinfectant as, "…an agent that frees from infection, …that destroys disease or other harmful microorganisms but may not kill bacterial spores. It refers to substances applied to inanimate objects." He goes on to define a sporicide as "…an agent that destroys microbial spores, especially a chemical substance that kills bacterial spores."

What we are discussing is a practice more accurately described as a sanitization program, but certainly not "disinfectant rotation"—a term that continues to confuse practitioners and regulators alike.

Summary

The need for the rotation of disinfectants in a pharmaceutical cleanroom sanitization program is not supportable from a scientific basis. The assumptions that proponents of the practice assert as facts, e.g. generation of resistant organisms, greater efficacy of alternating agents, are not supported by the literature. However, even when using a validated disinfectant as part of a well-managed cleanroom sanitization program, periodic use of a sporicide is a prudent—even an essential—component of the sanitization program. It is needed to address the occasional appearance of spore-forming organisms in the environmental monitoring program and therefore ensure the cleanest possible environment for manufacturing. We need to clearly describe our practices and leave behind the inaccurate phrase "disinfectant rotation," as it does not describe the current practice of an effective cleanroom sanitization program and only confuses discussion of the issues involved.

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The following is the text of the article published in the March 2005 issue of A2C2 Magazine.

E.K. Sartain. "Regulatory Update: Rotating Disinfectants in Cleanrooms: Avoid Going in Circles," A2C2 Magazine, Vol. 8, No. 3, (March, 2005) pp. 32-33.

Regulatory Update, Elaine Kopis Sartain, March 2005*

This is the first in a series of quarterly columns authored by Elaine Kopis Sartain. Elaine Kopis Sartain is the Director of the Technical Services Department for the Life Sciences Division of STERIS Corporation, a manufacturer of contamination control and prevention equipment and products. Her primary focus is on microbial control in cleanrooms and other critical environments, and on the selection and validation of CIP cleaning agents.

Elaine provides assistance to STERIS customers in the selection and application of disinfectants and cleaners. She also provides educational seminars and literature to customer groups. Elaine has lectured on microbial control in cleanrooms throughout North America, Europe, and Asia, and has authored numerous published articles on contamination control related topics for industry and professional publications.

Elaine holds a Bachelor of Science degree in Chemistry from Southern Illinois University. She is a member of the Association of Official Analytical Chemists, the American Chemical Society, the Institute of Environmental Sciences and Technology, and the Parenteral Drug Association. Additionally, Elaine is a faculty member of the PDA Training and Research Institute.

I RECENTLY HAD A CONVERSATION with the manufacturing manager for a biotechnology firm who was having problems with recurring microbial excursions in fermentation areas. During the course of our discussion, he informed me that they use a phenolic disinfectant exclusively for one month and then switch to a bleach solution that they also use exclusively for one month. I asked him to explain the rationale for this rotation scheme and he told me that he was not really sure where the rationale originated, but knew that it had been validated.

The obvious question that occurred to me (though I did not ask it) was, "If it's a validated rotation, then why are you regularly experiencing microbial excursions?" Of course the answer to this may involve more than the facility's rotation scheme, but the fact that this cleanroom manager could not articulate why he was following this particular disinfectant rotation gave me pause.

I have had, literally, thousands of similar conversations with cleanroom industry customers over the years and have drawn the following conclusions:

* There is no universal understanding of why rotation is being done

* There is no universal agreement about which chemistries should be rotated

* There is no universal agreement about the value of rotation

* There is no universal agreement about the optimal frequency of rotation

Why Rotate Disinfectants?

The fundamental purpose of rotation is to prevent selection for resistant organisms; not to prevent organisms from becoming resistant to disinfectants, as is widely believed. Although microorganisms do become resistant on occasion to antibiotic medications, I am not aware of any data demonstrating that microorganisms "become resistant" to disinfectants. These for mulations are simply too toxic and the concentrations are too high, under proper conditions, for resistance to develop.

What actually happens is that either an ineffective chemistry (e.g., alcohol against spore-forming microorganisms) is applied or suboptimal concentrations or contact times are used, so that the expected disinfection performance is not achieved. If one continues with a microbial control program that kills only certain organisms (e.g. vegetative bacteria) while having no impact on others (e.g. spore-formers) then eventually the program does exactly what it has inadvertently been designed to do—select for specific organisms that are inherently resistant to, and cannot be controlled by, the disinfectant technology being applied.

Regulatory Expectations
Though it is not clearly defined by regulatory authorities, the rotation of disinfectants is certainly a regulatory expectation and has been for several years. To illustrate, I quote the following guidelines and observations:

* From the 483 Observation: “Sanitizing agents (disinfectants) used in the aseptic processing area and the surrounding cleanrooms are not rotated…” (GMP Trends, December 1, 1997).

*“The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect …resistant strains.” (Rules and Guidance for Pharmaceutical Manufacturers and Distributors, {Orange Guide} Annex 1, Section 37, 2002).

*“Issues associated with the successful implementation of such a program [cleaning and sanitization] are the development of written procedures, staff training, and decisions on disinfectant rotation…” (USP <1072 > Disinfectants and Antiseptics, In-Process Revision, Pharmacopeial Forum Vol. 29 (3), May-June 2003).

There is little doubt that rotation of disinfectants is required in order to be compliant with US and EU regulatory agencies. In order to be most effective, however, the goal should reach beyond regulatory compliance to achieving improved microbial control through the implementation of a scientifically valid rotation program.

Elements of an Effective Rotation Program
A sound disinfectant rotation program should include chemistries that control a wide variety of organisms and that mitigate damage to cleanroom surfaces. Unfortunately, at this time it is virtually impossible to optimize performance in both of these areas with a single type of chemistry. For this reason, a three-part program should be employed.

1. Routine disinfectants should be used for daily cleaning of non-product contact surfaces and should be able to effectively control vegetative bacteria and remove soil while minimizing damage to cleanroom surfaces and risks to personnel working in the area.

2. In addition, since routine disinfectants will generally not be efficacious against bacterial endospores such as the Bacillus species, a sporicidal agent should also be applied periodically. Since most sporicidal disinfectants are either highly toxic or very corrosive, they should not be considered for daily use.

3. Finally, because both of the above types of chemistry typically leave residues, a residue removal agent (i.e. isopropyl alcohol) should be available and used as needed. An effective rotation program will include all three of these disinfectant types.

Another common rotation scheme that remains a source of debate is the alternation of two similar types of chemistry. The idea behind this type of rotation is to alternate products that have different efficacy profiles. The only reason to support the alternation of two phenol or two quaternary ammonium chloride formulations, however, is if data demonstrates that there is a fundamental formulation-related difference in performance between the two similar products. Likewise, alternating between bleach and oxidizing chemistries such as a hydrogen peroxide or a peracetic acid blend for spore control makes little sense unless there is a fundamental difference in performance that is verifiable.

Another variable that should be considered is the frequency of rotation. If one is alternating between two virtually identical chemistries that offer no distinguishable difference in performance, then the frequency of rotation is a moot point. If, however, one is rotating different chemistries that offer different efficacy profiles, then the rotation frequency should be driven by antimicrobial performance that is verifiable through environmental monitoring data.

As a final general guidance on the subject of disinfectant rotation, I quote again from the USP <1072> In-Process Revision: “It is prudent to augment the daily use of a bactericidal disinfectant with weekly (or monthly) use of a sporicidal agent.” … “Other disinfection rotation schemes may be supported on the basis of review of the historic environmental monitoring data.” Whatever the rationale for its development, any disinfectant rotation program should be able to support ongoing, documented, and thorough antimicrobial efficacy.

*E.K. Sartain. “Regulatory Update: Rotating Disinfectants in Cleanrooms: Avoid Going in Circles,” A2C2 Magazine, Vol. 8, No. 3, (March, 2005) pp. 32-33.