

Useful Guidelines on Sterilization & Contamination Control

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A product recall is problematic for any manufacturer. In the last year alone, recalls of pharmaceutical and health-related products have included baby lotions, parenteral nutrition products, nasal decongestant sprays and alcohol swabs used in preparation for patient injections—all resulting from microbial contamination. Today, consumers can still rely on the U.S. drug supply as being one of the most secure and well-protected in the world. However, increasingly complex and globalized sourcing and development of pharmaceutical products have made it necessary for manufacturers to heighten their vigilance over product quality.

The extent of microbial contamination in any finished pharmaceutical product must always be a major consideration for a manufacturer. Whether sterile or non-sterile, any finished pharmaceutical product has an existing bioburden, or degree of microbial presence that can be accounted for, based on the raw material from which it is sourced and the process for its manufacture. In the case of sterile products such as parenteral drugs (which are administered into a patient's bloodstream), products must be manufactured and handled to avoid any microbial presence. In non-sterile products such as solid oral dosage forms or syrups, a small amount of microorganisms is tolerated in a product's makeup.

As the standards-setting organization for the identity, strength, quality and purity of drugs and their ingredients marketed in the United States, the U.S. Pharmacopeial Convention (USP) has been developing and updating several standards related to microbiological presence and control. Many of these activities will be highlighted in a July 2012 workshop taking place at USP's headquarters in Rockville, Md.

USP's written or documentary standards are published in USP's official compendia, *U.S. Pharmacopeia* and the *National Formulary (USP-NF)*. Within *USP-NF*, standards for an official article (a drug substance/ingredient or a drug product) can appear in that article's monograph, within relevant general chapters or in the *General Notices* section. A general chapter may contain tests, procedures and/or specifications that apply across multiple products. General chapters numbered below 1000 contain mandatory requirements, whereas chapters numbered 1000 to 1999 are considered interpretive and informational.

They contain no mandatory requirements for an article, unless they have been specifically called out as applicable (e.g., a requirement in an individual monograph). For example, all products purported to be sterile must meet the requirements of General Chapter *Sterility Tests*, given that sterility assurance can only be gained through robust and validated sterilization processes. General Chapter *Sterilization and Sterility Assurance of Compendial Articles* provides

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guidelines and is informational, but is not a required standard unless it is called out in a particular monograph or a below-1000 general chapter.

Sterility Assurance & Sterilization

A current activity for USP related to sterilization and sterility assurance has been the development of the 1229.x-series of general chapters. Until recently, General Chapter was the single source of standards in *USP-NF* for general principles on sterility assurance as well as sterilization processes. Stakeholder feedback to USP indicated that greater detail was needed on specific sterilization processes. Thus, the 1229.x-series is being developed to address those gaps. Future revisions to will maintain the chapter's focus on sterility assurance. General Chapter will serve as an overarching chapter dedicated to general concepts of sterilization. Subsequently, 11 related chapters will be developed, out of which eight will focus on distinct processes for sterilization, how those processes are to be developed and which materials are most suitable for their use.

1. *Steam Sterilization by Direct Contact*
2. *Steam Sterilization of Aqueous Liquids*
3. *Sterilizing Filtration of Liquids*
4. *Chemical Sterilization*
5. *Gaseous Sterilization*
6. *Dry Heat Sterilization*
7. *Radiation Sterilization*
8. *Vapor Sterilization*

The other three general chapters in the 1229.x series will address areas related to these processes:

1. *Monitoring of Bioburden*
2. *Biological Indicators for Sterilization*
3. *Physicochemical Integrators and Indicators for Sterilization*

Development and revisions to USP's standards are published in the *Pharmacopeial Forum (PF)* — USP's online mechanism for receiving public comments from interested stakeholders. In the March–April 2012 issue of *PF*, General Chapters and

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will be posted to receive comments between March 1 and May 31, 2012. Similarly, General Chapter will be posted in the May–June 2012 issue of *PF*. Interested parties are strongly encouraged to provide feedback by going to www.usp.org/usp-nf/pharmacopeial-forum [1].

Control and Monitoring in Aseptic Environments

Another USP general chapter which recently has undergone major revision is General Information Chapter *Microbiological Control and Monitoring of Aseptic Processing Environments*. By changing the focus from the evaluation and classification of clean rooms to key guidance that supports microbiological control of aseptic processing environments, this revised chapter now proactively addresses ways to help eliminate microbial growth, particularly those introduced through human contact. Guidelines in this chapter as well as monitoring parameters for microbial evaluation should be applied only to clean rooms, restricted-access barrier systems and isolators used for aseptic processing. Revised chapter also references the ISO 14644 Standard for clean rooms, which has replaced Federal Standard 209E previously referenced in . One of the most significant changes in this chapter has been the introduction of the use of contamination rates in lieu of straightforward microbial counts with regard to microbiological control and monitoring. Revised General Chapter will be official on May 1, 2012, in *USP(35)-NF(30)*.

A Risk-Based Approach to Contamination & Bioburden Control

As mentioned, contamination risks are closely linked to the control of product bioburden. For non-sterile pharmaceutical products, very little information on bioburden control is currently available in pharmacopeias or regulatory guidance documents. The quality of raw materials, the surrounding environment during manufacturing, and personnel conducting quality control activities are just some of the critical factors that can contribute to product bioburden. Additionally, differences among non-sterile products and their uses can make a “one-size-fits-all” approach to contamination control challenging.

For example, compare the following dosage forms — a tablet, a syrup and a suppository. Water activity plays a major role in the extent of microbial growth and contamination for each dosage form. Environmental controls should be considered as well the route of administration of the dosage form to a patient. Extend the exercise to patient populations receiving the drug, and new factors subsequently must be taken into account regarding risk. Is the patient immune-compromised? Is the drug being administered to a patient who is pregnant? Is an infant receiving the drug?

Clearly, a calculation of minimal risk for a healthy individual can render different results for an individual in a different — and perhaps, more vulnerable — patient population. Thus, traditional approaches to contamination control based on monitoring alone may not be as helpful as risk-based programs based on greater levels of specificity. By incorporating product makeup, routes of administration, affected patient populations and the effect of the bioburden on product efficacy into their considerations, manufacturers can then develop more robust programs to

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control microbial contamination.

USP's proposal to develop a chapter on risk-based approaches for bioburden control in non-sterile products is expected to be published and open for comment in the *Pharmacopeial Forum* by late 2012 or early 2013.

Replacing Microbial Assays with Rapid Methods

Conventional microbiology tests found in the pharmacopeias, such as sterility tests, rely on the demonstration of microbial growth. Limitations of these tests include their low sensitivity as well their time- and labor-intensive nature. USP is seeking to identify new referee tests or procedures (used by FDA or a third party to assess regulatory compliance) based on modern methods that can detect and enumerate microorganisms in a more rapid and sensitive manner.

USP is also in the process of updating General Chapter *Validation of Alternative Microbiological Methods* as a guide to users interested in validating microbiological methods, including those based on modern technologies.

In addition, USP is exploring the replacement of traditional microbial assays used as potency assays for antibiotic drugs with more rapid high performance liquid chromatography (HPLC) assays. As with microbiology test methods for compendial purposes, recommendations to users on the validation of these HPLC assays as viable alternatives to antibiotic microbial assays will be a focus for USP.

USP's Ongoing Efforts

As USP gathers more feedback from industrial and regulatory stakeholders on aspects of microbiological contamination and activity critical to pharmaceutical products, USP's standards will increasingly reflect more modern technologies and approaches that can better undergird product quality and help to maintain consumer confidence in these products.

For more information, please visit www.usp.org/meetings-courses/workshops/microbiological-control-compndial-articles-workshop-current-status-and-future-directions-compndial [2].

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Links:

[1] <http://www.usp.org/usp-nf/pharmacopeial-forum>

[2] <http://www.usp.org/meetings-courses/workshops/microbiological-control-compndial-articles-workshop-current-status-and-future-directions-compndial>