

USP <1211>: The Compendial Informational Chapter on Sterility Assurance Origins and Future Direction

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The author provides a history of the information chapter USP <1211> "Sterilization and Sterility Assurance of Compendial Articles," from the early 1900s to the current version.

In 1900, the eighth revision of the *United States Pharmacopeia (USP)* was recast from its traditional focus of how to make medicines to the role it would eventually take as a book that describes the safe making of medicines. The US Pharmacopeial Convention resolved to "append assay processes to as many of the potent drugs and preparations made therefrom as may be found possible, provided that the processes of assay are reasonably simple and lead to fairly uniform results in different hands" (1). This publication was followed shortly by the Federal Food and Drugs Act of 1906, which elevated the position of USP and increased its authority dramatically. It was against this background that the first informational chapter about sterilization appeared.

The original chapter. The original chapter on sterilization appeared in USP IX, which became official in September 1916 (2). Although this chapter was sparse on technical detail, it provided a background discussing the need to sterilize various medicines, containers, and stoppers with recommendations as to how to achieve this sterilization. Part of this early emphasis stems from USP's focus at that time on the practicing pharmacist and the need to put procedures in place that were accessible to the practitioner (1).

Bear in mind, that this chapter was published more than 20 years before the passage of the Food Drug & Cosmetic (FD&C) Act of 1938, which gave the US Food and Drug Administration the authority to require proof of a product's safety before marketing, and almost 50 years before the first good manufacturing practice (GMP) was finalized (3–5). As an aside, the importance of sterilization and sterility assurance continues to be a grave issue to this day. It was the 1972 Devonport incident involving lax control of a sterilization process and the resultant damage that drove modern concepts of sterility assurance as an operational imperative (6, 7).

The 1947 revision. The 1916 informational chapter was extensively revised in 1947 (and increased in length by approximately sevenfold) to provide a great more detail about many types of sterilization methods, several of which are no longer in use (8). This version provided information about

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what would probably be called “compendial conditions” for sterilization by dry heat (>1 h at >170 °C), for “steam under pressure” (115.5 °C for 30 min, 121.5 °C for 20 min, or 126.5 °C for 15 min), and for “free-flowing steam.” This last technique was used in a series of exposures to kill vegetative cells with respites to allow spore germination before repeated exposure to steam. Also known as tyndallization, this method of sterilization is no longer recommended (9). The informational chapter also included a discussion of “fractional moist-heat sterilization at low temperatures” (inspissation), in which the medicine is heated at 60–80 °C for 4–7 days, as well as a discussion of sterilization by boiling in an oil bath. Interesting methods all, although on the whole this author is glad that validation and demonstration of efficacy has become the expectation. This 1947 chapter has some specific recommendations for sterilization by filtration and aseptic processing (along with a direction that the label is to state “Prepared by Aseptic Manipulation”).

Revisions in the 1960s. The title of the chapter was changed back to “Sterilization” for USP XVI (10). This version was a complete rewrite of the chapter. It included a special note that while the “fractional sterilization” methods might work well for bacterial growth media, it is not appropriate for pharmaceutical preparations because spores may not germinate in them (not mentioned is the issue of metabolic byproducts created by the germinating spores if the process works).

This version includes a greatly expanded section about filtration and aseptic manufacturing, including an emphasis on the control of the fill environment. A strong suggestion is included to the pharmacist and operators to perform aseptic manipulations under hoods or shields in an area protected from visitors. A new section was added to the chapter on the need to monitor the environment, with settle plates and media fills recommended. Finally, the chapter states that making sure the janitorial staff cleans the area after the shift, leaving a full overnight period before the next day’s fill, is considered very important. This chapter was rewritten for USP XVII (11). Although most changes were editorial, specific instructions for types of sterilization methodologies were included as separate sections and new methods—sterilization by ethylene oxide and sterilization by irradiation—were included for the first time.

Revision of 1970s. The chapter “Sterilization” was amended again for USP XVIII (12). In addition to extensive editorial changes, two important new sections were added. The first section dealt with biological indicators and the need for appropriate selection of the indicator (one for heat may not be a suitable species for irradiation) as well as the need for competent manufacture of the indicator itself to maintain its relevant properties (e.g., heat resistance or similar property). The second new section dealt with the sterility test. The opening paragraph of this section is so entertaining that I have to share it:

The significance to be attached to a demonstration by test that a drug or device has been rendered sterile is determined largely by the extent of the control exerted during the manufacturing and sterilization processes. The

object of the sterilization process is to make the article safe for use, but the tests may be expected to reveal only that living organisms have been removed or destroyed to the extent where they no longer multiply in appropriate culture media under favorable conditions. Interpretations of the results of sterility tests must allow for the possibility that the degree of contamination is of a low order of magnitude. Confidence in the results of the tests with respect to a given lot of articles is based upon knowledge that the lot has been subjected to a sterilization procedure of proven effectiveness. Where feasible, the effectiveness of the process should be demonstrated each time it is carried out by including marked, intentionally contaminated controls, or indicators, which are examined under the conditions of the tests.

This passage is somewhat ironic because speakers to this day insist that USP created a flawed test for sterility that should have been fixed long ago. Although this argument is undoubtedly true, this test was first entered in the *British Pharmacopoeia* of 1930, then in USP of 1932 with no significant improvements in the intervening 77 years. One would think someone would have come up with a better assay by this time.

The 1970 version of the USP chapter provides some instruction about change control (not in those terms, of course) and the need to control the sterility test environment. Although no one can doubt the importance of some guidance about how to perform and interpret the sterility test, the inclusion of this information in the chapter would create difficulties lasting to the present. The 1970 revision of the chapter continued and expanded somewhat the discussion of aseptic processing with monitoring by settle plates and media fills that was introduced in 1960.

The version of the chapter that appeared in USP XIX (13) reintroduces the major section about sterilization methods, establishes biological indicators as a major section, and creates a major section entitled “Sterility Testing of Lots.” The sections contain a great deal of detail. For example, the biological indicators section provides a method to confirm heat lethality of the spores. In addition, the section “Sterility Testing of Lots” contains recommendations about the media to be used, sample plans, and number of units to be tested. The particulars described in the chapter “Sterilization” were not necessarily in agreement with the contemporary referee chapter “Sterility Tests” (14).

Revision of 1980s. The chapter was further revised for USP XX (15). The major organizational scheme from 1975 remains, but much of the detail has been removed. In particular, the section on biological indicators now uses the parameter of “D-value” to describe the desired heat resistance of the different spores, and the section about sterility testing has been toned down dramatically and is no longer conflicting with the “Sterility Tests” chapter. In addition, this version clearly states that <71> “Sterility Tests” is the official referee test. For those interested in the history of the sterility test chapter, USP XX included the first mention of “First Retest” and “Second

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Retest” in the then 48-year-old test (16). It should also be noted that *USP XX* is the first volume that uses the chapter numbering system where “Sterilization” carries the chapter number (1211).

The current version

USP XX generated controversy in the industry, and given the emphasis placed on control of the sterilization process, additional detail was proposed in 1982 (17) for addition to the introductory section of the chapter, which was proposed to undergo a name change to “Sterilization and Sterility Assurance of Compendial Articles.” This section described sterilization process validation as having an installation qualification, an operational qualification, a confirmatory stage, and a final stage (for completion of documentation). Selection and control of biological indicators for sterilization validation are described, as is a general review of process control subjects. Each method of sterilization included in the chapter is expanded to include at least a short discussion of validation concerns. There is a great deal of material added to the ionizing radiation and the filtration sections in this regard.

The 1982 *Pharmacopeial Forum* in-process revision draft also expanded the sterility testing section. Among the additions was a definition of product “lot” for sterility-test purposes and the assertion that a 1–2% false-positive rate was acceptable for the sterility test. This addition was viewed as justification for a second-stage test if the first-stage test failed.

A further revision (with extensive editorial rewrites) appeared in the May–June 1983 *Pharmacopeial Forum* (18) followed immediately by a second rewrite in the Sept.–Oct. *Pharmacopeial Forum* (19). The second draft of 1983 contained modest editorial changes, with the exception of the removal of a description of minimum standards for an aseptic manufacturing facility and some of the more onerous requirements for sterility testing (e.g., requiring the test facility be fully validated and the use of negative controls on the test). It was this version that appeared in *USP XXI* (20).

Refinements to the basic chapter were proposed in 1986 (21) to clarify some points regarding filtration and aseptic processing and to keep pace with changes in the contemporary sterility test chapter, primarily clarification of the bacteriostasis/fungistasis test (22). This version appeared in *USP XXII* (23).

Concerns were raised in the field about the handling of sterilization by filtration in the revised chapter and a proposed revision to address these concerns appeared in 1990 (24). These changes were accepted and appeared in *USP 23* (25). The chapter has not changed appreciably since.

Revisions currently under consideration

The sterilization chapter is significantly, and obviously, in need of revision (26, 27). This task was attempted with a proposed short-term revision published in 2004 for review (28). The major changes proposed in the 2004 revision were:

- Elimination of references to the old sterility test (71) and

to first- and second-stage testing

- Updating the names of microorganisms to current taxonomy
- References to units of measure (Mrad) currently in use
- Elimination of references to discontinued standards (especially Fed Standard 209)
- Reference to new consensus standards (ISO 13408-1)
- Discussion of contemporary aseptic processes.

These changes were intended to be a short-term correction to eliminate the more glaring concerns in (1211). However, there was significant comment from the field in this proposal. The chapter was thought to need reorganization to keep the focus within individual sections on process, equipment, and product more tightly directed. The chapter as a whole needed closer conformance to existing consensus standards in terms of moist heat under pressure, dry heat, and aseptic processes. As with many documents about sterilization, readers felt that clarification of ambiguous terms was needed as well as a clarification of definitions. There was also strong sentiment that the sterility test should not be discussed at all in this chapter because it is a separate chapter in its own right. Finally, there was a request for more detail about the use of isolators for aseptic processing.

Clearly, this version did not help clarify the situation. Therefore, no further action was taken, and this version did not become official. A proposal for a partial rewrite is expected in *Pharmacopeial Forum* before summer 2009. This rewrite will remove obviously incorrect information about sterilization and bring the chapter in line with the current sterility test chapter. This revision will therefore address the most egregious points of the current chapter (1211).

On a longer timeframe, serious changes to the organization of the chapter are under consideration. Among the changes being discussed are an increased focus on concepts and principles of quality control for sterile articles, an expanded discussion of process equipment capability, and operational abilities within the established parameters as well as information about other aspects of process validation.

The different methods of sterilization may be removed to different (new) chapters; specifically,

- Chemical sterilization: The chapter may include discussions on aldehydes, oxidizers, halides, acids, and bases.
- Dry-heat depyrogenation: This method will be described as predominantly used for glass and stainless-steel items that can withstand the applied temperatures (usually in the >200–300 °C range). This chapter will be used with a planned endotoxin monograph that has been drafted.
- Sterilization by filtration: This chapter will be a complete revision from the current text in (1211) to bring it more in line with current thought on filtration validation.
- Gas sterilization: This chapter is envisioned as applicable to single-phase gaseous processes only and uses ethylene oxide sterilization as a model for all the systems. The chapter will probably describe two different validation approaches: the traditional half-cycle method and a bracketing method. Gases

expected to be included are ethylene oxide, ozone and chlorine dioxide. These systems will be described as differing from vapor systems in that condensation is not a consideration.

- Dry-heat sterilization: A distinction will be made between dry-heat sterilization and depyrogenation because of major process differences. This chapter will most likely identify *Bacillus atrophaeus* spores as an appropriate biological indicator for sterilization by dry heat and define a temperature range for effective cycles while citing the mathematical correlation between physical data and microbiocidal activity.

- Radiation sterilization: Methods to be included in this chapter will be gamma rays, electron beams, and the minor contributors (i.e., x-rays, microwaves, and visible light). These processes have the potential to damage the product but provide precise parameters, and dose-setting and dose-substantiation procedures can be used to validate the radiation dose required to achieve sterility assurance level.

- Steam sterilization: This chapter may be separated into two parts (steam and terminal sterilization) to allow for differences, and greater clarity, or remain in one chapter that will list the "overkill approach" as the method of choice. This chapter will also stress the importance of clearly recognizing processes where over-processing is not a concern from those processes where over-processing can damage the product.

- Vapor sterilization: This chapter will be intended for condensing vapor systems (gas and liquid phases present simultaneously) such as hydrogen peroxide and peracetic acid systems. The presence of multiple phases that are present simultaneously complicates concentration determination at the point of sterilization, thereby making D-value determination problematic. The approaches for validation will be described as a hybrid of the liquid- and gas-sterilization methods. Two validation strategies will be presented: the traditional half-cycle method and the bracketing method.

Conclusion

USP has had the opportunity to contribute to sterility assurance since the early 1900s. The ability of USP to assemble experts and allow them to propose guidance on the basis of their experience and knowledge is a unique strength of the compendium in its role as a safeguard of the public's health. That the actions taken by the committee will change over time as our knowledge increases and the pharmaceutical and pharmacy industries change should not be a surprise. Indeed, this flexibility is a particular and planned strength of the USP system of "continuous improvement." As with many other chapters, evidence from the development of USP (1211) suggests that this process works best with a motivated committee and an industry engaged in the process.

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