The Role of USP in the Assessment of Microbiological Quality of Pharmaceuticals

A Five-Year Retrospective Leading to the Future

Roger Dabbah,* Joseph Knapp, Scott Sutton

The authors review the role of USP in the development and implementation of microbiological methods for the assessment of the quality of pharmaceuticals, excipients, drug substances, and drug formulations (sterile and nonsterile) by summarizing the considerable activities of the Microbiology Subcommittee in the 1995–2000 USP revision cycle. These activities are designed to support manufacturers and regulators in ensuring the microbiological quality of products in the twenty-first century.

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The traditional framework of the role of microbiology in the United States Pharmacopeia (USP) for the assessment of quality of pharmacopeial articles is illustrated in Figure 1. The application of advances in microbiological science that supports that framework has lagged behind the application of advances in chemical and physical sciences. The expansion and globalization of pharmaceutical markets have made microbiology a critical tool for manufacturers to use to ensure the microbiological quality of their products and for regulators to ensure that compliance is effectively protecting patients who are using the products.

The role of USP, a nongovernmental, not-for-profit organization, is to develop microbiological public standards that, along with other requirements, ensure the consistency of products from batch to batch as well as the microbiological quality of the products. The USP process is open, transparent, and effective and involves interested parties from industry, government, and academia.

The publication of proposals for the microbiological requirements in monographs or general chapters in Pharmacopeial Forum (PF) generally has elicited considerable comment from all interested parties because, in one way or another, microbiology is involved in the quality continuum that stretches from raw materials manufacture to the final product ready to be distributed in the marketplace. Additional support of the regulators and the manufacturers also is provided by the develop-

Figure 1: Framework of the role of microbiology in the assessment of microbiological quality of pharmaceuticals.
Alternative methods to USP standards can be used to deter-

They include scientific as well as legal standards. They are not quality control, batch-release requirements, al-

They are subjected to continuous revision to take advantage

They are developed with the active participation of industry,

They are developed in an open forum by duly-elected experts.

A product labeled sterile must remain sterile throughout its

or the “misbranding clause” in the

Cited by FDA for noncompliance using the “adulteration clause”

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standards because that is the responsibility of FDA. Pharma-

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The authority for the development of public standards for
drugs, including the microbiological requirements, is vested in
USP does not verify compliance of the products against USP
standards because that is the responsibility of FDA. Pharma-
aceutical products in the marketplace that do not comply with
USP standards, including microbiological standards, can be
cited by FDA for noncompliance using the “adulteration clause”
or the “misbranding clause” in the Code of Federal Regulations.
The following are the characteristics of USP standards:

● A product labeled sterile must remain sterile throughout its
shelf life.

● They are developed in an open forum by duly-elected experts.

● They are scientific standards developed by experts, not con-
sensus standards.

● They are developed with the active participation of industry,
government, and academia via publications in PF.

● They are subjected to continuous revision to take advantage
of advances in analytical technologies.

● They are not quality control, batch-release requirements, al-
though many organizations use standards as such.

● They include scientific as well as legal standards.

● Alternative methods to USP standards can be used to deter-
nine regulatory compliance to these standards and are ac-
cetable to the regulatory agencies provided that data of equiv-
alency are available for audit by FDA inspectors.

Given the characteristics of USP standards that include micro-
biological requirements, the impact of microbiological stan-
dards and methodologies on the industry and regulators is sig-
nificant. The Committee of Experts has to be conservative when
proposing changes because validation and revalidation of micro-
biological methods for all products could be required. How-
ever, the advances in analytical technologies, especially in the
automation and identification of microorganisms, cannot be
ignored and pose a challenge to the USP Analytical Microbiol-
ogy (AMB) Committee of Experts.

The challenge to the Committee of Experts is to respond to
the needs of manufacturers and regulators to develop and up-
date various microbiology chapters that directly affect the as-
surance of microbiological quality of pharmaceutical products.

In summarizing the activities of the 1995–2000 Revision
Cycle AMB Committee of Experts, one can appreciate the ef-
forts and results that the committee has achieved and con-
tinues to achieve in ensuring the microbiological quality of
pharmaceutical products.

In Table I we have summarized the activities related to gen-
eral chapters. When appropriate, the international harmoniza-
tion status of these chapters is indicated. Harmonization ini-
tiatives with the Pharmacopoeias of Europe (EP) and Japan

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<th>Chapter</th>
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<td>51: “Antimicrobial Preservative Effectiveness”</td>
<td>Harmonization was very controversial. Methodology was harmonized, but criteria of effectiveness was not harmonized with EP. Final update was published in USP 24. Harmonization work ended.</td>
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<td>55: “Biological Indicator Resistance Performance Tests”</td>
<td>In Supplement 6 (15 May 1997) of USP 23. This new chapter was revised, and in addition to the Spearman-Karber method used originally for D value calculation, two other methods, the survival curve method and the Stumbo Murphy Cochran method, also were included. These changes were official in the Second Supplement of USP 24.</td>
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<td>61: “Microbial Limit Tests”</td>
<td>This chapter has been controversial in its application by regulatory agencies and by manufacturers. Proposals to update chapter 61 by dividing it into two chapters, one chapter (61) for “Microbial Enumeration Tests” and one (62) for detection of “Objectionable Microorganisms,” were published in PF 25 (2) and generated a lot of comments. Harmonization discussion among microbiology experts of USP, JP, and EP resulted in a proposal published in PF 27 (1), Jan–Feb 2001, for public comments. Input of ICH 6A also was obtained.</td>
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<tr>
<td>71: “Sterility Tests”</td>
<td>Extensive revisions were proposed and implemented in the Eighth Supplement of USP 23. Continuous revisions that resulted from public comments led to another round of proposals. The revisions were implemented in USP 24. Additional discussion with EP and JP has resulted in a harmonized “Sterility Tests” chapter, and a proposal has been made in PF 26 (4), July–Aug 2000, for public comments.</td>
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<td>85: “Bacterial Endotoxins Test (BET)”</td>
<td>Over 650 USP monographs have a BET requirement. The endotoxin limits are calculated on the basis of the human pyrogenic dose (5 EU/kg body weight) divided by the maximum dose/kg/hour. A harmonized document that not only introduces the gel-clot method but also the turbidimetric and chromogenic methods was published in the Second Supplement of USP 24 with an implementation date of 1 January 2001. In addition, the Endotoxin reference standard for USP, EP, and the World Health Organization is from the same batch. (1 USP endotoxin unit = 1 IU of endotoxin)</td>
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In Table II we have summarized the activities of the AMB committee in terms of general information chapters. These chapters provide background guidance to manufacturers and regulatory agencies on microbiological testing. They also provide information and should not be interpreted as enforceable by FDA. A number of the information chapters are process control chapters that were developed during the 1995-2000 cycle, often at the request of industry.

A unique feature of the USP revision process is the publication in PF of stimuli articles for the revision process, which are essentially peer-reviewed articles by USP staff, members of the expert committees, or any other interested party. These stimuli articles often recommend expert committee changes in microbiology, essentially peer-reviewed articles by USP staff, members of the expert committees, or any other interested party. These stimuli articles often recommend expert committee changes in microbiology area, resulted in the development of chapters 2021, 2022, and 2023. These chapters provide background guidance to manufacturers and regulatory agencies on microbiological testing. They also provide information and should not be interpreted as enforceable by FDA. A number of the information chapters are process control chapters that were developed during the 1995-2000 cycle, often at the request of industry.

### Table II: Microbiology general information chapters activities during the 1995-2000 USP revision cycle.

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<td>1035: “Biological Indicators for Sterilization”</td>
<td>First proposed in 1994, then replaced by a new proposal in 1997. This chapter became official in the Second Supplement of USP 24. It includes information about the various types of biological indicators (BIs) and the differentiation between the responsibilities of the manufacturers and users of BIs.</td>
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<tr>
<td>1111: “Microbiological Attributes of Nonsterile Pharmaceutical Products”</td>
<td>After numerous attempts at updating this chapter, and on the basis of recommendations given to the subcommittee at the 1996 USP Open Conference on Microbiology, a proposal was made in the March–April 1999 issue of PF. Harmonization discussions among USP, JP, and EP, with input from ICH-Q6A, have been completed, and a proposal for harmonization to be considered by the pharmacopoeias is being reviewed by EP, the coordinating pharmacopia.</td>
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<tr>
<td>1116: “Microbiological Evaluation of Cleanrooms and Other Controlled Environments”</td>
<td>This chapter was developed at the request of a pharmaceutical trade association as a complement to the US Standard 209 E available from the Institute of Environmental Science and Technology for cleanrooms that did not include microbiological evaluation. This proposal was controversial and went through a number of iterations before being implemented in the Eighth Supplement of USP 23. Because of the continuous revision system used in USP, additional recommendations to modify this chapter were made and proposed in the May–June 1999 issue of PF 25 (3). It expanded the scope of the chapter to include aseptic manufacturing. This was very controversial and resulted in the formation of an ad hoc task force between USP and the Parenteral Drug Association to arrive at a better understanding of the issues raised by industry. Discussions are in progress.</td>
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<td>1207: “Sterile Product Packaging — Integrity Evaluation”</td>
<td>Guidance for container–closure integrity testing is provided in a proposal published in PF Nov–Dec 1997. Description of physical and microbiological testing methods that might be performed in the continuum from product development to shelf-life testing are discussed. A modified proposal will be sent to PF for additional public comments.</td>
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<td>1208: “Sterility Testing — Validation Isolator Systems”</td>
<td>Starting in 1997, several iterations of this chapter were proposed, with the latest one in the Jan–Feb 1999 issue of PF 25 (1). Isolators need not be installed in a cleanroom or a controlled-room environment. The official chapter has been published in the Second Supplement of USP 24.</td>
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<td>1222: “Terminally Sterilized Pharmaceutical Products — Parametric Release”</td>
<td>In 1997, a proposal was made in PF for an information chapter that discussed the various issues related to parametric release of products that are sterilized by moist heat, ethylene oxide, and radiation. Few comments were received and the proposed chapter will be published in PF In-Process.</td>
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<td>1227: “Validation of Microbial Recovery from Pharmacopeial Articles”</td>
<td>Started in 1996 with requests for guidance on validation of microbiological methods indicated in USP. Following the USP Open Conference on Microbiology in 1998, a new iteration was published in the Jan–Feb 1999 issue of PF 25 (1). Recommendations from interested groups strongly suggested the use of statistical analysis. A 70% recovery limit was set. The chapter became official in the Tenth Supplement of USP 23.</td>
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<tr>
<td>2021: “Microbial Enumeration Tests — Nutritional and Dietary Articles”</td>
<td>Compendial guidance in nutritional and dietary supplements areas, especially in the microbiology area, resulted in the development of chapters 2021, 2022 (“Microbiological Procedures for Determining the Absence of Objectionable Microorganisms in Nutritional and Dietary Articles”), and 2023 (“Microbiological Attributes of Nonsterile Nutritional and Dietary Articles”). These were published in PF Previews 25 (5), Sept–Oct 1999. Comments were received, and modified proposals are in preparation to take advantage of the harmonization work done for chapters 61, 62, and 1111.</td>
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</table>
microbiological tests or the implementation of new tests. These publications allow interested parties to comment on potential revisions at the earliest possible date. The presence of new methods proposals in the stimuli section of PF should not be interpreted as an endorsement by the Expert Committee or as a signal that these methods will be included in USP in the future.

These articles are published to generate comments and to bring to the attention of the expert committee and the readers of PF new developments in the field of microbiology that can be applied to new USP tests or considered to be alternative methods to USP microbiological testing.

In Table III we have summarized the microbiology-related stimuli articles published in PF during the 1995–2000 revision cycle.

The introduction and expansion of molecular microbiology have finally moved microbiology from an art to a science. Advances in microbiology sciences will have to be applied to conventional microbiology. This is the newly elected USP Expert Committee's work plan: to bring conventional microbiology into the twenty-first century for use by twenty-first century pharmaceutical manufacturers and regulators.

The accomplishments of the 1995–2000 Microbiology Subcommittee could not have been achieved without the help of the 1995–2000 Microbiology Expert Committee and the Advisory Panel on Microbiological Control and Process Validation, which also have prepared the terrain for further accomplishments in the 2000–2005 revision cycle. Table IV lists the members of these two committees and the members of the advisory panel.