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

A Five-Year Retrospective Leading to the Future

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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-

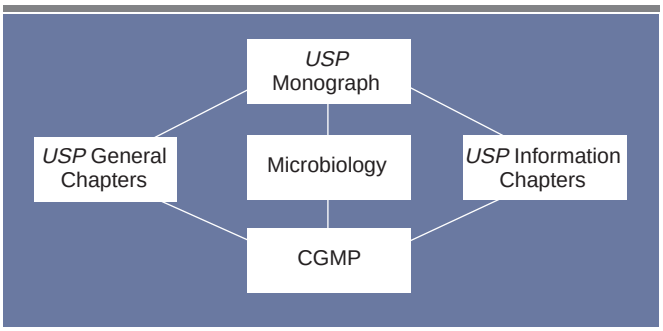

Figure 1: Framework of the role of microbiology in the assessment of microbiological quality of pharmaceuticals.

Table I: Microbiology general chapters activities during the 1995–2000 USP revision cycle.

Chapter	Status
51: "Antimicrobial Preservative Effectiveness"	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.
55: "Biological Indicator Resistance Performance Tests"	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 indicated. These changes were official in the Second Supplement of *USP 24*.
61: "Microbial Limit Tests"	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.
71: "Sterility Tests"	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.
85: "Bacterial Endotoxins Test (BET)"	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)

ment, proposal, and final acceptance of general information chapters to be applied to the microbiological quality assessment of pharmacopeial articles.

The authority for the development of public standards for drugs, including the microbiological requirements, is vested in USP as indicated in the Federal Food, Drug, and Cosmetic Act. USP does not verify compliance of the products against USP standards because that is the responsibility of FDA. Pharmaceutical 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 consensus 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, although many organizations use standards as such.
- They include scientific as well as legal standards.
- Alternative methods to USP standards can be used to determine regulatory compliance to these standards and are acceptable to the regulatory agencies provided that data of equivalency are available for audit by FDA inspectors.

Given the characteristics of USP standards that include microbiological requirements, the impact of microbiological standards and methodologies on the industry and regulators is significant. The Committee of Experts has to be conservative when proposing changes because validation and revalidation of microbiological methods for all products could be required. However, the advances in analytical technologies, especially in the automation and identification of microorganisms, cannot be ignored and pose a challenge to the USP Analytical Microbiology (AMB) Committee of Experts.

The challenge to the Committee of Experts is to respond to the needs of manufacturers and regulators to develop and update various microbiology chapters that directly affect the assurance of microbiological quality of pharmaceutical products.

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

In Table I we have summarized the activities related to general chapters. When appropriate, the international harmonization status of these chapters is indicated. Harmonization initiatives with the Pharmacopoeias of Europe (EP) and Japan

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

Information Chapter	Status
1035: "Biological Indicators for Sterilization"	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.
1111: "Microbiological Attributes of Nonsterile Pharmaceutical Products"	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 pharmacopeia.
1116: "Microbiological Evaluation of Cleanrooms and Other Controlled Environments"	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.
1207: "Sterile Product Packaging — Integrity Evaluation"	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.
1208: "Sterility Testing — Validation Isolator Systems"	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.*
1222: "Terminally Sterilized Pharmaceutical Products — Parametric Release"	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.*
1227: "Validation of Microbial Recovery from Pharmacopeial Articles"	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.*
2021: "Microbial Enumeration Tests — Nutritional and Dietary Articles"	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.

(JP), under the aegis of the Pharmacopeial Discussion Group, also have been linked to the International Conference on Harmonization (ICH) because ICH documents, especially the Q6A document, reference harmonized pharmacological methods as a goal.

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 mi-

Table III: Stimuli articles.

Article	*PF*	Comments
"Harmonization of Microbiological Methods — a Status Report" (R. Dabbah and J. Knapp)	Nov–Dec 1997, **23** (6)	Highlights of similarities and divergences between the EP and USP proposals for sterility tests and antimicrobial effectiveness testing.
"Predictive Antimicrobial Preservative Effectiveness Testing" (S. Shalkowsky)	July–Aug 1996, **22** (4)	Probability model based on short-term experiments measuring inhibition of growth. Can be used to predict the results of the compendial test.
"The Application of Water Activity Measurement to Microbiological Attributes Testing of Raw Materials Used in the Manufacture of Nonsterile Pharmaceutical Products" (R. Friedel)	March–April 1998, **24** (2)	The role of water activity in nonsterile articles is estimated, and a proposal to reduce microbiological testing based on water activity is made.
"Solid Phase Laser-Scanning Cytometry: A New Two-Hour Method for the Enumeration of Microorganisms in Pharmaceutical Water" (D.L. Jones, M.D. Brailsbord, and J.L. Drocourt)	Jan–Feb 1999, **25** (1)	Combines membrane filtration with a fluorescent substrate, epifluorescence microscopy, and laser cytometry to provide almost real-time results.
"Satisfying Microbiological Concerns for Pharmaceutical Purified Water Using a Validated Rapid Test Method" (K.Wills et al.)	Jan–Feb 1998, **24** (1)	A method for rapid check of microbial contamination of process water is described and validated.

Table IV: Members of the 1995–2000 Microbiology Subcommittee, the 2000–2005 Microbiology Expert Committee, and the 1995–2000 Advisory Panel.

1995–2000 Microbiology Subcommittee	2000–2005 Analytical Microbiology Expert Committee	1995–2000 Advisory Panel on Microbiological Control and Process Validation
Joseph E. Knapp, PhD, Chairman	Joseph E. Knapp, PhD, Chairman	Joseph E. Knapp, PhD, Chairman
Henry L. Avallone	Scott V.W. Sutton, PhD, Vice-Chairman	James E. Akers, PhD
Murray S. Cooper, PhD	Anthony M. Cundell, PhD	Michael J. Akers, PhD
Edward A. Fitzgerald, PhD	Edward A. Fitzgerald, PhD	Wei-Wei Chung, PhD
Barry D. Garfinkle, PhD	Dennis E. Guilfoyle, PhD	Richard Levy, PhD
Michael S. Korczynski, PhD	Michael S. Korczynski, PhD	Tibor Matula, PhD
John W. Levchuk, PhD	Robert B. Lemm, PhD	T.C. Soli, PhD
Robert F. Morrissey, PhD	Terry E. Munson	Morlys E. Weary
Terry E. Munson	Donald C. Singer	
Steven L. Nail, PhD	James E. Akers, PhD	
Scott V.W. Sutton, PhD		
Huib J.M. van de Donk, PhD		

crobiological 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 methods.

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. PT