

Technical Report No. 67

Exclusion of Objectionable
Microorganisms from Nonsterile
Pharmaceuticals, Medical Devices,
and Cosmetics

2014



PDA Exclusion of Objectionable Microorganisms from Nonsterile Pharmaceuticals, Medical Devices, and Cosmetics Technical Report Team

Authors

Anil Sawant, Ph.D., Johnson & Johnson (Co-chair)

Anthony M. Cundell, Ph.D., Consultant (Co-chair)

Donald G. Ahearn, Ph.D., Georgia State University

Matthew J. Arduino, M.S., Dr.P.H., Centers for Disease Control and Prevention

Julie Barlasov, MBA., Perritt Laboratories

Mark Dato, M.D., Ph.D., Procter & Gamble

Andrew Dick, Johnson & Johnson

Donald J. English, Avon Products, Inc.

Rhonda Ezell, Qualitest Pharmaceuticals

Dennis E. Guilfoyle, Ph.D., Food and Drug Administration

David Hussong, Ph.D., Food and Drug Administration

Mark Kaiser, Lancaster Laboratories

Michael Long, Dr.LP, Concordia Valsource

Judith Noble-Wang, Ph.D., Centers for Disease Control and Prevention

Per Arne Parment, M.D., Ph.D, Consultant

Dona Reber, Pfizer

David Roesti, Novartis

Frank Settineri, Consultant

Linda Skowronsky, GlaxoSmithKline

Donald Singer, GlaxoSmithKline

John Stone, Ph.D., Kao, USA

Scott Sutton, Ph.D., Microbiology Network, Inc.

Edward Tidswell, Ph.D., Baxter Healthcare

Myriam Sosa, Novartis

Exclusion of Objectionable Microorganisms from Nonsterile Pharmaceuticals, Medical Devices, and Cosmetics

Technical Report No. 67

ISBN 0-80-939459-70-4

© 2001 Parenteral Drug Association, Inc.

All rights reserved.



Table of Contents

1.0 INTRODUCTION	1	7.0 LABORATORY TESTING — MICROBIAL ENUMERATION, DETECTION AND IDENTIFICATION	33
1.1 Purpose.....	1	7.1 General Testing Requirements	33
1.2 Scope.....	1	7.2 Regulatory Requirements and their Relationship to Compendial Methods	34
1.2.1 Exclusions.....	2	7.3 Inconsistencies and Contradictions Among USP/NF Monographs	35
2.0 GLOSSARY OF TERMS.....	3	7.4 Laboratory Testing for Microbial Enumeration, Absence of Specified Microorganisms and Microbial Identification	35
3.0 REGULATORY, COMPENDIAL AND SCIENTIFIC ENVIRONMENT	5	7.4.1 USP/EP/JP Harmonized Chapters <61>, <62>, and <111>	35
3.1 GMP.....	5	7.4.2 Chinese Pharmacopoeia Appendix XI J — Microbial Limit Tests	36
3.2 Compendial Microbiological Testing	5	7.4.3 Chapter 23, “Microbiological Methods for Cosmetics” of the FDA’s BAM.....	37
3.3 Implications of the Human Microbiome Project..	7	7.4.4 Cosmetics Toiletries & Fragrance Association Methods for Microbial Content and Examination to <i>S. aureus</i> , <i>E. coli</i> and <i>P. aeruginosa</i>	38
3.4 Quality Risk Management	7	7.4.5 ISO Standards	38
4.0 INDUSTRY BENCHMARKING	9	7.4.6 Microbial Identification	40
5.0 PRODUCT TYPES AND FORMULATION.....	11	7.5 Screening for Objectionable Microorganisms ..	41
5.1 Microbial Risk Evaluation.....	11	7.5.1 Laboratory Management Recommendation to the Quality Unit for Batch Release	42
5.2 Hurdle Technology: Background	12	7.6 Sample Handling, Transportation and Storage ..	43
5.3 Hurdle Technology in Product Development....	13	8.0 CLINICAL CONSIDERATIONS FOR SELECTING ISOLATES FOR ASSESMENT OF THEIR STATUS AS OBJECTIONABLE OR NOT.....	44
5.4 Intermediate A _w Formulations	15	8.1 Microorganisms Associated with Product Recalls	44
5.5 High A _w Formulations.....	15	8.2 Microorganisms Associated with Clinically Significant Infections	44
5.6 Risk Assessment of the Manufacturing Processes of Pharmaceutical, Medical Device and Cosmetic Ingredients and their Use in Nonsterile Products..	16	8.3 Microorganisms Associated with Outbreak Investigations by the Centers for Disease Control and Prevention.....	45
5.7 Preservative Systems in Nonsterile Pharmaceutical and OTC Drug Products	16	8.4 <i>Burkholderia cepacia</i> Complex	48
5.8 Packaging Considerations for Nonsterile Product Dosage Forms.....	20	8.5 Pathogens Listed by Research Organizations, Regulatory Agencies and Authors of Prominent Microbiology Textbooks.....	49
5.8.1 Package Design, Material, Construction and Function	22	9.0 RISK ASSESSMENT AND MITIGATION	51
5.8.2 Manner and Site of Application Based on the Package	23	9.1 Risk-Based Approaches.....	51
5.8.3 Frequency and Duration of Product Package Use	24	9.2 Risk Assessment	51
5.8.4 Environment Under Which the Product Packaging is Used and Stored	24	9.2.1 Determination of Isolate’s Novelty	51
6.0 MITIGATING RISK THROUGH PROCESS DESIGN, MANUFACTURING AND PACKAGING OPERATIONS.....	26	9.2.2 Determination of Known Pathogenicity	52
6.1 Manufacturing Process Equipment.....	26	9.2.3 Assessment of Survivorship	52
6.2 Basic Hygienic Designs of Process Equipment...26	26	9.2.4 Determination of Product or Container Impact.....	52
6.3 Preventative Maintenance	27		
6.4 Cleaning and Sanitization Practices	27		
6.4.1 Cleaning In Place.....	28		
6.4.2 Choosing Detergents.....	29		
6.4.3 Draining and Drying of Equipment.....	31		
6.5 Manufacturing Processes and Microbial Content..	31		

9.2.5	Assessment of Quantity or Bioburden	52
9.2.6	Nature of Product.....	52
9.2.7	Route of Administration	53
9.2.8	Target Patient Population	53
9.3	Decision Tree	54

10.0 CONCLUSIONS	56
-------------------------------	-----------

11.0 REFERENCES	57
------------------------------	-----------

FIGURES AND TABLES INDEX

Figure 3.4-1	Application of Quality Risk Management... 8	Table 7.4.1-1	Harmonized and Recommended Microbiological Quality Requirements for Nonsterile Drug Dosage Forms (Adapted from <i>USP <1171></i> , 10)..... 36		
Figure 5.2-1	Hurdle Technology	12	Table 7.5-1	Decision Matrix for Screening for Objectionable Microorganisms..... 41	
Table 5.3-1	A _w Requirements for Growth of Representative Microorganisms Cited in Compendial Chapters.....	13	Table 8.3-1	Major Outbreaks Associated with Contaminated Nonsterile Products in 1971-2011	46
Table 5.3-2	A _w and Limits (Threshold) for Microbial Growth Associated with Different Pharmaceutical Dosage Forms.....	14	Table 8.3-2	Most Significant Microorganisms Associated with the Ten Most Common Product Recalls, Major Outbreaks Related to Nonsterile Products and Nosocomial Infections	48
Table 5.6-1	Risk Analysis of Ingredients by Starting Material and Process Origin.....	16	Table 8.5-1	Microorganisms Usually Associated with Human Disease When Isolated from Clinical Specimens	49
Table 5.7-1	Differences in Pharmacopoeia Log Reduction Acceptance Criteria by Product Type for Microbial Challenge Testing	17	Figure 9.3-1	Objectionable Microorganism Risk Decision Tree	55
Table 5.8.1-1	Applications of Different Resin Categories in Packaging	23			
Table 6.4.2-1	Characteristics of Cleaning Agents.....	30			
Table 7.1-1	Summary of Microbial Testing Methods that May be Employed for Pharmaceutical Drug Products, Consumer Health Products, Medical Devices and Cosmetics	33			

1.0 Introduction

The exclusion of objectionable microorganisms from nonsterile healthcare products is a challenge for companies because it can be viewed as an undefined critical quality attribute. All other chemical, physical and microbiological attributes (e.g. potency, content variability, microbial count) are defined by test methods and product specifications, whereas the exclusion of objectionable microorganisms is poorly defined. This consensus industry document was developed by representatives of the pharmaceutical, medical device and cosmetic industries, academia and regulatory agencies and provides guidance to stakeholders, including industry representatives and regulators, to address these issues.

1.1 Purpose

The purpose of this technical report is to provide guidance to the nonsterile product manufacturing industry on how to manage the microbial risks associated with manufacturing and storage and how to determine what isolates would be deemed an objectionable microorganism in nonsterile products that is in alignment with the microbial limits requirements for releasing these products into the marketplace. Nonsterile products exceeding the microbial count limit and/or containing specified microorganisms for their product type would be expected to be rejected. Specific microorganisms include microorganisms with compendial requirements to be absent in a particular dosage form, and/or required by a national board of health to be excluded from a registered non-sterile product.

The contamination of marketed products by potentially objectionable microorganisms continues to be an infrequent but chronic problem. A U.S. survey of reported microbiologically related recalls between 2004 and 2011 found that 72% of recalls of nonsterile products were associated with objectionable microorganisms rather than exceeding microbial enumeration limits (1). Of the 144 recalls for nonsterile products, 5% involved nonsterile pharmaceutical drug products, 42% were for OTC drug products, 31% were for cosmetics, 14% were for medical devices and 8% were for dietary supplements. The average rate of reported recalls is 20 per year.

1.2 Scope

The scope of this technical report is the exclusion of objectionable microorganisms from nonsterile pharmaceutical drug products, over-the-counter (OTC) drug products; medical devices; cosmetics; and personal care products in the pharmaceutical, medical device, cosmetics and consumer healthcare industries (referred to as “our industry” in the remainder of this report). Objectionable microorganisms for nonsterile products, as cited in the United States Code of Federal Regulations (CFR) Title 21, Part 211.113, are microorganisms whose growth or persistence in nonsterile products can cause harm to users of those products and degrade the physico-chemical, functional and/or therapeutic attributes of the products (2).

Since all viable microorganisms are excluded from sterile products, the term “objectionable microorganisms” is used to refer only to nonsterile products. Some discussion of microorganisms contaminating sterile products and food may be included in this report for informational purposes, but, in general, such discussion is out of scope for the technical report.

This report provides the following information:

- References to literature on microbial contamination of nonsterile products
- Product types and their formulations as these relate to microbial contamination
- Manufacturing and packaging design and control
- Microbial enumeration, detection and identification
- Clinical aspects of objectionable microorganisms
- Risk assessment and mitigation