Technical Report No. 67
Exclusion of Objectionable Microorganisms from Nonsterile Pharmaceuticals, Medical Devices, and Cosmetics
The content of this technical report represents a consensus and not necessarily the views of the organizations that employ the team members.
Exclusion of Objectionable Microorganisms from Nonsterile Pharmaceuticals, Medical Devices, and Cosmetics

Technical Report No. 67

ISBN: 978-0-939459-70-4
© 2014 Parenteral Drug Association, Inc.
All rights reserved.

PDA
Parenteral Drug Association
Table of Contents

1.0 INTRODUCTION ...................................................... 1
  1.1 Purpose .......................................................... 1
  1.2 Scope ............................................................ 1
    1.2.1 Exclusions .................................................. 2

2.0 GLOSSARY OF TERMS ............................................. 3

3.0 REGULATORY, COMPENDIAL AND SCIENTIFIC
  ENVIRONMENT .................................................. 5
  3.1 GMP .............................................................. 5
  3.2 Compendial Microbiological Testing ....................... 5
  3.3 Implications of the Human Microbiome Project .. 7
  3.4 Quality Risk Management .................................. 7

4.0 INDUSTRY BENCHMARKING .................................... 9

5.0 PRODUCT TYPES AND FORMULATION ...................... 11
  5.1 Microbial Risk Evaluation .................................. 11
  5.2 Hurdle Technology: Background .......................... 12
  5.3 Hurdle Technology in Product Development ............ 13
  5.4 Intermediate A<sub>n</sub> Formulations ................. 15
  5.5 High A<sub>n</sub> Formulations ................................ 15
  5.6 Risk Assessment of the Manufacturing Processes 
      of Pharmaceutical, Medical Device and Cosmetic
      Ingredients and their Use in Nonsterile Products .. 16
  5.7 Preservative Systems in Nonsterile 
      Pharmaceutical and OTC Drug Products .............. 18
  5.8 Packaging Considerations for Nonsterile 
      Product Formulations ................................. 20
    5.8.1 Package Design, Material, 
          Construction and Function......................... 22
    5.8.2 Manner and Site of Application
          Based on the Package .................................. 23
    5.8.3 Frequency and Duration of Product 
          Package Use ............................................. 24
    5.8.4 Environment Under Which the Product 
          Package is Used and Stored ......................... 24

6.0 MITIGATING RISK THROUGH PROCESS
  DESIGN, MANUFACTURING AND PACKAGING
  OPERATIONS .................................................. 26
  6.1 Manufacturing Process Equipment ....................... 26
  6.2 Basic Hygienic Designs of Process Equipment ... 26
  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

7.0 LABORATORY TESTING — MICROBIAL
  ENUMERATION, DETECTION AND
  IDENTIFICATION ................................................. 33
  7.1 General Testing Requirements ............................ 33
  7.2 Regulatory Requirements and their 
      Relationship to Compendial Methods ................. 34
  7.3 Inconsistencies and Contradictions Among 
      USP/NF Monographs ......................................... 35
  7.4 Laboratory Testing for Microbial Enumeration,
      Absence of Specified Microorganisms and 
      Microbial Identification ................................ 35
    7.4.1 USP/EP/JP Harmonized Chapters
          <61>, <62>, and <1111> ......................... 35
    7.4.2 Chinese Pharmacopoeia 
          Appendix XI J – Microbial Limit Tests ...... 36
    7.4.3 Chapter 23, “Microbiological Methods for
          Cosmetics,” of the FDA’s BAM ...................... 37
    7.4.4 Cosmetics Toiletries & Fragrance Association
          Methods for Microbial Content and Examination
          for S. aureus, E. coli and P. aeruginosa ........... 38
    7.4.5 ISO Standards ......................................... 38
    7.4.6 Microbial Identification .......................... 40
  7.5 Screening for Objectionable Microorganisms .. 41
    7.5.1 Laboratory Management Recommendation
          to the Quality Unit for Batch Release ........... 42
  7.6 Sample Handling, Transportation and Storage .. 43

8.0 CLINICAL CONSIDERATIONS FOR SELECTING
  ISOLATES FOR ASSESSMENT OF THEIR STATUS
  AS OBJECTIONABLE OR NOT ................................. 44
    8.1 Microorganisms Associated with
        Product Recalls ......................................... 44
    8.2 Microorganisms Associated with
        Clinically Significant Infections ................... 44
    8.3 Microorganisms Associated with Outbreak
        Investigations by the Centers for Disease Control
        and Prevention .............................................. 45
    8.4 Burkholderia cepacia Complex ......................... 48
    8.5 Pathogens Listed by Research Organizations,
        Regulatory Agencies and Authors of Prominent
        Microbiology Textbooks ............................... 49

9.0 RISK ASSESSMENT AND MITIGATION ..................... 51
  9.1 Risk-Based Approaches ..................................... 51
  9.2 Risk Assessment ............................................. 51
    9.2.1 Determination of Isolate’s Novelty ............... 51
    9.2.2 Determination of Known Pathogenicity ......... 52
    9.2.3 Assessment of Survivorship ....................... 52
    9.2.4 Determination of Product or 
          Container Impact ..................................... 52
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. Specified 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 U.S. 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 physicochemical, functional and/or therapeutic attributes of the products (2).

Since all viable microorganisms are excluded from sterile products, the term “objectionable microorganism” 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
Definitions of technical terms as used in this report can be found in the glossary (Section 2.0). The task force members strongly believe that the correct usage of technical terms is fundamental to the rigorous discussion of a technical issue, hence the inclusion of a glossary. Whenever, possible definitions used are from regulatory and compendial sources. The principles and tools used to manage objectionable microorganisms are defined in Section 3.0 of this report.

In addition, this report provides a risk assessment decision tree for the evaluation of microorganisms of potential concern and summary regulatory expectations (Section 9.0).

A risk-based approach is taken in this technical report because a microorganism isolated from a product cannot be considered objectionable without consideration of the product’s attributes, number of organisms found, their potential pathogenicity, their ability to survive and grow in the product and the intended use of the product. Any decision about the product’s disposition needs to be made in this context.

No definitive list of objectionable microorganisms is provided in this technical report, but microorganisms of potential concern are highlighted from the literature concerning product contamination, infection outbreaks (especially those associated with nonsterile products), product recalls and clinical experience with known pathogens and other opportunistic microorganisms at the site of administration of non-parenteral-drug formulations.

The absence of a list of objectionable microorganisms from this technical report acknowledges that the manufacturer of the product has all of the variable information, about a product and its intended use, needed to make an informed decision regarding the product’s disposition. This belief is consistent with the U.S. cGMP regulations, which assign the responsibility for excluding objectionable microorganisms specifically to the manufacturer. Furthermore, the publication of a list might discourage microbial risk management by manufacturers and encourage manufacturers to simply check off microorganisms from the list without a critical review.

This document is intended to be globally applicable. When country-specific regulations are cited, they are meant to serve as examples of such and are not binding to the industry stakeholders outside the country’s jurisdiction.

1.2.1 Exclusions

Microbial toxins and viruses were determined out of scope of this technical report for the following reasons. Bioburdens below the microbial limits specified by standard-setting organizations are not expected to generate clinically significant quantities of these toxins. If, for example, the weight of 10^6 conidia of *Aspergillus flavus* is approximately 10 mg and the conidia contain about 650 parts per million (ppm) of aflatoxins B1 and G1 (3), a single conidium contains approximately 2.0 × 10^2 ng of aflatoxin (limits or detection approximately 1 ng/g). Therefore, ingestion of nearly 3 × 10^6 conidia of *A. flavus* would be required to achieve even a detectable level of aflatoxin, and this level would still be well below U.S. Food and Drug Administration (FDA) limits for food. In another example, critical reviews of the health implications of mycotoxins in indoor environs, including the “toxic black mold” *Stachybotrys chartarum*, have found no causal relationship between inhaled mycotoxins and adverse effects on human health (4-6).

The absence of viruses is not considered a critical quality attribute for nonsterile products manufactured in compliance with cGMP regulations or other quality standards and, hence, is out of scope for this technical report.