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

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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

The content of this technical report represents a consensus and not necessarily the views of the organizations that employ the team members.

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1.0 Introduction

The exclusion of objectionable microoganisms 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 10^9 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^{-3} 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.