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OBJECTIONABLE MICROORGANISMS

A CHALLENGE OR A DILEMMA

KEYWORDS

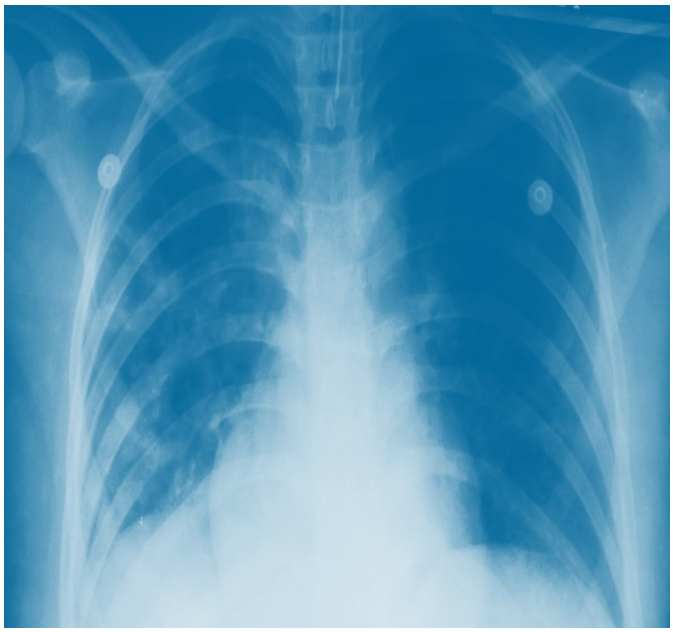
Objectionable, Compendial, Pathogenecity, Virulence, Clinical

ABSTRACT

The compendial tests described for testing non-sterile products were not designed to be all-inclusive, i.e., to detect all potential pathogens. To identify organisms that can cause direct of indirect harm to the patient, an extensive effort for identifying these objectionable organisms, their clinical relevance as well as methods of detection for these microorganisms would be required. The compendial chapters for testing non-sterile products do not provide specific methods, nor do they provide procedures for detecting thousands of other potentially pathogenic organisms. The discussion of "What is an Objectionable Organism?" is a critical one, and one that demands a commitment from management and participation from all departments involved in the manufacture and release of a non-sterile product. Personnel with extensive experience in clinical microbiology who can make an educated judgement are extremely important.

INTRODUCTION

No non-sterile drug manufacturer wishes to release a product contaminated with objectionable microorganisms, but how does the manufacturer know which organisms are objectionable in their product and how do they ensure their drugs do not contain them? Specified organisms outlined in compendia do not include all the organisms that can be harmful to the patient via a specific mode of administration. Moreover, there could be indirect harm to the patient if the objectionable organism migrates to other parts of the body or affects critical organ function. There are general guidelines proposed for identifying objectionable organisms, however some of the information required for following these guidelines may not be available to the persons tasked with this important assignment. A holistic science based approach is required which includes understanding the organism, its mode of infection, its established pathogenicity or opportunistic behavior, the method it uses to cause harm as well as the level of virulence.



An objectionable organism is one which can either cause illness or degrade the product thus making it less effective. The U.S. Food and Drug Administration (FDA) states, "Appropriate written procedures designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established." (21 CFR 211.113) FDA continues, "Appropriate laboratory testing must be conducted on each batch of drug required to be free of objectionable organisms." (21 CFR 211.165)

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THE CHALLENGE

Identifying objectionable organisms in a non-sterile product is a challenge most quality control microbiologists have to face at least once in their career. This is a daunting task for microbiologists who have no training in clinical microbiology. Often the information required about the patient population the non-sterile drug is administered to may not be available or vague. There is an increasing requirement for all non-sterile manufacturers to establish a list of organisms that are objectionable in the product they manufacture. However there is no defined guideline on how to go about this daunting task.

SPECIFIED ORGANISMS LISTED IN THE PHARMACOPEIA

Per 21CFR 211.113. Control of microbiological contamination, appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed (7).

Regulators have acknowledged that the USP Microbiological Attributes Chapter <1111> provides little specific guidance other than the significance of microorganisms in non-sterile pharmaceutical products should be evaluated in terms of the use of the product, the nature of the product, and the potential hazard to the user (4).

TGA Order 77 states it very clearly that the microbial attributes of a non-sterile medicine described in the Order and in the pharmacopoeias should not be regarded as comprehensive microbial limit specifications, but rather as the minimal requirements to be met throughout the shelf life of the medicine. TGA expects that the sponsor will determine the risk to their product from other objectionable microorganisms (2).

USP chapter <1111> and Ph Eur section 5.1.4 state that while the tests for Specified Microorganisms indicate requirements to examine certain organisms depending on the product type, these lists are not exhaustive, and for particular sample preparations it may be necessary to test for other microorganisms. This is dependent on the nature of the product, its starting materials and the manufacturing process (1, 3).

Keeping in mind the statements from the FDA, Pharmacopieas and guidances, identifying objectionable microrganisms, their impact on the patient, and also development of methods to test them routinely and validating the test method is crucial. Compendia only provide test methods for the specified microorganism, hence it falls on the microbiologist to understand growth characteristics of the organisms that are deemed to be objectionable in the product. This may involve using conventional microbiology and biochemical methods such are carbon utilization and ancillary tests.

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Proposed vs Attainable Risk Assessment

Some non-sterile drugs may be for a known patient population where identifying risk of an organism could be easier than in products where the immune health, gender, and the age of the patient is not known.
The following factors are proposed by regulators to be evaluated when identifying objectionable microorganisms in non-sterile products. Since microbiologists are rarely privy to some of the information required to perform an informed risk assessment, one should understand the difference between true pathogens and opportunistic pathogens.

- Whether or not the product supports growth.
  - The composition of the product and whether the organism will use it as a carbon source needs to be understood. Additionally, the moisture content and other abiotic and biotic factors that can support growth and proliferate should be carefully considered. This information is rarely known to the microbiologist or may not be considered during risk assessment.
- Whether the product has adequate antimicrobial preservation.
  - Antimicrobial efficacy testing is performed using a panel of organisms suggested in USP Chapter <51>. Though the antimicrobial property of the product will deter the growth of the tested USP challenge organism, there is no guarantee that other organisms will not circumvent the antimicrobial in the product and may survive or even thrive in the product.
- Water Activity.
  - Water activity data can provide valuable information on the organisms that may survive or proliferate in the product over its shelf life. However, the number of objectionable microorganisms present in the product is a key factor for determining infectivity.
- The use of the product, due to the fact that hazard varies according to the route of administration via the eye, nose, or respiratory tract.
  - It is known from the archives of clinical publications that the hazardous effect of the objectionable organisms may go beyond the initial route of administration. Causative organisms of pneumonia may get disseminated to other sites (i.e., brain, meninges, skin, liver, spleen, kidneys, adrenals, heart, eyes) and sepsis syndrome and well as blood vessel invasion leading to other health challenges. Nasal infections may lead to pulmonary infections, cutaneous infections may lead to sepsis, and the organism that causes eye lid infections may also cause keratitis. Hence the understanding of health hazards beyond the route of administration are equally important.
- The method of application.
  - The risk due to method of application can vary in each product. One also has to consider whether the product is for single-use or multi-use as environmental factors may add to contamination or increase of bioburden in the product.
- The presence of disease, wounds, or organ damage.
  - This information about disease or organ damage will never be available to the microbiologist; however where there is obvious route of infection such as contact with blood vessels in wound care products possibility of systemic infections should also be considered.
- The intended recipient; as risk may differ for neonates, infants, and the elderly.
  - Unless the product is exclusively for neonates and infants or elderly, research for objectionability of the organism may become difficult; however if targeted research is performed for each of the patient populations, relevant information may be retrieved.
- The use of immunosuppressive agents and corticosteroids.
  - This information will rarely be available for the microbiologist performing risk assessment and attempting to identify objectionable microorganisms in the product.

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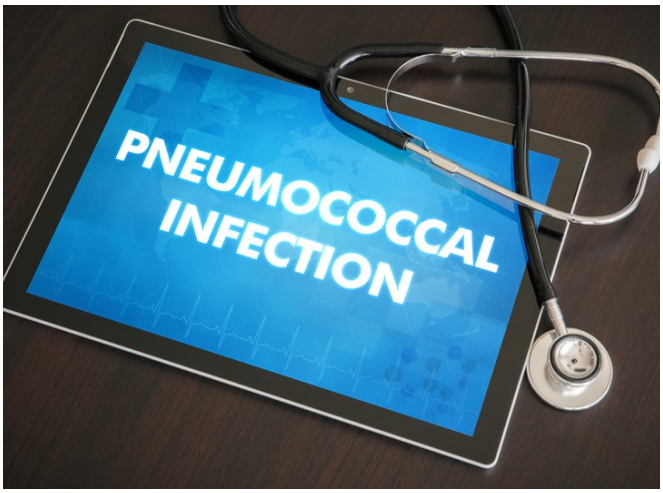
Types of Pathogens

Knowing that there always will be a lack of some important information; how should one assess if the organism is objectionable in the product of not. The first thing to understand is if the organism is a dedicated pathogen and does not require that the host be immunocompromised or injured. These dedicated pathogens have developed highly specialized mechanisms for crossing cellular and biochemical barriers and for eliciting specific responses from the host organism which contribute to the survival and multiplication of the pathogen.



Other microorganisms replicate in an environmental reservoir such as water or soil and only cause disease if they happen to encounter a susceptible host; these are known as facultative pathogens. Opportunistic pathogens are the ones that are normally benign but have an underlying ability to cause disease in an injured or immunocompromised host.

Infections Beyond Point of Entry

Though objectionable organisms are important to address in non-sterile products, it is also important to understand septicemia and systemic infections. Sepsis is among the most common causes of death in hospitalized patients. Its death toll is in the same range as that of myocardial infarction (45).

While any type of infection — bacterial or fungal — can lead to sepsis, the most likely causes include (49):

- Pneumonia
- Abdominal infection
- Kidney infection
- Bloodstream infection (bacteremia)

This makes it clear that nasal, inhalation or even oral non-sterile products with causative organisms can cause collateral damage if the host response is not optimal. Various skin and soft tissue infections (SSTIs) include a wide variety of infections of the epidermis, dermis, subcutaneous tissue, fascia and muscle. Any contaminated non-sterile product which comes in contact with blood vessels has the opportunity to cause sepsis or other systemic infections within the host (50). Hence when conducting risk assessment, the clinical implications of the organism beyond the route or point of administration should not be ignored.

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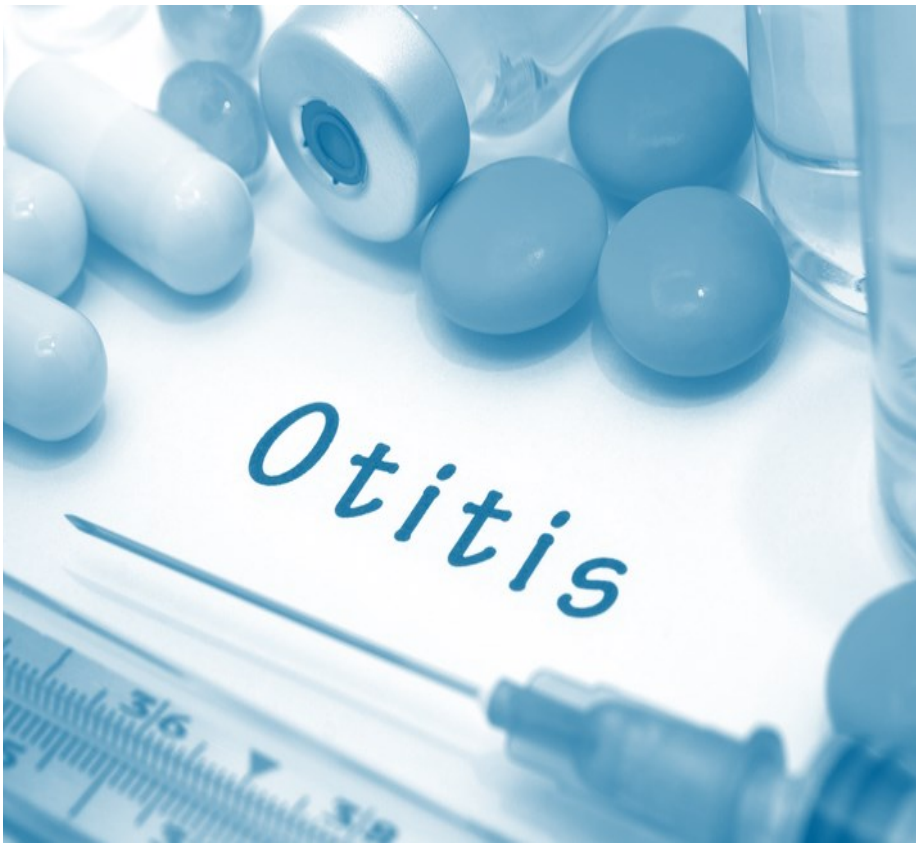
Identifying Objectionable in the Product

The criticality of knowing the various types of colonies and identifying unique isolates from either or both Total Plate Count testing and enrichment testing is rarely emphasized . A product may pass TAMC or TYMC tests, however there could be predominance of an organism or a few colonies of an objectionable organism. For example TAMC for an oral dosage form passes TAMC but the majority of the colonies are Bacillus cereus which is objectionable via oral mode of administration (5). Another good example would be Aspergillus fumigatus colonies in nasal products, where this mold is the main causative agent for fungal pneumonia in immunocompromised patients (6).

Research Strategy for Risk Assessment

Before any risk assessment is performed it is valuable to validate the microbial identification result. An incorrect identification may make the research futile leading to incorrect assumptions. All relevant peer reviewed medical articles should be researched utilizing specific indications as well as the organisms to assess risk. Review of the CDC site as well as CDC's morbidity mortality reports and publications of emerging infections provide valuable information. Clinical microbiology text books are very helpful in gathering information on specific organisms and mode of infection especially for organisms with well established pathogenicity.

It is important that the product release or rejection is not based on just one reference or article such as FDA's "Bad Bug Book" (8). It is evident from medical journals that infectious agents evolve and new infections are continually discovered. A relevant example of such a scenario is the New England Compounding Center fungal meningitis outbreak, which began in September 2012, as it sickened over 800 individuals and resulted in the deaths of 76, two of the isolates had not previously caused fungal meningitis. Emerging pathogens should also be researched (11).



Additional information of infectivity, pathogenicity as well as virulence of the organism should be researched. Some organisms will cause infections with a few cells while others require larger number of cells to become infectious. The mechanism used by the organisms to cause harm should be also well understood, such as by use of endotoxins, exotoxins or mere growth and proliferation within human tissue (9,10) .

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CONCLUSION

Establishing objectionable organisms warrants extensive research of reliable clinical resources and risk-based assessment of the relevant factors. This should be conducted by personnel with specialized training in microbiology, preferably clinical microbiology, and with the interpretation of microbiological data. This assessment starts with ensuring that microbial identification results are valid. No one resource will provide all information required to make an educated decision about the microorganism's history or capability of causing infection via the mode of administration for a set patient population. Most importantly infectivity as well as virulence should be considered to avoid pitfalls such as rejecting a product that is safe or releasing a product that is not safe.

ABOUT THE AUTHOR

Ziva Abraham is the President and Founder of Microrite, Inc., a California based consulting firm providing consulting and training services to pharmaceuticals, biotechnology, medical devices and in vitro diagnostics in the areas of quality assurance, quality control, microbiology, and validation. Ziva has over 25 years of academic, research, clinical and industrial experience in microbiology, and quality assurance. Ziva has received her Master's Degree in microbiology and has worked on developing microbial insecticides using entomogenous bacteria and fungi towards her doctoral research. Her career also includes founding and managing clinical laboratories for Maccabi Medical in Israel. She has trained personnel from various industries in microbiology techniques and methods. She uses her extensive experience to teach why assessing risk of microbial contamination should be in the forefront of any company that has products for human/veterinary use. Her experience in clinical laboratories has provided her with the framework to understand the effects of microbial contamination in products from a patient safety perspective.

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