

## Objectionable Microorganisms: Keeping Bad Bugs Out of Good Products

By: Laurie Kundrat



No pharmaceutical company wants to sell a non-sterile drug which is contaminated with objectionable microorganisms, but how does a company know which organisms are objectionable and how do they ensure that their drugs do not contain them?

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

USP <1111>, "Microbiological Examination of Nonsterile Products" lists several organisms which, depending on the route of administration, can be objectionable in a drug. The microorganisms are *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and bile-tolerant gram-negative bacteria. When relevant, USP monographs call for the absence of one or more of these organisms. The organisms can be detected using methods described in USP <62>, "Tests for Specified Organisms". The tests call for the use of enrichment and selective media.

USP <1111> cautions other organisms can also be objectionable. It is the responsibility of the manufacturer of the drug to test for microorganisms which can cause potential harm. In order to determine if an organism is objectionable, the manufacturer must consider the risk imposed by the organism. Factors to take into consideration are the microorganism's characteristics, the route of administration of the drug, the nature of the product, and the intended recipient.

### **The microorganisms:**

A manufacturer can detect objectionable organisms in its product by:

1. Performing tests for specified microorganisms as described in USP <62>.
2. Identifying all suspicious colonies growing on agar plates used in microbial enumeration tests. To find out more about microbial enumeration tests, see USP <61>.
3. Performing a risk analysis to determine which organisms would be objectionable and then devising a plan for detecting the organisms.

Microorganisms, once isolated from a product, can be identified using phenotypic or genotypic methods. There are several microorganism identification systems which use phenotypic (biochemical) means to identify an organism. Genotypic testing can be done to the species or strain level. Some genotypic methods are PCR, 16S and 23S rRNA sequencing, and analytical ribotyping.

Several resources are available for assessing the potential harm a microorganism can cause. Information about the microorganism can be found in the U.S. Food and Drug Administration Bad Bug Book, Manual of Clinical Microbiology, Bergey's Manual of Systematic Bacteriology, and in scientific articles found online. The National Institute of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) has classified human etiologic agents on the basis of hazard. Microorganisms are listed in Risk Groups 1-4, 4 being the most dangerous.

Keep in mind that some microorganisms produce toxins. Other organisms produce spores which are more difficult to kill than vegetative bacteria.

In recent years, there have been several recalls of non-sterile product due to objectionable organisms. Among those, non-sterile providine iodine prep pads were recalled because analytical testing showed the presence of *Elizabethkingia meningoseptica*, also, non-sterile alcohol swabs were recalled due to potential contamination with *Bacillus cereus*.

### **The route of administration:**

Whether an organism is objectionable or not depends on the route of administration. For example, USP <1111> says *Candida albicans* should not be present in drugs when the route of administration is vaginal.

An organism not listed in USP <1111>, *Burkholderia cepacia*, can be particularly harmful to cystic fibrosis patients when inhaled. In 1992, Metaproterenol Sulfate Inhalation Solution, a bronchodilator solution, was recalled because the product was contaminated with *Pseudomonas gladiolil cepacia*. The FDA determined that the contamination could be life-threatening to patients with chronic obstructive airway disease, with cystic fibrosis (CF), or with compromised immune systems. In 2012, there was an outbreak of *Burkholderia cepacia* complex in the intensive care unit at a German hospital. The outbreak was traced back to alcohol-free mouthwash.

**Nature of the product:**

Certain characteristics, such as high water content and closures that do not restrict access to the environment, make it easier for organisms to proliferate.

Some components in the drug may be susceptible to certain categories of microorganisms. For example, animal components may be susceptible to contamination with *Salmonella* species. Some drugs may contain nutrients which an organism can metabolize, thus degrading the product. Information about which nutrients a microorganism metabolizes can be found by performing a battery of biochemical tests such as the ones found in the API®, Biolog® or Vitek® 2 systems.

Be suspicious if the total aerobic count for the drug is higher than usual. It might mean that the drug's preservative is not performing to specification or that it was made incorrectly. It is also possible that a raw material, used to make the drug, was contaminated.

**The intended recipient:**

Who will be using the drug? Elderly and immuno-compromised patients are more susceptible to microorganisms that healthy individuals tolerate. In 2001 MICRONASE® tablets were recalled because fungal elements were found in some lots of tablets. The company reported that the fungi/molds detected may make it difficult to treat infections in immuno-compromised patients such as diabetics and HIV and renal transplant patients who also have diabetes.

Another consideration is whether the organism produces substances, such as penicillin, which can cause allergic reactions in some recipients.

**What can laboratories do to ensure that non-sterile products are safe?**

- Laboratories can do the following:
- Perform a risk assessment to determine which microorganisms could be harmful based on the route of administration, the user and the properties of the drug.
- Scan for potential problems by researching past recalls in similar products. An archive of U.S. Food and Drug Administration Warning Letters is available on the FDA's website.
- Use enrichment and selective media to find objectionable organisms.
- Identify suspicious colonies found when performing total aerobic counts.
- Follow pharmacopeia guidelines for microbial enumeration and tests for specified microorganisms.
- Perform growth promotion testing on all batches of media used in aerobic plate counts and tests for specified and objectionable organisms.
- Validate all tests used for isolating and identifying organisms.
- Routinely perform environmental monitoring. Identify the organisms that are isolated. Determine if these organisms could degrade the drug or be harmful to users of the drug.
- Perform disinfectant challenge testing to determine which disinfectant(s) to use at the manufacturing site.
- Perform bioburden testing in order to discover any weaknesses in the manufacturing process.
- Keep current with trends in pharmaceutical microbiology by attending webinars and conferences and reading scholarly articles.

## Biography:



Laurie Kundrat is a Technical Support Specialist at Microbiologics, Inc. Laurie received a Biology degree from Case Western Reserve University and earned a Medical Technology degree from Fairview General Hospital. With over 25 years of experience as a microbiologist, Laurie has grown to love all types of bacteria and she also loves talking to customers and helping them use Microbiologics products successfully.

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