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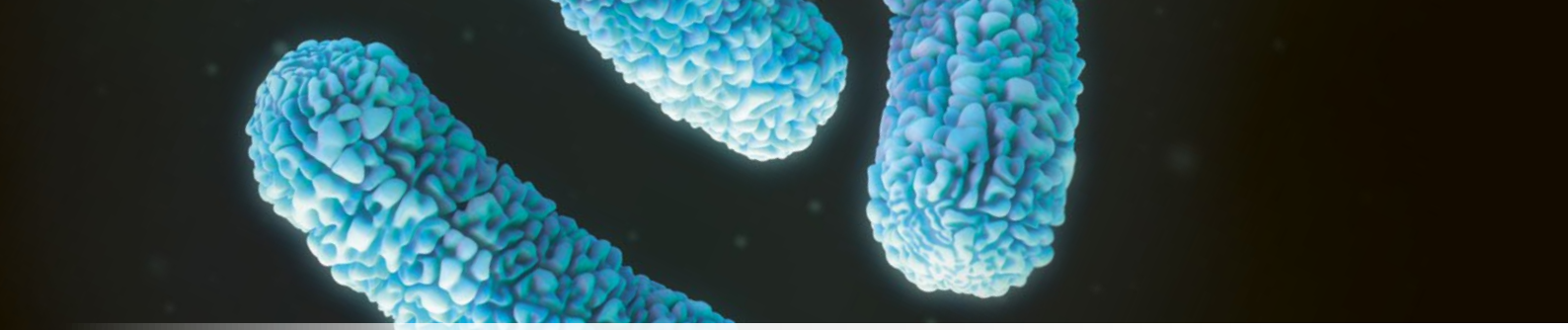
ANALYTICS

N° 1
January 2020

Pharma

Objectionable microorganisms



Objectionable microorganisms

Introduction

A large part of the drugs on the market are non-sterile pharmaceutical products in various dosage forms such as ointments, sprays, tablets, liquids or powders. As the name implies, it is not necessary for these products to be sterile. However, depending on the area of application, strict specifications apply with regard to the maximum microbiological contamination (bacteria, yeasts and moulds). For example, products for use on the skin should have a maximum of 200 CFU/g aerobic, mesophilic germs (TAMC; total aerobic microbial count) and a maximum of 20 CFU/g yeasts and moulds (TYMC; total yeasts and moulds count) according to the recommendations in the pharmacopoeiae1. In addition, they should not contain potentially dangerous germs of the species *Pseudomonas aeruginosa* and *Staphylococcus aureus*[1]. This is to prevent patients who use the product for healing purposes from contracting an infection caused by the drug. But what about other, potentially dangerous germs that may be contained in the product but whose presence does not have to be explicitly excluded by laboratory analyses? Can germs that are detected during analysis for TAMC and TYMC be neglected as long as the specification limit is not exceeded? What if the analysis for *Pseudomonas aeruginosa* and *Staphylococcus aureus* detects other germs by chance? Manufacturers of pharmaceuticals should evaluate these aspects in a process and product specific manner in the context of a risk assessment.

Definition of "objectionable microorganisms" and risk analysis

So-called "objectionable microorganisms" are not precisely defined. This includes microorganisms whose growth or retention in the non-sterile product is harmful to the patient.[2] On the other hand, this refers to microorganisms which may impair the physico-chemical, functional or therapeutic properties of the drug.[2] Consequently, different microorganisms are important depending on the product and application. The faecal bacterium *Escherichia coli,* for example, is not critical in principle in an ointment for cutaneous application, as long as it does not impair the product. Nevertheless, a manufacturing company would have to check where the germ comes from and how it could get into the production line or the product in order to reduce the general risk of contamination.

Table 1:

Risk factor	Low risk	High risk
Quality of raw materials	Sterile raw materials	Unprocessed natural products
Quality of production water	Water for injection purposes (Ph. Eur. Mono. 0169)	Normal drinking water
Production site	Sterile filling in isolator	Old production site
Ambient air	Clean room with HEPA filtered air	Normal ambient air
Product matrix (composition)	• Low a_w-value • pH below 3 or above 9 • Preserving agent • Contains antibiotics, alcohol, etc.	• High a_w-value • Neutral pH • Buffer (physiolog. ionic strengths)
Containers	Single-use cartridge	Multiple-opening tubes with large product volume
Application type	Harmless skin diseases with intact skin layer	Inhalation, oral intake, injections, mucous membranes
Users	Healthy adults	Premature births, children, immunosuppressed, elderly, injured, life-threatening sick people

As different micro-organisms can be considered critical depending on the product and intended use, no clear guidance can be defined. The American Food and Drug Administration (FDA) therefore also writes only[3]

- that suitable, documented processes must be implemented and followed in production to prevent "objectionable microorganisms" in non-sterile products,
- that sufficient laboratory analyses must be carried out on each batch of product, which must be free from objectionable microorganisms,
- that each product and its packaging or closure mechanism must be assessed with regard to its microbiological risk in terms of its intended use.

However, the FDA does not give any explicit guidelines regarding certain microorganisms that may not be contained in a product. This requires an independent risk analysis by the manufacturer. The pharmacopoeiae therefore also point out that, in addition to their recommendations, other microorganisms may need to be analysed depending on the risk factor[1] (**Table 1**).

The following procedure is therefore recommended for manufacturers of pharmaceuticals:

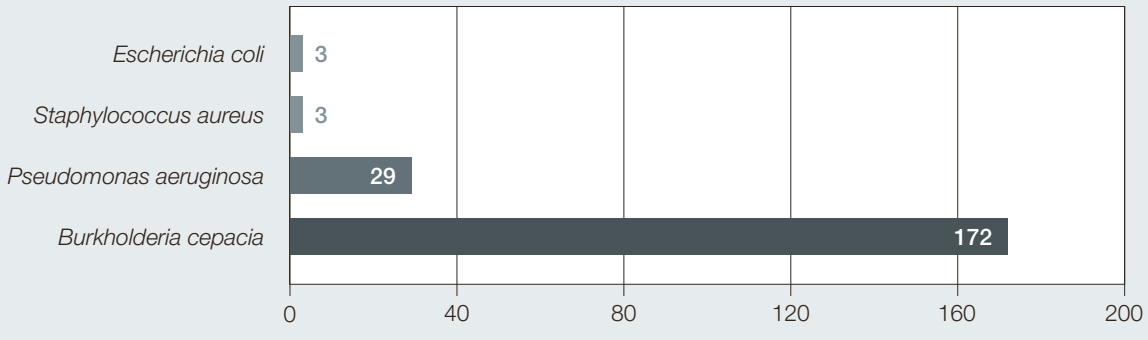
- **Pro-active:** In a risk analysis it has to be assessed, which microorganisms pose a risk for the product in question or the user of the product.
- **Pro-active:** In a risk analysis it has to be assessed, which germs could enter the product due to the risk factors (**Table 1**).
- **Reactive:** The grown colonies in the laboratory analyses of the raw materials, the end product and the environmental monitoring (process water, air) should be identified. In this way it can be determined whether there are previously unnoticed "objectionable microorganisms" or whether the same species are repeatedly detected over time.

Based on the above considerations, it can be decided whether a product should be routinely tested for further "objectionable microorganisms" in addition to the requirements of the pharmacopoeiae. Nowadays, sophisticated techniques are available for this purpose. On the one hand, the composition of the biomolecules of an unknown colony can be determined by mass spectrometry using MALDI-TOF and compared with a database. On the other hand, colonies can be sequenced at genetic level and the base sequence can also be compared with databases. This enables a precise identification of a large number of micro-organisms. Since sequencing is relatively expensive, the first step is usually a MALDI-TOF analysis. If this analysis leads to no or insufficient results, additional sequencing can be performed.

Case study *Burkholderia cepacia* complex

The *Burkholderia cepacia* complex (BCC) describes a group of different *Burkholderia* species such as *Burkholderia cenocepacia* or *Burkholderia multivorans.* These are gram-negative, aerobic and opportunistic human pathogens. Particularly at risk are immunosuppressed persons, children, elderly persons and patients with lung diseases. For example, BCC species cause severe lung infections in patients with cystic fibrosis. For this reason, BCC species may not be present in inhalation medications. In addition, oral products (not only medicines, but also cosmetic products such as mouth rinses) are associated with a risk of inhalation of aerosols. Contamination with BCC has already led to various deaths and product recalls[4].
Routinely, most non-sterile pharmaceutical products have not yet been tested for BCC species and the germs found in laboratory analyses are usually not identified. Therefore, it is possible that a product contains 50 CFU/g aerobic, mesophilic germs and is placed on the market without an identification of the corresponding germs, since it complies with the limit value of max. 200 CFU/g. Due to the lack of identification, it cannot be ruled out that it is BCC. The product may therefore contain an "objectionable microorganism" and should not have been placed on the market depending on its intended use.

1 Recalls by the FDA (1995 – 2019)[5]



In addition, the germs listed as standard in pharmacopoeiae requiring mandatory testing are rather rarely detected. However, due to their history and listing, they are strongly paid attention to. On the other hand, contamination by less known or completely unknown microorganisms is hardly noticed. For this reason, statistics that provide information about which microorganisms led to product recalls are very interesting. An evaluation of the recalls in the U.S. from the period 1995 to 2019 by the FDA showed that the germs analysed classically according to pharmacopoeiae were not found very frequently[5]: *Pseudomonas aeruginosa* (29 recalls), *Staphylococcus aureus* (3 recalls), *Escherichia coli* (3 recalls).[5] 1 On the other hand, there are 172 recalls due to *Burkholderia cepacia,* which is not examined as standard. In the last 7 years in particular, a large number of recalls have been triggered due to *Burkholderia cepacia,* probably also due to the increased sensitivity of the authorities and correspondingly more targeted analyses. Since BCC is probably a more large-scale problem than previously assumed, the American Pharmacopoeia introduced a new, specific analysis method for BCC on December 1st, 2019.[6]

Conclusion

Non-sterile pharmaceutical products may contain a maximum number of microorganisms, but no objectionable microorganisms. Defining and controlling them requires a thorough risk analysis on the part of the manufacturer and detailed analyses on the part of the quality control laboratory. In this way, negative effects on patients and financial losses due to product recalls can be prevented. □

References

1 *Ph. Eur. (European pharmacopoeia), version 10.0, chapter 50104; harmonized with the USP (United States pharmacopoeia), version 42 NF 37 2S, chapter <1111>.*

2 *PDA (Parenteral Drug Association), technical report no. 67, 2014, Exclusion of Objectionable Microorganisms from Nonsterile Pharmaceuticals, Medical Devices, and Cosmetics.*

3 *FDA (U.S. Food and Drug Administration), Code of Federal Regulations, Title 21, §211.113, §211.165, §211.84*

4 *Cundell T., 2019, Excluding Burkholderia cepacia complex from aqueous, non-sterile drug products, American Pharmaceutical Review.*

5 *Jimenez L., 2019, Analysis of FDA Enforcement Reports (2012-2019) to Determine the Microbial Diversity in Contaminated Non-Sterile and Sterile Drugs, American Pharmaceutical Review.*

6 *USP (United States pharmacopoeia), version 42 NF 37 2S, chapter <60>.*

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