

EVALUATION OF THE MICROBIOLOGICAL QUALITY OF NON-STERILE DRUGS PREPARED IN A HOSPITAL PHARMACY

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Background and aim

The compounding of unlicensed, non-sterile pharmaceutical preparations is an integral part of the services of the University Hospital Basel (USB) hospital pharmacy. The manufactured non-sterile preparations may contain microorganisms, which can enter the product with the raw materials or from the manufacturing environment. Microbiological stability is an essential parameter for the quality of a pharmaceutical preparation. Instability due to a contamination can alter the biochemical properties of the product, leading to a change in the shelf life, the loss of efficacy, or in rare cases, to serious health problems for the patients.

For non-sterile pharmaceutical preparations the requirements of the European Pharmacopoeia (EP) regarding the microbiological quality apply, that in the manufacture and packaging, as well as during storage and distribution, suitable measures have to be taken to ensure their microbial quality.

This study evaluates the microbiological quality of non-sterile pharmaceutical preparations of the hospital pharmacy of the University Hospital Basel. A risk-based approach was chosen for the identification of the most microbiologically susceptible non-sterile pharmaceutical preparations of each dose form.

Materials and methods

The USB hospital pharmacy manufactures 42 non-sterile stock pharmaceutical preparations and the EP defines limits of colony forming units (CFU) for different non-sterile products. Three different types of non-sterile dosage forms are compounded: solid dosage forms (<1000 CFU), liquid dosage forms (<100 CFU) and semi-solid dosage forms (<100 CFU).

A risk matrix was created, taking into account the characteristics of the active substance and the formulation, as well as the manufacturing process risk of the individual pharmaceutical dose form. For each of these three criteria, different characteristic parameters were defined and rated. Higher weighting factors reflect a greater microbiological risk, whereas lower were assigned to lower risk parameters for potential microbiological growth. By multiplying the resulting risks, the risk priority number (RPN) was obtained as the individual microbial risk for each product.

To confirm the microbiological quality, tests were conducted using membrane filtration with the Milliflex® Plus Bioburden filtration device (Fig. 1) or the surface-spread method according to EP 2.6.12 in a laminar flow bench. Suitability tests were carried out in advance in the presence and absence of the selected products with five ATCC (American Type Culture Collection) test strains: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Candida albicans* and *Aspergillus brasiliensis*.

The product tests were carried out in duplicates for each product and mean values were calculated from any counted CFU. The samples of each product were taken from stock batches close to their expiry date or from retention samples.

All suitability tests and product tests were conducted using trypticase soy agar plates with an incubation period of 2-5 days at 30-35°C.



Fig. 1: Milliflex® Plus Bioburden device

Results

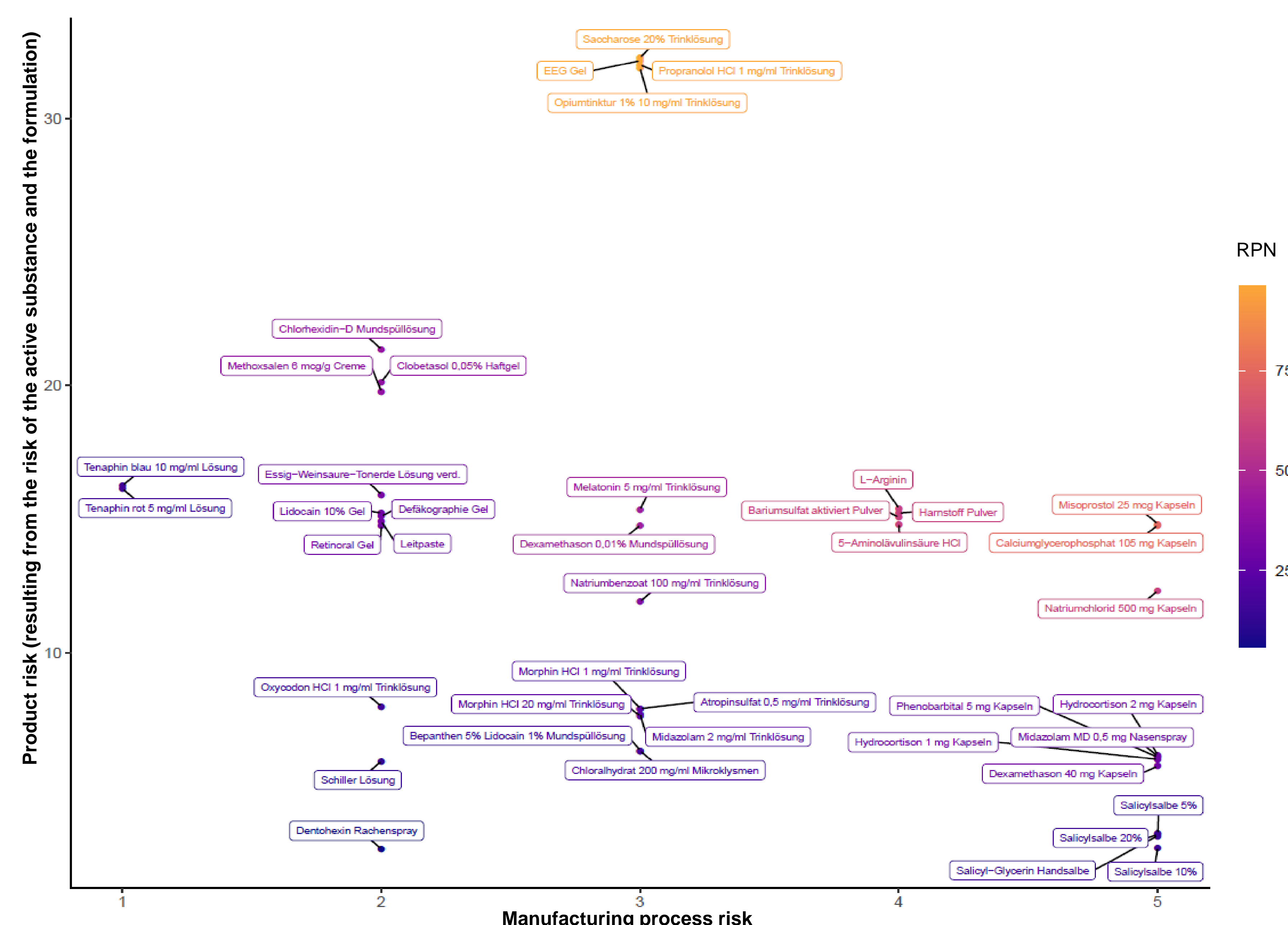


Fig. 2: Risk matrix of the 42 non-sterile products based on the risk of the product and the manufacturing process; the resulting risk priority numbers (RPN) are highlighted by colour.

The risk matrix (Fig. 2) mapped all products of low, medium and high microbiological risk and allowed to determine seven non-sterile pharmaceutical preparations of the different pharmaceutical dose forms with the highest risk for a possible microbiological contamination (worst-case drugs): calcium glycerophosphate capsules, clobetasol adhesive gel, EEG gel, misoprostol capsules, opium tincture, propranolol solution and sucrose solution. These worst-case products were to be tested according to EP 2.6.12.

Membrane filtration was suitable for five products (EEG gel, misoprostol capsules, opium tincture, propranolol solution and sucrose solution); the surface-spread method was suitable for the calcium glycerophosphate capsules and the clobetasol adhesive gel.

The permitted recovery rate of the test strains of 50% to 200% was fulfilled for all tested products and the chosen method was suitable for each specific product.

The seven worst-case products of the different dosage forms were tested in duplicate and only one sample of the opium tincture and the EEG gel showed a microbial growth of one and three colony-forming units (CFU), respectively (pictures of the agar plates see Fig. 4 and 5). All other tested product samples showed no microbial growth.

These results are fully within the requirements of the European pharmacopoeia.

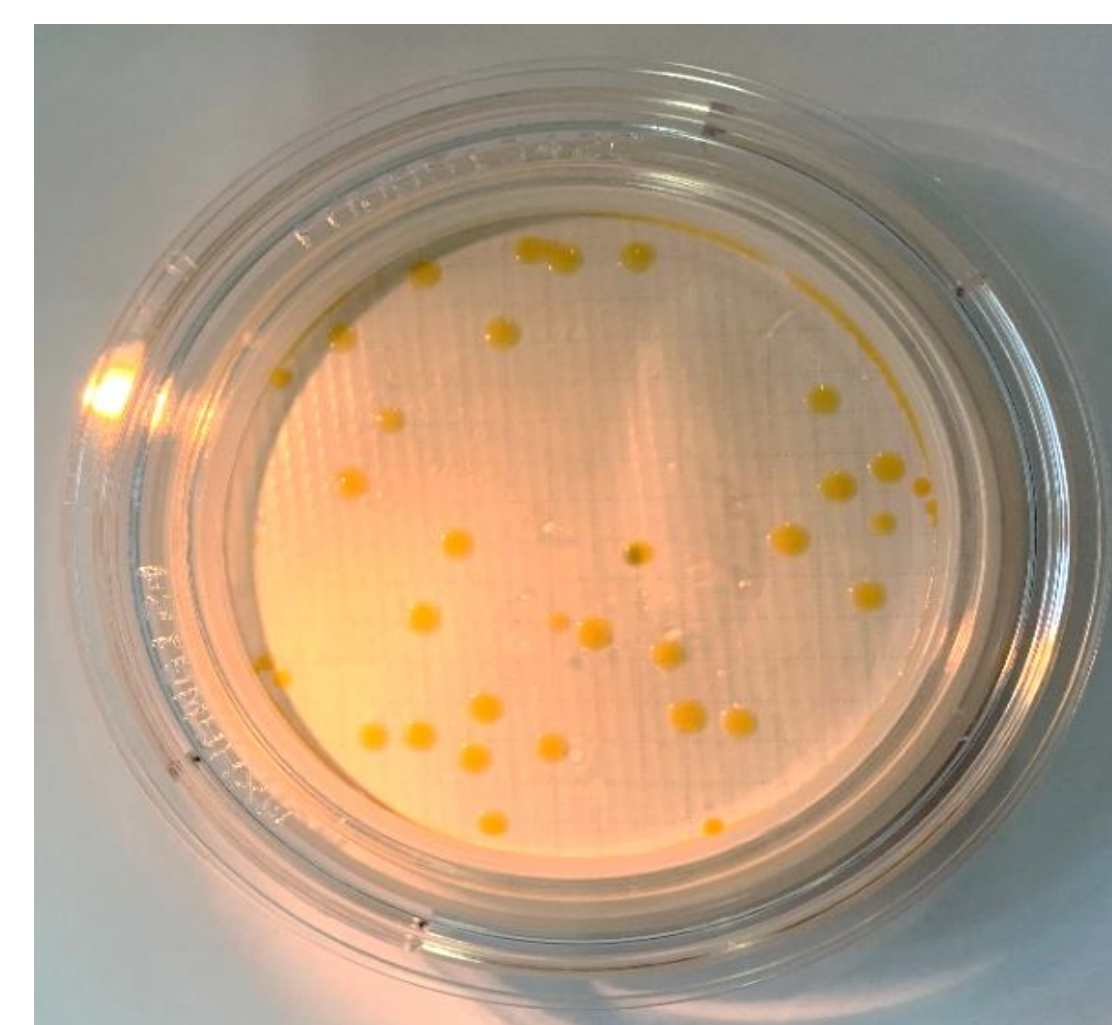


Fig. 3: Suitability test: Example of growth of *Staphylococcus aureus* in sucrose solution



Fig. 4: Product test: Opium tincture: 1 CFU (red circle).

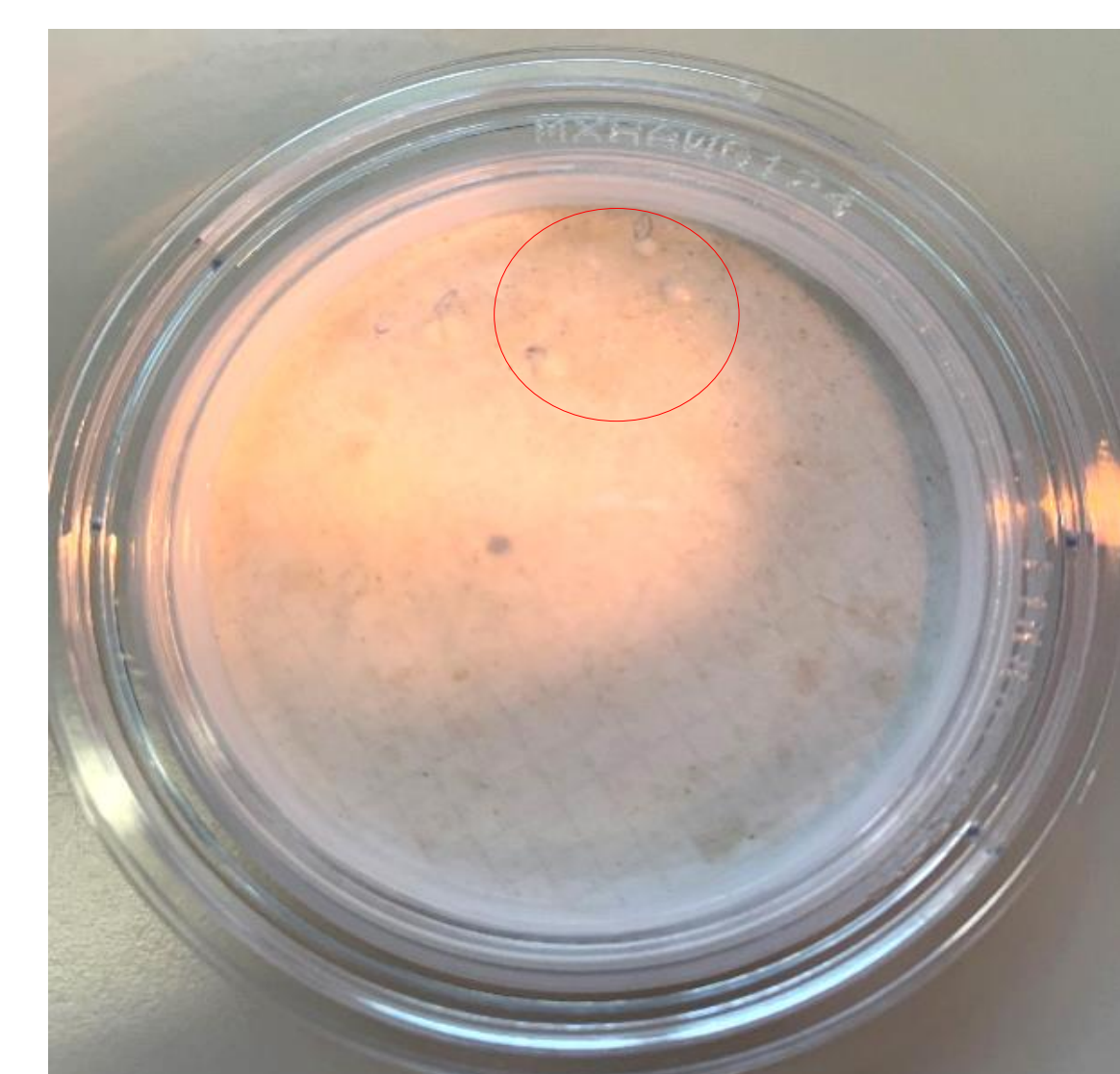


Fig. 5: Product test: EEG gel: 3 CFU (red circle).

Conclusion and relevance

With the developed risk matrix, worst-case drugs could be identified. The formulation risk is useful to identify the microbiologically more susceptible water-containing and weakly preserved non-sterile products; the substance risk revealed the products with hygroscopic properties and herbal or mining origins, and the manufacturing process risk revealed the products that are manufactured openly and with a lot of manual manipulations.

The suitability tests were appropriate and allowed to carry out the microbiological examination of the evaluated worst-case products. Only neglectable microbiological growth even of the pharmaceutical preparations with the greatest risk was observed, so that overall the requirements of the pharmacopoeia were fulfilled.

This study demonstrates that non-sterile production of different dosage forms (incl. packaging and storage) in a hospital pharmacy can guarantee the microbiological quality of pharmaceutical preparations, if production follows the regulatory framework of the European Pharmacopoeia and the basic GMP requirements.