FEDERAL INSTITUTE FOR DRUGS AND MEDICAL DEVICES

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Comments of the German delegation

Draft monograph proposal for a Pharmacopeial Text

Allocation (recommendation): *5.1.X General Texts on Microbiology*

X Unpreserved Dosage Forms in Multi-Dose Containers

X.1 Definition

Unpreserved dosage forms in multi-dose containers means the whole system of a drug, usually intended for multiple application, consisting a preservative-free liquid or semi-solid formulation in a primary container system preventing microbial contamination.
The primary container system consists of a reservoir container and an appropriate application unit, which are able to protect the content of the reservoir container reliably from microbial contamination and corresponds to the requirements of the chapters 3.1 and 3.2. The sterilised container system is sufficiently robust.

The sterility of the content during storage and the sterility of the content as well as an appropriate microbiological quality of the dosage administered during the in-use period have to be ensured.

Such drug products include dosage forms as preparations for *ophthalmic* (1163), *nasal* (0676), *oromucosal* (1807), *auricular* (0652), c*utaneous* (0132) use and *inhalation* (0671).

X.2 Production

The drug product has to be manufactured in a way to ensure the sterility of the formulation in the reservoir container as well as the microbiological safety of the doses until the end of the in-use period.
Recommendations on this aspect are provided in chapter 5.1.1 *Methods of Preparation of Sterile Products*.

X.3 Shelf life

The sterility of the formulation in the reservoir container has to be ensured for the whole shelf life.

X.4 In-use period

An appropriate microbiological quality of every dose has to be ensured for the whole in-use period after opening.

As in general the criteria of the sterility and microbial-free condition of the dose administered under the standard application conditions cannot be met, appropriate microbiological quality criteria have to be determined and justified.
If requirements on the microbiological quality are stated in the monograph of the respective dosage form they should be adapted.

The microbial growth in the area responsible for the microbiological status of the applied dose (e. g. in the application unit) should be prevented or at least reduced to the lowest level possible.

In order to be able to ensure the required microbiological quality of the dose administered, the sterility of the formulation in the reservoir container has to be ensured for the whole in-use period.

Sufficiently reliable statements on the safety and reliability of the primary container system can only be made by product specific, realistic in-use simulations and worst-case studies.

In particular product-specific tests should be carried out on critical functional elements of the container system and the application unit as well as the functionality of special construction features which are important for the reliability of the container system with regard to the proposed microbiological quality.
The choice of the test organisms used with regard to the risk of microbial contamination due to susceptibility of the preparation to microbial proliferation or due to the intended use has to be justified. The tests should be carried out under the recommended or expected storage and in-use conditions (e. g. temperature, humidity, position).

These tests do not have to be carried out on every batch, but in the course of the pharmaceutical development.

X.5 Tests

- Sterility test (2.6.1) on the contents after production (each batch)
- Sterility test (2.6.1) on the contents at the end of the shelf-life period (each batch)
- Sterility test (2.6.1) on the contents during in-use simulations and worst-case studies
- Test of the microbiological quality of the dose to be administered during in-use simulations and worst-case studies (2.6.12, 2.6.13 if applicable)

The monographs of the respective dosage forms should be updated by the following sentence:
“Recommendations regarding multi-dose containers preventing microbial contamination of the contents after opening are provided in chapter 5.1.X.”