LOGFILE Leitartikel 47/2020

Microbiological testing frequencies for non-sterile pharmaceutical preparations

Excerpt from the GMP Compliance Adviser, Chapter 14.F.8.1

by Cornelia Bodinet

The microbiological quality of non-sterile pharmaceutical preparations not only depends on the type of raw materials and active ingredients used but also on other parameters, e.g. the preservation of the product, hygiene measures in the company, etc. The marketing authorisation documentation usually specifies how often the microbiological purity of the finished product must be tested. The specification that each batch must be tested is becoming more common.

If this is not the case and depending on the preparation, random testing can be carried out, based on a risk analysis if required. The ICH Q6A Guideline Specifications, Test Procedures and Acceptance Criteria for New Drug Substances and New Products contains a decision tree for determining the frequency of routine testing (every batch or random testing) (Figure 1).

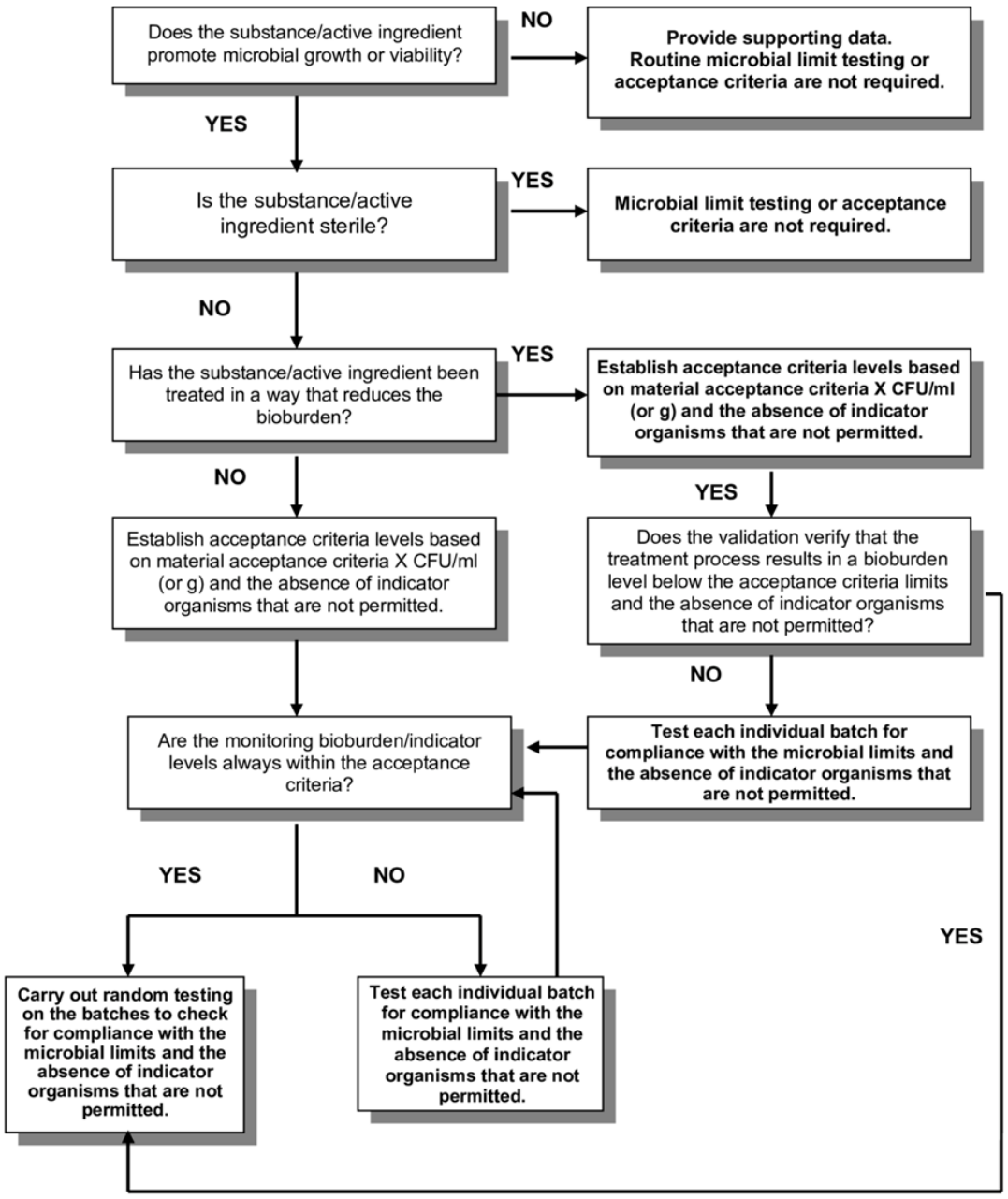

Figure 1: Decision tree – microbiological quality of non-sterile medicinal preparations in accordance with ICH Q6A.

It is not enough to specify random sampling or batch by batch testing only. If random sampling is possible in accordance with Figure 14.F-15, the frequency must also be defined. This information also must be specified in the marketing authorization. In practice, the drug products are first grouped together according to the contamination risk.

For example, they could be assigned to the following groups:

A: Insufficiently tested preparations

This group initially contains all new preparations from in-house production and external production as well as drug products with significant changes in the formulation and manufacturing process. After five batches, they are classified as critical (B) or non-critical (C).

B: Critical preparations

This group contains all preparations with a microbial count that exceeds the limits.

C: Non-critical preparations

This group contains all preparations with a microbial count that does not exceed the limits for the last five batches at least.

Figure 2 shows the corresponding testing frequencies and the relevance of the result for the release.

Preparations		Testing frequency	Relevance for release
A	Insufficiently tested preparations	The first five batches are tested.	The microbial count result must be available for batch release.
B	Critical preparations	Every batch and every section is tested (e.g. partial batches or beginning/middle/end of the batch).	The microbial count result must be available for batch release.
C	Non-critical preparations	Either one batch per quarter or every fifth batch is tested (whichever is the lower number).	The microbial count result is not required for batch release.

Figure 2: Testing frequencies of non-sterile preparations

This type of classification must be managed in a flexible way. If microbial counts that exceed limits occur for non-critical preparations, the environment of the batch is tested (usually five previous and five subsequent batches). During the testing phase, the microbial count result should be considered during the batch release. Afterwards, the classification is checked as described under A.

Starting materials

As a result of the large number of starting materials that are typically used in pharmaceutical companies, the question arises whether it is necessary to test every starting material and every batch of the starting material. The pharmacopoeias contain requirements for a small number of starting materials only.

The ICH Q6A guideline Specifications, Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products contains a decision-making aid for determining the test frequency of microbiological tests for starting materials (Figure 3).

This shows that the test and test frequency depend on the contamination risk of the starting material.

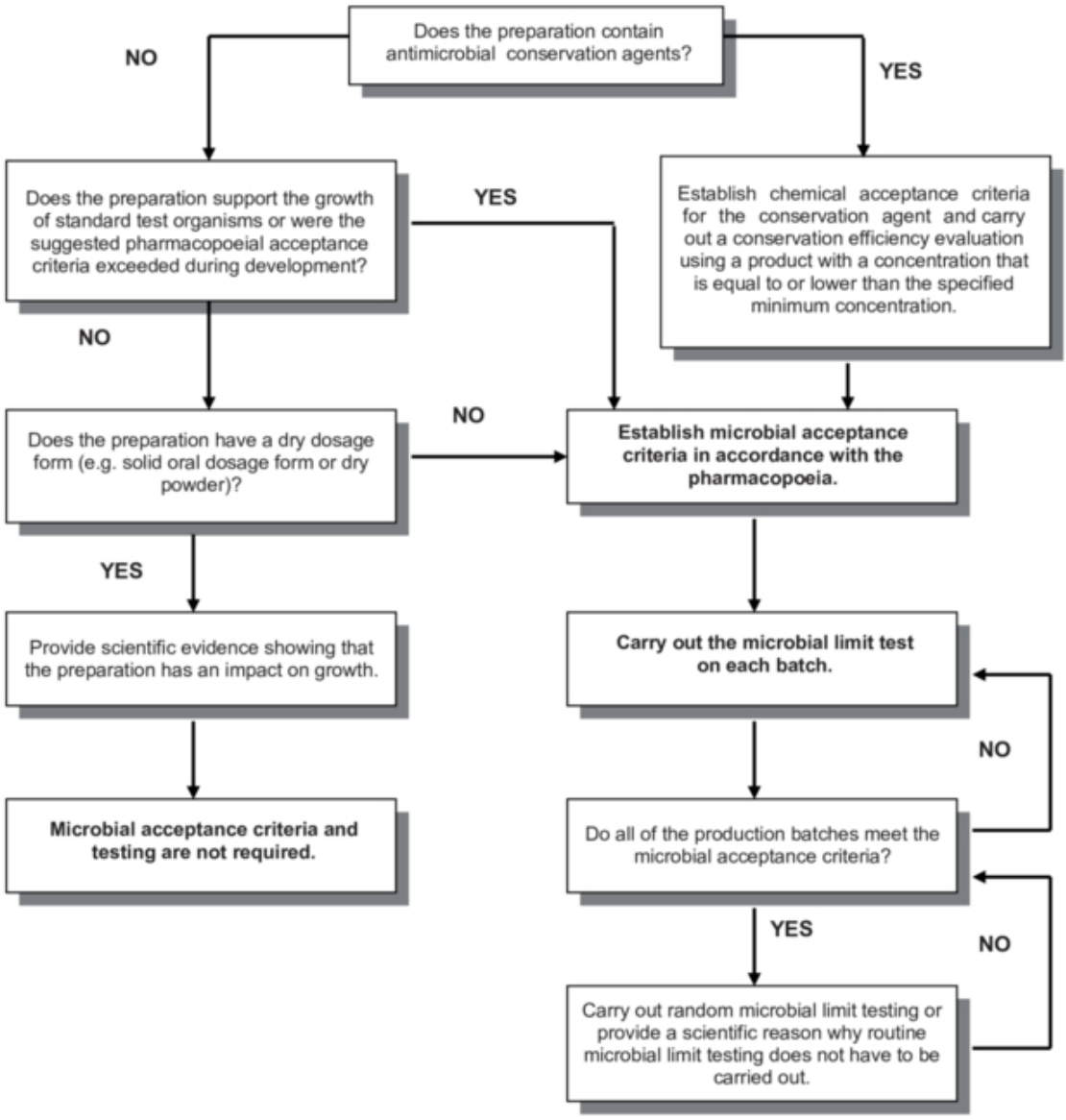

Figure 3: Decision tree – microbiological quality of substances and active in-gredients in accordance with ICH Q6

Another approach is to divide the starting materials into different classes based on the contamination risk (see Figure 4).

Class 1: Contains all the materials for which there are microbiological require-ments in the pharmacopoeia (mandatory testing) and starting materials of herbal, animal or mineral origin. Contaminants can be expected in these materials.

Class 2: This includes synthetic starting materials and natural materials that are reliably disinfected during manufacture, e.g. through extraction. Random sampling is carried out on these materials.

Class 3: This includes materials for which contamination can be ruled out, e.g. nitric acid.

Class	Criterion	Testing frequency
1	Starting material is critical or subject to mandatory testing.	Each batch is tested.
2	Starting material is non-critical.	Every fifth batch is tested, or at least 1 batch per year.
3	Contamination risk is improbable due to the material properties or manufacturing process.	No testing
4	New substances	Until final assignment to class 1 to 3, every batch is tested.

Figure 4: Testing frequency of starting materials.

The certificates of analysis for the raw materials should be requested and the information about the microbiological quality should be checked.

This text is an excerpt from Chapter 14.F.8.1 of the GMP Compliance Adviser.

Author

Cornelia Bodinet, PhD
Graduate Biologist
Schaper & Brümmer, Salzgitter, Germany
cornelia.bodinet@schaper-bruemmer.de

GMP Compliance Adviser

The GMP Compliance Adviser is the world's most comprehensive GMP online knowledge portal that successfully combines theory and practice. It is used by more than 10000 professionals in over 50 countries. The GMP Compliance Adviser is divided into two parts:

- GMP in Practice: "How-to-do"-interpretations and knowledge of our noted industry specialists and according to international GMP regulations.
- GMP regulations: The most important GMP regulations from Europe, USA, Japan and many more

>>> Secure your access now!