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INTRODUCTION

This document is intended to provide harmonized guidance on the selection of the most appropriate microbial limits laid down in the existing chapters of the European Pharmacopoeia (Ph. Eur.) during the different stages of the manufacture of a homeopathic medicinal product in order to facilitate consistent assessment and mutual recognition as laid down in Directive 2004/27/EC. Guidance given is appropriate for both registration under the simplified procedure (Article 14) and authorization of homeopathic medicinal products (Article 16). Sterile dosage forms and methods of sterilisation are excluded from the scope of this paper.

A homeopathic medicinal product is defined in Directive 2001/83/EC as amended as:

“All medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles”

The Directive also defines the term substance as:

“All matter irrespective of origin which may be:

- human, e.g. human blood and human blood products
- animal, e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products.
- vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretions, extracts.
- chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis”

Substances used in homeopathic medicinal products as the active principle may be prepared as either the homeopathic stock or its potencies. The stock itself may consist of processed or unprocessed substances. Homeopathic medicinal products may contain either one active principle or a combination of two or more active principles. Substances used in homeopathic medicinal products are frequently of natural origin and may have a higher level of microbial contamination (bioburden) than chemical substances. In addition, the microbial population present may differ qualitatively and quantitatively. Viruses may also be a cause for concern for certain substances, particularly those of human and animal origin used as the “active” principle in homeopathic medicinal products. Currently, there is no specific guidance or recommendation regarding microbial quality control for
homeopathic medicinal products and in the absence of such guidance both applicants and
competent authorities attempted to apply the existing microbial limits laid down in the European
Pharmacopoeia (Ph. Eur.). This has proved difficult and resulted in an un-harmonized approach
across Europe as different Member States have interpreted and enforced the limits in different
ways.

The terms used are taken from the human medicines Directive 2001/83/EC and the European
Pharmacopoeia.

The five main components involved in the production of homeopathic medicinal products which are
important from a microbial quality control aspect are:

1. Raw materials
2. Homeopathic stocks
3. Homeopathic preparations
4. Finished products (dosage forms)
5. Vehicles

This document presents four decision trees which cover the four main components for which the
selection of appropriate microbial limits for quality control has proved to be problematic.

“Vehicles” (ethanol, purified water, glycerol, lactose, sucrose) used in the production of
homeopathic medicinal products are all covered by monographs in the Ph. Eur. and a decision tree
for this component is therefore considered unnecessary.

1. Raw materials

Raw materials for the production of homeopathic preparations may be of natural or synthetic origin.

1.1 Raw materials of botanical origin

This group of raw materials, which includes whole or parts of plants which may be fresh or dried, is
covered by Ph. Eur. monograph 1038 *Homeopathic preparations*, which states that raw materials of
botanical origin comply with the requirements of the monograph *Herbal drugs for homeopathic
preparations* (2045). Monograph 2045 states in the production section that “*Herbal drugs for
homeopathic preparations are, as far as possible, free from impurities such as soil, dust, dirt and
other contaminants such as fungal, insect and other animal contaminants. They do not present signs
of decay*”. Adequate measures must be taken to ensure that the microbiological quality of
homeopathic preparations containing one or more herbal drugs comply with the recommendations
given in general chapter 5.1.4. *Microbiological quality of non-sterile pharmaceutical preparations
and substances for pharmaceutical use.*
**Fresh material of botanical origin:** it is not possible to test the microbiological quality for such material because fresh herbal drugs must be processed “as rapidly as possible after harvesting” in line with the Ph. Eur. Monograph 2045, *Herbal drugs for homeopathic preparations*. Therefore, the microbial quality of the mother tincture is controlled.

**Dried material of botanical origin:** dried material is expected to be collected and processed in accordance with the principles of *Good Agricultural and Collection Practice* (GACP) to ensure microbial contamination is kept to a minimum. As there are no existing microbial limits in the European Pharmacopoeia microbial testing of dried material is expected to be decided on a case by case basis. As the homeopathic preparations are expected to comply with the recommendations given in general chapter 5.1.4. *Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use* microbial quality control measures on the dried herbal drug may be needed to ensure compliance. When setting microbial limits, due consideration should be given to the source of the raw material (wild or cultivated), any pre-treatment employed, manufacturing process-(es) to be used and the intended use of the finished product.

### 1.2 Raw materials of zoological or human origin.

This group of raw materials is also covered by Ph. Eur. monograph 1038 which states that for raw materials of zoological or human origin, adequate measures need to be taken to minimize the risk of agents of infection, including viruses (5.1.7), in the homeopathic preparations, rather than in the raw material itself. Homeopathic medicinal products of zoological or human origin are diverse in nature. The preparations include materials from a wide range of species, from humans to bacterial and viral agents and from both healthy and pathological sources. The quality and safety of homeopathic materials derived from these sources should be considered on a case by case basis considering the individual character of each product and its intended use. Requirements to be fulfilled are outlined in the HMPWG guidance note *Points to Consider on the Safety of Homeopathic Medicinal Products from Biological Origin* document. In general, the quality and safety of homeopathic medicinal products of zoological or human origin should be considered within the same principles as conventional medicinal products. The Ph. Eur. monograph 1038 also emphasises the need to minimize the risk of TSE and agents of infection such as viruses and bacteria.

### 1.3 Raw materials of chemical or mineral origin.

These are also covered by Ph. Eur. monograph 1038 which states that raw materials comply with any requirements of the relevant monographs of the Ph. Eur. This group can be further sub-divided into three further categories:

1. raw materials with a Ph. Eur. monograph in the non-homeopathic part of the European Pharmacopoeia (e.g. *Borax* - Ph. Eur. 0013).
(ii) raw materials that are currently not covered by a Ph. Eur. monograph (e.g. Aurum metallicum).

(iii) raw materials with a Ph. Eur. monograph in the homeopathic part of the European Pharmacopoeia (e.g. Calcium iodatum for homoeopathic preparations -Ph. Eur. 2144).

Category (i) is straightforward as Ph. Eur. chapter 5.1.4.-2 Acceptance criteria for microbiological quality of non-sterile substances for pharmaceutical use is applicable. For the other two categories Ph. Eur. chapter 5.1.4 (Table 5.1.4-2) can only apply on a non-mandatory basis because the general Ph. Eur. monograph Substances for pharmaceutical use (2034) is not applicable to raw materials for homeopathic preparations, except where there is an individual monograph for the substance in the non-homeopathic part of the Pharmacopoeia. The absence of Ph. Eur. requirements in an individual monograph does not mean there is no need to test for microbial quality. It is up to the manufacturer, in the light of a risk assessment that takes account of the intended use and the available quality of the substance, to take adequate measures to ensure that the microbiological quality of homeopathic preparations is appropriately controlled. The decision tree in annex I depicts the various situations envisaged.

2. Homeopathic stocks

Homeopathic stocks are substances, products or preparations used as starting materials for the production of homeopathic preparations. Homeopathic stocks can be divided into three sub-categories.

2.1 Homeopathic stocks of chemical or mineral origin

These stocks should be treated in exactly the same way as raw materials of chemical/mineral origin as the stocks in these cases are usually the substance itself. Depending on the nature of the substance and its intended use, the microbiological test can be performed either on the raw material/homeopathic stock or on the most concentrated homeopathic preparation (e.g. D1). Furthermore, in case of only testing the microbial quality of the raw material a justification for the microbial quality of the most concentrated homeopathic preparation should be submitted giving due consideration to the microbial quality of the excipients used in its manufacture e.g. microbial quality of the D1 would need justification if not tested.

2.2 Homeopathic stocks of zoological or human origin

These stocks should be handled in the same manner as raw materials of zoological or human origin and should therefore be considered on a case by case basis and controlled in accordance with the
2.3 Homeopathic stocks of botanical origin.

These stocks are complex and cannot be handled in the same manner as raw materials of botanical origin. The Ph. Eur. general monograph 2034 *Substances for pharmaceutical use* does not apply to herbal drugs, herbal drugs for homeopathic preparations, herbal drug preparations, extracts, or mother tinctures for homeopathic preparations. Therefore, the acceptance criteria for substances for pharmaceutical use as laid down in Ph. Eur. chapter 5.1.4 (Table 5.1.4-2) can only apply to stocks from botanical origin (mother tinctures, glycerol macerates) on a non-mandatory basis.

Furthermore, in some cases the stock may become the finished product in which case the acceptance criteria as laid down in Ph. Eur. chapter 5.1.4 (Table 5.1.4-1) would apply based on the route of administration. In other cases, the stocks may undergo different types of treatment that may have varying capabilities to remove or inactivate agents of infection and this should be taken into consideration when deciding which microbial limits to apply. It is therefore evident that it is not possible to develop a single set of limits to cover all scenarios and the limits applicable should be driven by the intended use of the stock. This means that if the stock is intended to be the finished product the acceptance criteria as laid down in Ph. Eur. chapter 5.1.4 (Table 5.1.4-1) should apply based on the route of administration. If the stock will undergo further processing, then the acceptance criteria for substances for pharmaceutical use as laid down in Ph. Eur. chapter 5.1.4 (Table 5.1.4-2) may be applied on a non-mandatory. However, the applicant could justify different limits in the stock based on the proven capability of subsequent processing steps to inactivate and/or remove agents of infection. If appropriately justified, skip-lot testing is possible.

In addition, *Good Manufacturing Practice* (GMP) considerations should be taken into account at this stage as they should apply to the homeopathic stock. However, if one set of limits is accepted for a particular finished product but the same stock is used in a different product or for a different purpose, any difference in microbial limits that is allowed has the potential to cause confusion for GMP inspectors. It should be remembered when deciding limits to control microbial quality, that the stock may not undergo further treatment and could become the finished product. Therefore, in these situations the worst-case scenario needs to be considered when establishing limits for microbial control.

The decision tree in annex II depicts the various situations envisaged.
3. Homeopathic preparations

According to the definition in the Ph. Eur. (monograph 1038), *Homeopathic preparations are prepared from substances, products or preparations called stocks in accordance with a homeopathic manufacturing procedure. A homeopathic preparation is usually designated by the Latin name of the stock, followed by an indication of the degree of dilution and/or potentisation, if applicable.* Homeopathic preparations may be liquid potencies or dry powder triturations. When setting microbial limits, the same principles apply as for the homeopathic stocks, as homeopathic preparations could be the finished product or an intermediate potency which is stored or could be freshly prepared for immediate use; undergoing further processing to the next potency without being stored. Thus, for homeopathic preparations the microbial limits that are applicable depend upon how the preparations will be used.

If the homeopathic preparation is the finished product the acceptance criteria for microbiological quality is dependent upon the route of administration. The limits applicable are those laid down in Ph. Eur. chapter 5.1.4 (Table 5.1.4-1). If the homeopathic preparations are to be further processed into an intermediate which will be stored for future use, the limits for substances for pharmaceutical use as set out in Ph. Eur. chapter 5.1.4 (Table 5.1.4-2) may apply. Finally, if potencies are freshly prepared for immediate use and will not be stored, then microbial limits are not considered appropriate as the preparation will be immediately used to prepare the next potency and subsequently any excess will be discarded.

These proposals are in line with Ph. Eur. monograph 2045 which states that *adequate measures must be taken to ensure that the microbiological quality of homeopathic preparations containing 1 or more herbal drugs comply with the recommendations given in general chapter 5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use.* However, as this monograph is only applicable to homeopathic preparations derived from botanical stocks these limits are applicable to other homeopathic preparations by analogy.

The decision tree in annex III depicts the various situations envisaged.

4. Finished products (dosage forms)

Finished products are covered by Ph. Eur. monograph 1038 which states that *a dosage form of a homeopathic preparation should comply with any relevant dosage form monograph in the European Pharmacopoeia.* The microbial limits for finished dosage forms are laid down in Ph. Eur. chapter 5.1.4 (Table 5.1.4 – 1) and should be applied to the finished pharmaceutical product based on the
route of administration. For example, the Ph. Eur. clearly states that both pillules and tablets can be intended for oral or sublingual use. The applicant should be free to choose based on the intended route of administration for the finished product. In these particular cases, it is important for the finished product to be clearly labelled with the intended route of administration. Where both routes of administration are possible, the most stringent acceptance criteria (oromucosal use) should be followed.

The content of water in a product for oral use is used to decide if the microbial limits for non-aqueous preparations or those for aqueous preparations laid down in Ph. Eur. chapter 5.1.4 (Table 5.1.4 – 1) are applicable. In case of doubt whether a product falls into the category aqueous or non-aqueous, the stricter requirement (aqueous) applies.

Data are available on the bactericidal effects of ethanol as a function of concentration and contact time. The content of ethanol in the finished product can therefore be used to decide if the microbial limits for non-aqueous preparations or those for aqueous preparations laid down in Ph. Eur. chapter 5.1.4 (Table 5.1.4 – 1) are applicable. In order to use different limits than those stipulated for aqueous preparations (Ph. Eur. 5.1.4) when testing liquid preparations containing water, for example if the preparation also contains ethanol, it must be shown that the content of ethanol has a preservative effect. This can be done by testing the relevant preparation according to Ph. Eur. 5.1.3 Efficacy of Antimicrobial Preservation. If appropriately justified, skip-lot testing is possible.

The decision tree in annex IV depicts the various situations envisaged.
DECISION TREES FOR THE SELECTION OF MICROBIAL LIMITS FOR NON-STERILE HOMEOPATHIC RAW MATERIALS/ STOCKS/ PREPARATIONS AND PRODUCTS

ANNEX I: RAW MATERIALS

What type of raw material is it? Is it of botanical origin, zoological/human origin or of chemical/mineral origin?

Botanical origin

Zoological or human origin

Chemical or mineral origin

Is it fresh or dried?

Fresh

Dried

Material should be processed as rapidly as possible after harvesting in accordance with the principles of GACP to ensure microbial contamination is kept to a minimum.

No limits apply.

Microbial quality to be tested on the mother tincture.

Is there a Ph. Eur. monograph for the material?

Yes

Non-homeopathic part

Homeopathic part

Is the monograph in the homeopathic part or the non-homeopathic part of the European Pharmacopoeia?

Ph. Eur. Chapter 5.1.4 (Table 5.1.4 - 2) limits are applicable.

See individual monograph or Ph. Eur. Chapter 5.1.4 (Table 5.1.4-2) limits apply on a non-mandatory basis, unless otherwise justified by the applicant. Depending on the nature of the substance and its intended use, different acceptance criteria may be justified.
ANNEX II: HOMEOPATHIC STOCKS

What type of homeopathic stock is it?
Is it of botanical origin, zoological/human origin or of chemical/mineral origin?

Botanical origin e.g. mother tincture; glycerol macerate

Is the stock the homeopathic medicinal product?

Yes

Microbial quality and safety has to be assessed on a case by case basis and depends on the individual character of each product and its intended use.

Refer to the following for guidance:

- HMPWG Points to consider on safety of homeopathic medicinal products from biological origin
- Ph. Eur. monograph 1038

No

(See Annex IV)

Ph. Eur. Chapter 5.1.4 (Table 5.1.4-2) limits apply on a non-mandatory basis, unless otherwise justified by the applicant.

Where a single stock is intended for two different purposes (i.e. as a finished product and as the basis of a homeopathic preparation in different applications) the limits should be based on the worst-case scenario (i.e. those of the finished product).
ANNEX III: HOMEOPATHIC PREPARATIONS

What type of homeopathic preparation is it?
Is it a liquid potency or a dry powder trituration?

Liquid potency

Is the homeopathic preparation freshly prepared for immediate use, an intermediate potency or the finished product?

Preparation is freshly prepared for immediate use. Will be used immediately and not stored. Any excess will be discarded.

Microbial limits are not applicable

Ph. Eur. Chapter 5.1.4 (Table 5.1.4 – 2) if applicable

Dry powder trituration

Preparation is an intermediate potency intended to be stored for future use.

Preparation is the finished product.

(see Annex IV)

Where a preparation is intended for two different purposes (i.e. as a finished product and be stored for future use in the production of higher potencies or different finished products in other applications) the limits should be based on the worst-case scenario (i.e. those of the finished product).
Is the homeopathic stock or preparation considered to be the finished medicinal product or have they been incorporated into a pharmaceutical dosage form?

**Yes**

Ph. Eur. Chapter 5.1.4 (Table 5.1.4 – 1) is applicable and depends on the route of administration

**No**

(see Annex II or III)

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<tr>
<th>Route of administration Ph. Eur. 5.1.4-1</th>
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<td>Non-aqueous preparations for oral use</td>
<td>Oral preparations without water, e.g. Tablets, Oral powders</td>
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<tr>
<td>Aqueous preparations for oral use</td>
<td>Oral preparations containing water</td>
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<td>Oromucosal use</td>
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<td></td>
<td>Homeopathic pillules, coated*</td>
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<td></td>
<td>Tablets (special route of admin: e.g. under the tongue)</td>
</tr>
<tr>
<td></td>
<td>Liquid preparations (special route of admin: e.g. to be kept in the mouth before swallowing)</td>
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</table>

*exception see monograph 2079 and 2786: In case of clear labelling “for oral use” the specification for non-aqueous preparations for oral use can be applied.