# HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP (HMPWG)

# POINTS TO CONSIDER ON SAFETY OF HOMEOPATHIC MEDICINAL PRODUCTS FROM BIOLOGICAL ORIGIN

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**PLAN**

## 1. Introduction

Homeopathic medicinal products of biological origin are diverse in nature. The preparations include materials from a wide range of species, from humans to bacterial and viral agents and from healthy as well as from pathological sources. The large spectrum of substances implies that the quality and safety of homeopathic medicinal products should be considered on a case-by-case basis taking into account the individual character of each product and its intended use.

This document outlines the requirements to be fulfilled by homeopathic medicinal products, from biological origin, in the registration procedure. In general, homeopathic medicinal products of biological origin should warrant sufficient quality and safety within the same principles of the other medicinal products.

Special precaution should be taken with nosodes due to their intrinsic pathological nature and origin.

Biological materials, due to their complex nature, require additional precautions related to the quality and safety of the preparation. According to the tissue/species from where they originate, special attention should be paid to the microbiological and viral safety, transmissibility of Spongiform Encephalopathies (TSE), or adverse effects caused by additives/excipients. Therefore, homeopathic medicinal products should demonstrate, amongst other, quality specifications for starting materials and first safe preparations, as well as in-process quality controls.

Depending on the nature of the biological starting material, safety studies in relation to the risk of transmitting infection agents have to be performed with either the first safe preparation or, if possible, at the level of the stock. Regarding viral safety, viral validation studies related to the species of origin should be addressed.

A risk assessment with respect to viral safety must be carried out for homeopathic medicinal products containing materials of biological origin. Risk assessment has to consider all the factors that may influence the potential level of infectious particles in the homeopathic medicinal product and the potential risk to the patient derived from its intended use.

This document gives guidance on the minimum requirements to ensure the quality and safety of the biological materials used in homeopathic medicinal products taking into consideration their biological origin and the manufacturing steps involved up to the first safe preparation.

## 2. Scope

This guideline applies only to homeopathic medicinal products subject to simplified registration.

Their intended use may involve application in skin lesions and mucosa, therefore safety measures must have equivalent strength as for parenteral forms.

Starting materials of biological origin may be obtained from:

- humans, e.g. human cell lines, healthy tissues or fluids, or nosodes such as human lesions/infected materials;
- animals e.g. whole animals, organs, tissues, animal secretions, toxins, healthy or diseased tissues and extracts (nosodes), blood products, parasites, animal cell lines;

- micro-organisms (e.g. bacteria, viruses, microscopic fungi, plant parasites);
- plants e.g., parts of plants, plant secretions, extracts, mother tinctures, pollen, plant cell lines, macroscopic fungi.

Plant materials are outside of the scope of this guidance. The quality required for those products is defined elsewhere. Concerning fungi, only macroscopic fungi are considered of plant origin and therefore fall outside this document – microscopic fungi are to be considered together as microscopic organisms and shall comply with this document.

## 3. Preparations involved in the manufacturing process

In the context of the present guidance the terms used were drawn from Directive 2004/27/CE and the European Pharmacopoeia. For clarification the manufacturing processes within their own variability, are considering to include:

1. Human and animal species and microorganisms as source materials.
2. Starting materials corresponding to homogeneous preparations of tissues/cells or extracts with no further processing.
3. Homeopathic stock obtained through manufacturing steps that may involve macerations, enzymatic treatments, dilutions, extractions or any other means to attain the bulk from where homeopathic dilutions will be prepared.
4. First safe preparation, as the fraction obtained at any level of the manufacturing process up to the last removal/inactivation step. First safe preparation should comply with the principles of minimization the risk of transmission of pathogenic agent.
5. Nosodes, consisting in homeopathic preparations made from products of human or animal disease processes, from pathogens or their metabolic products, from the decomposition products of animal organs, or from cultured microorganisms.

## 4. Biological starting materials used for the production of homeopathic medicinal products

### 4.1. Sourcing of biological starting materials

#### *4.1.1 Animal origin*

When animal materials are sourced for production, safety precautions should be taken to avoid transmission of pathogenic agents to humans and/or animals. Starting materials of animal origin should comply with the principles of minimization the risk of transmission of pathogenic agents, taking into account the species specificities regarding harbouring infectious agents other than those related with the expected homeopathic therapeutic agent. Possible species infectivity will be taken in consideration in the viral validation studies for the choice of relevant or, if needed, model viruses and will be part of the risk assessment.

Under this principle, sourcing of the animal species should comply with guidance from OIE to guarantee the sanitary safety of world trade in animals and animal products. Whenever applicable, relevant texts of the European Pharmacopoeia and clearly defined qualification procedures should be considered.

The general principles laid down below in this guidance should be followed. When alternative procedures are applied justification is required.

The manufacturer of the stock or homeopathic medicinal product should ensure that animal materials come from documented and recorded sources and should perform regular audits of the suppliers. The supplier of animals should be subject to routine legal supervision by a competent veterinary authority. Any exception to these should be justified.

Healthy animals should be used for the production of homeopathic medicinal products unless properly justified. Whenever possible, donor animals should be held in closed breeding and production herds. Wild animal should be avoided as far as possible.

The animals should be kept in groups and isolated from contact with other animals at all times during transfer or use. The strain, origin and, if possible, number of the animals should be specified. When diseased animals are used, such as in nosodes, the characteristics of the pathologic condition and transmissibility should be clearly defined. If an illness is induced in the animal, the nature, source and strain (if relevant) of the substance/agent used should be documented.

When animal species of higher order are sourced, a regular health monitoring system should be in place ensuring that the animals are subject to continuous and systematic veterinary and laboratory monitoring to ensure freedom from infectious agents. This should include constant monitoring of the animal herd by the veterinarian, routine pathological examination of randomly selected animals, serological analysis for a range of virus, bacteria and parasites and examination of the health status. The results of the health monitoring of the animal should be well documented.

The manufacturer of the homeopathic medicinal product should ensure that newly emerging serious veterinary diseases in the animal species supplied, are immediately reported to the competent authorities.

#### *4.1.1.1 Viral and microbiological contamination*

Special consideration should be given to possible viral and microbiological contamination and tests for relevant viruses should be performed. The microbiological quality should meet the requirements of the European pharmacopoeia.

In general, viral status of the species involved should be properly characterised taking into consideration the intended use. For those species remote to human and/or animal with unknown risk of carrying human and/or animal pathogens, other factors should be taken in consideration, namely the possibility of direct or indirect disease transmission.

#### *4.1.1.2 Transmission of TSE*

When considering specifically the risk of transmission of TSE, raw and starting materials, excipients as well as reagents participating in the manufacturing process, namely from bovine, ovine and caprine origin, and any other TSE susceptible species, should comply with Commission Directives 2001/83/EC as amended by Commission Directive 2003/63/EC or 2001/82/EC, fulfilling the requirements laid down in the Note for Guidance on “Minimising the risk of transmitting animal spongiform encephalopathies via human and veterinarian medicinal products” and its revisions and exemptions as defined for medicinal products.

Whenever parts of animals suitable for human consumption are used, a veterinary certificate should be sufficient to demonstrate compliance of starting material used for homeopathic medicinal products considering its restricted oral and external use.

#### *4.1.2 Medicinal products*

Starting materials currently used as medicinal products such as serums, vaccines, toxins etc. should have the same quality as that for the approved medicinal products and should comply with CPMP/BWP/3354/99 “Note for Guidance on Production and Quality Control of Animal Immunoglobulins and Immunosera for Human Use”.

#### *4.1.3 Human origin*

When using starting materials of human origin for production of homeopathic medicinal products for human use the problem of transmission of adventitious agents (viral and non-viral) should be addressed starting at the level of donor selection and in relation to the tissue involved. Proper criteria for donor eligibility have to be clearly defined. The requirements on tissue donors must follow the Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004 and Commission directives implementing Directive 2004/23/EC.

Human material may contain blood or may have been exposed to it during the extraction process, so the transmission of viruses is of particular concern, therefore the selection of the donors must follow the Commission directive 2004/33/EC of 22 March 2004 “implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components” and other Commission directives implementing Directive 2002/98/EC.

Cross species infectivity should be addressed if the product is used in a different species.

#### *4.1.4 Products derived from human, animal and microbial cell lines*

Human, animal and microbial cell lines used for production or as starting materials, should follow the recommendations covered in the guideline CPMP/ICH/294/95 “Derivation and Characterisation of Cell Substrates used for the Production of Biotechnological/Biological Products” or Guidelines for production and control of immunological veterinary medicinal products Volume 7B Eudralex, CPMP/BWP/1793/02 “Note for Guidance on the Use of Bovine Serum in the Manufacture of Human Biological Medicinal Products” and CVMP/743/00 “Note for guidance on Requirements and Controls applied to Bovine Serum (Foetal or Calf) used in the production of immunological Veterinary Products”.

Furthermore, human and animal cell lines as starting materials should be prepared according to the recommendations set for allogeneic and xenogeneic cell therapy products, respectively in CPMP/BWP/41450/98 “Points to Consider on the manufacture and quality control of human somatic cell therapy medicinal products” and CPMP/BWP/3326/99 “Concept Paper on the Development of a CPMP Points to Consider on Xenogeneic Cell Therapy”.

#### *4.1.5 Products derived from virus preparations*

Where a homeopathic medicinal product is derived from a virus preparation, there should be strong assurance that the virus has been effectively inactivated during the manufacturing process and the appropriate validation of the inactivation process should be performed.

#### *4.1.6 Genetically modified organisms*

The use of genetically modified organisms as starting materials should be in accordance with the Directives 2001/18/EC and 90/219/EEC (as amended).

## 5. Manufacturing process and safety of the Homeopathic Medicinal Product and of the first safe preparation

### 5.1 First safe preparation

The first safe preparation should be defined on a case-by-case basis. First safe preparation can be defined at any level of the manufacturing process up to the last removal/inactivation step introduced in the process.

Only first safe preparations may be used to produce the homeopathic medicinal products, which should comply with the principles of minimization the risk of transmission of pathogenic agent, taking into account the species infection potential other than the homeopathic therapeutic agent.

For manufacturing of human and/or animal derived homeopathic medicinal products, both pathogenic and healthy, an adequate determination of what shall be considered as the first safe preparation, for each stock is essential. This determination ensures the correct definition of viral studies to be applied in order to evaluate putative infectivity. Safety studies, taking both viral and non-viral adventitious agents into consideration, should be performed at this lowest level prior to manufacturing further dilutions and/or other homeopathic preparations.

### 5.2 Manufacture of the homeopathic medicinal product and first safe preparations

Dilutions alone and *per se* do not ensure biological safety of the first safe preparation. Manufacturing steps at the level of homeopathic dilutions such as solvent/detergent, filtration or pasteurisation may contribute to the safety of the first safe preparation. First safe preparations should be properly characterised in terms of microbiological, viral and TSE safety. Viral validation studies should be performed on the production of this first safe preparation. The effectiveness of the manufacturing process to inactivate or remove adventitious agents is important for the biological safety of the first safe preparation of the homeopathic medicinal product. Adequate measures are to be taken to minimise the risk of agents of infection in the homeopathic preparations - it must comply with the requirements of the European Pharmacopoeia monograph on Homeopathic Preparations.

Validation of the process of viral inactivation/removal should be addressed in specially designed viral validation studies with model viruses performed according to the Guideline CPMP/BWP/268/95 “The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses”.

### 5.3. Human origin

Starting materials from human origin should be considered potentially infectious. When human tissues or excretions are used, manufacturing should include validated steps to reduce/eliminate contamination of the starting material and to maximise the elimination of putative pathogenic agents that might be present. Manufacture of the homeopathic medicinal product from human origin should comply with the manufacturing section of the guideline CPMP/BWP/269/95 Rev. 3 “Note for guidance on Plasma Derived Medicinal Products” with due adaptations properly justified according to the material involved and the intended use.

### 5.4 Transmission of TSE

Starting materials and other substances participating in the manufacturing process such as reagents obtained from tissues of bovine, caprine and ovine species as well as other species sensitive to TSE's should comply with the principles of minimising the risk of transmission of TSE defined in the Commission directives 2001/83/EC, as amended by Commission Directive 2003/63/EC or 2001/82 /EC, fulfilling the requirements laid down in the "Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathies via human and veterinarian medicinal products". Compliance with the principles of minimising the risk of transmitting animal spongiform encephalopathy should be demonstrated by providing a certificate of suitability delivered by the EDQM, or by providing complete scientific data for the product as stipulated in the Appendix II of the Resolution AP-CSP (99) 4 (adopted by the public health committee).

### 5.5 Products derived from Biotechnology

Homeopathic medicinal products derived from biotechnology should comply with all relevant guidelines related to biotechnology, taking into consideration the risk of contamination with adventitious agents, through the recombinant cell line used for production (CPMP/ICH/139/95 Guideline "Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products"). Also, when a cell line is used, this cell line should be fully characterised according to the relevant requirements, e.g. CPMP/ICH/294/95 Guideline "Derivation and Characterisation of Cell Substrates used for the Production of Biotechnological / Biological Products"; CPMP/ICH/295/95 Guideline "Viral Safety Evaluation of Biotechnology Products derived from Cell lines of Human or Animal Origin" and /or guidelines for production and control of immunological veterinary medicinal products Volume 7 B Eudralex . If relevant, the CVMP/743/00 "Note for guidance on Requirements and Controls applied to Bovine Serum (Foetal or Calf) used in the production of immunological Veterinary Products" should also be taken into account.

## 6. Risk assessment of homeopathic medicinal products from biological origin

A risk assessment, considering all the factors that may influence the potential transmission of infection agents to the recipients should be carried out under the principals outlined in the European Pharmacopoeia (5.1.7). Risk assessment will take into account the species origin, the tissues and cells, the manufacturing steps involved and the intended use.

Viral contamination of a homeopathic medicinal product may arise from the source material or from adventitious agents introduced by the production process.

Where the risk of contamination exists, three principal complementary approaches can be adopted to control potential viral contamination of the medicinal product:

- Selection of source materials and testing for viral contaminants, whenever human pathogens are considered to be present.
- Testing the capacity of the production process to remove and/or inactivate viruses up to the first safe preparation.
- Testing for viral contamination considered relevant at appropriate stages of production.

The risk assessment should be performed considering:

- the species of origin,

- the organ, tissue, fluid of origin,

- the potential contaminants in view of the origin of the starting material and the possibility to harbour human pathogens preferably including field data,

- potential contaminants from the manufacturing process from risk materials used during manufacture for example, enzymes, culture media, etc

- the infectivity and pathogenicity of the potential contaminants for the intended recipients of the homeopathic product, taking account of the administration protocol,

- controls carried out on the starting material and at the first safe preparation.