

**HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP
(HMPWG)**

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

DISCUSSION IN THE HMPWG	January 2001-April 2005
RELEASE FOR CONSULTATION	March 2005
DISCUSSION IN THE HMPWG	December 2005
ADOPTION FOR TRANSMISSION TO HMA	March 2007
ADOPTION BY HMA	July 2007
REVISION IN THE HMPWG	June 2014-December 2014
RELEASE FOR CONSULTATION	January 2015
DISCUSSION IN THE HMPWG	May 2015
TRANSMISSION TO BIOLOGICS WORKING PARTY (BWP) FOR OPINION	June 2015
AGREED BY BIOLOGICS WORKING PARTY (BWP)	November 2015
ADOPTION BY HMPWG	April 2016

PLAN

1. Introduction
 2. Scope
 3. Preparations involved in the manufacturing process
 4. Biological starting material used for the production of homeopathic medicinal products
 - 4.1. Sourcing of biological materials
 - 4.1.1. Animal origin
 - 4.1.1.1 Viral contamination
 - 4.1.1.2 Transmission of TSE
 - 4.1.2. Medicinal products
 - 4.1.3. Human origin
 - 4.1.4. Products derived from human, animal and microbial cell lines
 - 4.1.5. Products derived from virus preparations
 - 4.1.6. Genetically modified organisms
 5. Manufacturing process and safety of homeopathic medicinal products and of the first safe preparation
 - 5.1. First safe preparations
 - 5.2. Manufacturing of homeopathic medicinal products and of first safe preparations
 - 5.3. Human origin
 - 5.4. Transmission of TSE
 - 5.5. Products derived from biotechnology
 6. Risk assessment of homeopathic medicinal products from biological origin
- Annex:** Decision Tree on the evaluation of safety of homeopathic medicinal products manufactured from raw material of human, animal or microbiological origin and establishment of first safe preparation.

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 applied to 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 requirements, 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 infectious 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 to 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) and macroscopic fungi.

Plant and macroscopic fungus materials are outside of the scope of this guidance. The quality required for those products is defined elsewhere. 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 2001/83/EC, as amended 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. 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. 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.
5. Intermediate product corresponding to a preparation obtained from a starting material through a homeopathic manufacturing procedure.
6. 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 of the risk of transmission of pathogenic agent.

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 into consideration in the virus 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 The World Organisation for Animal Health (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 for 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.

Newly emerging serious veterinary diseases in the animal species supplied should be 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 encephalopathy via human and veterinary medicinal products”(EMA/410/01 rev.3) 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 Note for Guidance 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), EMA/CHMP/BWP/457920/2012 rev1 “Guideline on the Use of Bovine Serum in the Manufacture of Human Biological Medicinal Products” and EMEA/CVMP/743/00-Rev.2 “Revised guideline on requirements and controls applied to bovine serum used in the production of immunological veterinary medicinal 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 EMEA/CHMP/410869/2006: GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS and EMEA/CHMP/CPWP/83508/2009 “GUIDELINE ON XENOGENEIC CELL-BASED MEDICINAL PRODUCTS”.

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 (see Annex).

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

For manufacturing of human and/or animal derived homeopathic medicinal products, obtained from both pathogenic and non-pathogenic raw materials, 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 virus validation studies to be applied in order to evaluate putative infectivity. Comparable preparations -defined on the basis of zoological taxonomy of animal species and the type of tissue, the manufacturing method and the used vehicle and physical treatment of raw materials - can be used to perform virus validation studies when healthy animal materials are used. 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, steam sterilisation 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. Virus 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 should be demonstrated by virus validation studies (the justification for and the extent of the required validation studies should be decided on a case-by-case basis), since it 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. There should be strong

assurance that potential adventitious agents have been effectively removed and/or inactivated during the manufacturing process. This should be demonstrated by performing appropriate validation studies or referring to appropriate homeopathic manufacturing procedures described by the European Pharmacopoeia or, in the absence thereof, by the Pharmacopoeias currently used officially in the Member States.

Validation of the process of viral inactivation/removal should be addressed in specially designed virus validation studies with model viruses performed according to the Note for Guidance 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 eliminate potential 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 EMA/CHMP/BWP/706271/2010: Guideline 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 encephalopathy agents via human and veterinary medicinal products” (EMA/410/01 rev.3). Compliance with the principles of minimising the risk of transmitting animal spongiform encephalopathies 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 (07) 1 (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 Note for Guidance “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 Note for Guidance “Derivation and Characterisation of Cell Substrates used for the Production of Biotechnological / Biological Products”; CPMP/ICH/295/95 Note for Guidance “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 EMEA/CVMP/743/00-Rev..2 “Revised guideline on requirements and controls applied to bovine serum 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 infectious agents to the recipients should be carried out under the principles outlined in the European Pharmacopoeia General Chapter (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.

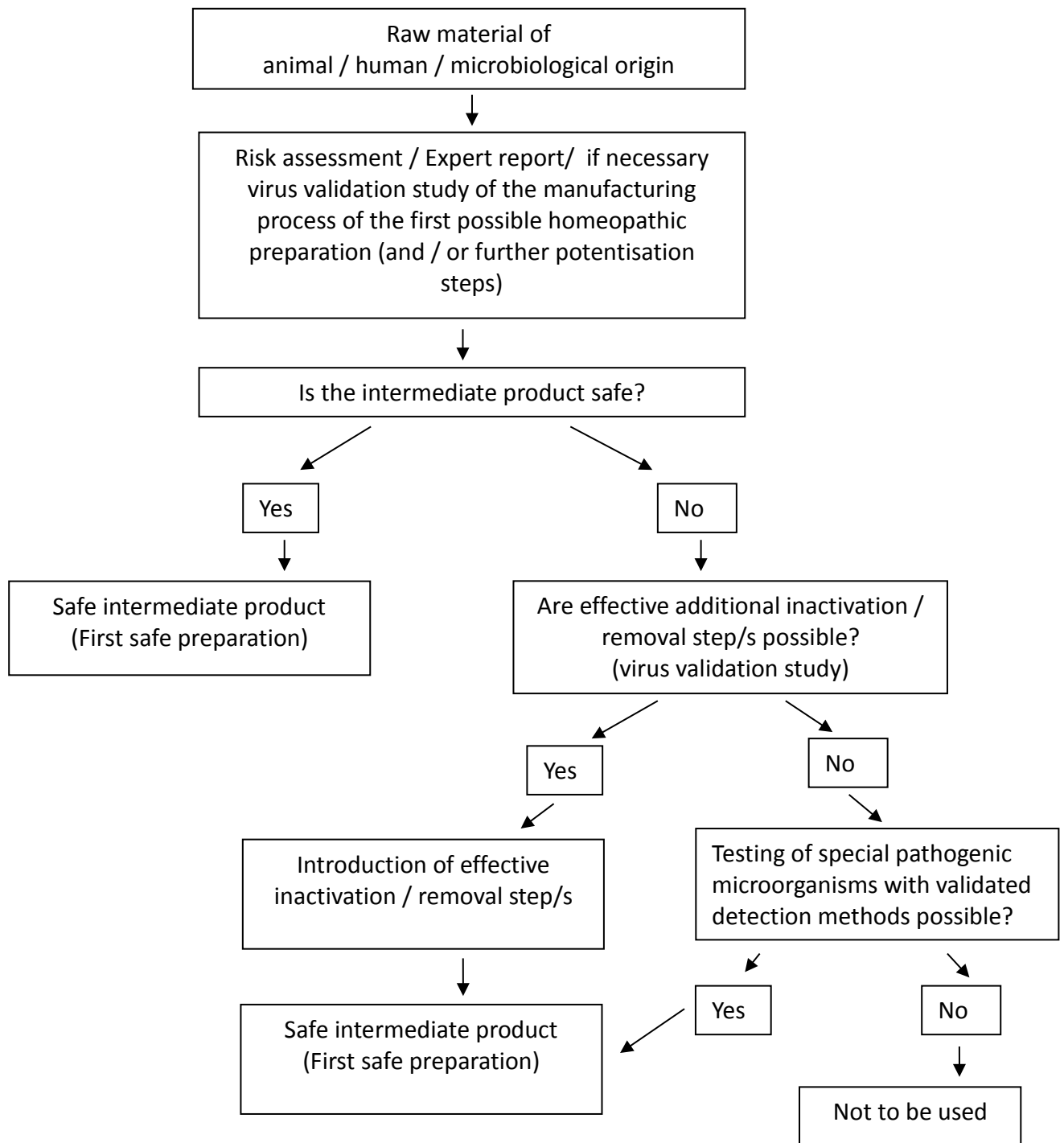
Where the risk of contamination exists, three principal complementary approaches should be adopted to control potential viral contamination of the medicinal product:

- Selection of source materials and testing for viral contaminants, whenever human pathogens are considered to be present.
- Validation of 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 and/or pathogens to human, in view of the origin of the starting material and the possibility to harbour human pathogens and preferably including field data,
- potential contaminants from the manufacturing process from raw 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.

Annex: Decision Tree on the evaluation of safety of homeopathic medicinal products manufactured from raw material of human, animal or microbiological origin and establishment of the first safe preparation.



* adapted from N. Schultz et al. Viral safety in homeopathic medicinal products. *Pharmaeuropa Bio & Scientific Notes* 2011-1:55-65

1. A risk assessment with respect to viral safety must be carried out for homeopathic medicinal products containing materials from biological origin.
2. If the intermediate product is considered safe this preparation corresponds to the First Safe preparation.
3. In contrast, if the intermediate product is not considered safe, additional steps for the inactivation or removal of adventitious agents should be considered. If appropriate methods are found, virus validation studies should be performed before introduction into the manufacturing process in order to produce a safe intermediate product.
4. If effective additional inactivation/removal steps cannot be introduced into the manufacturing process (due to manufacturing requirements, e.g.) or if they do not exist and tests are not feasible, the product should not be used.