N.º 045/CA
Data: 02-05-2005

Assunto: Documento "Points to Consider on Safety of Homeopathic Medicinal Products for Human and Veterinary use from Biological Origin"

Para: Requerentes de registo de produtos farmacêuticos homeopáticos

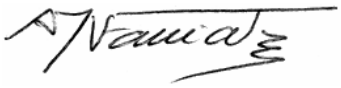
Contacto no INFARMED: Centro de Informação do Medicamento (CIMI) 21 798 73 73

Os produtos farmacêuticos homeopáticos de origem biológica são compostos por uma gama de *stocks* muito variada. Para além de ter de obedecer aos critérios de qualidade e segurança prescritos nas Instruções aos requerentes para registo (simplificado) de produtos farmacêuticos homeopáticos, o registo de produtos farmacêuticos homeopáticos de origem biológica, deverá cumprir requisitos adicionais de segurança, directamente relacionados com a sua natureza.

O documento *Points to consider on Safety of Homeopathic Medicinal Products for Human and veterinary use from Biological Origin* contempla os requisitos mínimos que deverão ser observados quando da submissão de pedidos de registo de produtos farmacêuticos homeopáticos de origem biológica, tendo sido aprovado pelo Grupo de Trabalho de Produtos Homeopáticos (*Homeopathic Medicinal Products Working Group*).

Abaixo encontra-se a versão PDF do referido documento para consulta.
Quaisquer comentários deverão ser enviados para o seguinte endereço electrónico:
centro.informação@infarmed.pt até 30 de Junho de 2005

O Conselho de Administração



(António Faria Vaz)

POINTS TO CONSIDER ON SAFETY OF HOMEOPATHIC MEDICINAL PRODUCTS FOR HUMAN AND VETERINARY USE FROM BIOLOGICAL ORIGIN

04-03-2005

PLAN

1. Scope

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, for human and veterinary use, should warrant sufficient quality and safety within the same principles of the other medicinal products.

This guideline applies only to homeopathic medicinal products for oral and external use as stated in article 14 of the Directive 2001/83/EC, amended by Commission Directive 2003/63/EC, or in article 17 of the Directive 2003/82/EC. For parenteral forms, quality and safety should be demonstrated according to article 16 or 19 of the same Directives, respectively

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.

Biological raw 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 raw materials and first safe dilutions, as well as in-process quality controls. Depending on the nature of the biological raw material, safety studies have to be performed with either the first safe dilution or, if possible, at the level of the stock. Regarding viral safety, viral validation studies related to the species of origin should be addressed. Special precaution should be taken with nosodes due to their intrinsic pathological nature and origin.

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 dilution.

2. Biological raw materials used for the production of homeopathic medicinal products

2.1. Origin of biological raw materials

Raw 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 (out of the scope of this document) e.g., parts of plants, plant secretions, extracts, mother tinctures, pollen, plant cell lines, macroscopic fungi.

2.2. Sourcing of biological raw materials

2.2.1 Animal origin

When animal raw materials are sourced for production, safety precautions should be taken to avoid transmission of pathogenic agents to humans and/or animals. Raw materials of animal origin should be shown to be free from any human and/or animal pathogenic agent, other than the homeopathic therapeutic agent.

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 raw material should ensure that animal raw material comes from documented and recorded sources and should perform regular audits of the suppliers. Any exception to this should be justified.

The supplier of animals should be certified by a competent veterinary authority, i.e. one which performs routine legal supervision of animal husbandry.

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 number of the animals should be specified. When diseased animals are used, 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.

2.2.1.1 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 human or veterinary 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.

2.2.1.2 Transmission of TSE

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

When considering specifically the risk of transmission of TSE, raw materials, excipients as well as reagents participating in the manufacturing process, namely from bovine, ovine and caprine origin, 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.

2.2.2 Medicinal products

Source materials currently used as medicinal products such as serums, vaccines, toxins etc. should have the same quality as that for the approved medicinal products.

2.2.3 Human origin

When raw materials of human origin are used 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.

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".

Cross species infectivity should be addressed when human materials are used in veterinary and vice-versa.

2.2.4 Products derived from human and animal cell lines.

Human and animal cell lines products 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 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".

Human and animal cell lines 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".

2.2.5 Genetically modified organisms

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

3.Manufacturing process and safety of the Homeopathic Medicinal Product and of the first safe dilution

3.1 First safe dilution

Only first safe dilutions may be used to prepare the homeopathic medicinal products, which should be free from pathogenic agents

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 dilution, 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.

3.2. Manufacture of the homeopathic medicinal product and first safe dilutions

Dilutions alone and *per se* do not ensure biological safety of the first safe dilution. Manufacturing steps at the level of homeopathic dilutions such as solvent/detergent, filtration or pasteurisation may contribute to the safety of the first safe dilution. First safe dilutions 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 dilution. The effectiveness of the manufacturing process to inactivate or remove adventitious agents is important for the biological safety of the first safe dilution 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".

3.3. Human origin

Raw 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 raw 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 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 human or veterinary use.

3.4. Transmission of TSE

Raw 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).

3.5. 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.

GLOSSARY

- Raw material: material (raw + starting) used for the production of homeopathic preparations.

- First safe dilution: first level of potentisation for which the biological safety is guaranteed for the preparation of homeopathic medicinal products.

- Homeopathic preparation: can be a stock or a homeopathic medicinal product according to cfr European Pharmacopoeia

- Potentisation : cfr according to European Pharmacopoeia

- Stock: can be a homeopathic preparation e.g. mother tincture, or a substance used as a starting point for the preparation of the homeopathic medicinal product

- Nosodes are 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 micro organisms.