Safety issues
in the preparation of homeopathic medicines

World Health Organization

Safety issues in the preparation of homeopathic medicines

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Foreword

Homeopathy is a system of medicine born in Europe in the last part of the eighteenth century. The homeopathic doctors use homeopathic medicines, which are prepared following a well-defined procedure, starting from substances derived from the mineral, herbal and animal worlds. The techniques of preparation of these drugs include the dilution of the raw material, in hydroalcoholic solutions or in other excipients, and the potentization of the product into different grades. In some cases, the dilution is so high that it is almost impossible to find one molecule of the original raw material. Of course this fact has created an intense debate between, on one side, people who have experienced positive effects from homeopathic therapy and strongly believe in it and, on the other side, people who criticize these products, as being contrary to all the requirements of modern pharmacology.

The use of homeopathic medicines has spread more and more, and nowadays it is widespread not only in the European region but also in south Asian countries and North and South American countries. With the worldwide increase in the use of homeopathic medicines and the rapid expansion of the global market, the safety and the quality of homeopathic medicines has become a major concern for health authorities, pharmaceutical industries and consumers. The safety of the homeopathic medicines largely depends on their quality. Requirements and methods for the quality control of finished homeopathic medicines are far more complex than for chemical drugs, particularly for the combined or mixed homeopathic medicines. Furthermore, the quality of the homeopathic medicines is influenced both by the quality of the procedure used during their production and the quality of the raw material. Products which meet high quality standards are needed to allow the patient to make safe use of the homeopathic medicines. Nowadays, this is more and more important because, as a consequence of market globalization, many of the raw materials and medicines used in the homeopathic systems come from different countries.

In the Lombardy region about 20% of the population regularly uses homeopathic medicines, but almost 60% of the population use them occasionally for their health and well-being and these numbers are increasing. Moreover, more than 34% of people use homeopathic medicines for self-healing. Of course, these people need to be guaranteed the same high level of quality and safety that is offered to the entire Lombardy population. Since 2002, the Social-Health Plan of the Lombardy Region has supported the principle of freedom of choice among different options of care.

Faced with the present situation, it is extremely important for the protection of consumers to assure basic requirements for homeopathic medicines at the international, national and regional levels. For this reason, the Regional Government of Lombardy has provided its support and cooperation to WHO to develop this technical document, in order to ensure that homeopathic medicines meet minimum standards and to guarantee the high quality of homeopathic medicines, both in Lombardy and worldwide. In addition, it is our wish that this

technical document be used as a reference to facilitate establishment of regulation in those countries where no regulations have yet been developed. This document could also be used for the promotion of citizens' awareness about safety and quality of homeopathic medicine.

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Preface

Herbal medicines have been increasingly used over the past three decades. For example, in Europe in 2003, herbal medicine sales were worth 5 billion US dollars.[1] The cost of the traditional Chinese medicines used in China in 2008 was 26 billion US dollars.[2] The value of Japan's production of its traditional medicines, known as *kampo* medicines, reached almost 1 billion US dollars in 2007.[3]

Homeopathy is one of the most commonly used forms of herbal medicines.[4] There is a large market for homeopathic products around the world. For example, in 2008, Australia spent 7.3 million US dollars on homeopathic medicines;[5] France spent more than 408 million; Germany 346 million and the United Kingdom more than 62 million US dollars.[6] In the United States, adults spent 2.9 billion US dollars on homeopathic products in 2007.[7]

Given the importance of homeopathic medicines, health authorities – and consumers - are quite naturally concerned with their safety. Since homeopathic medicines are typically administered at a very high dilution, and ingredients may not even be detectable or quantifiable in the final products, homeopathic medicines are often thought to present no major safety concerns. Still, there are a few aspects of the production of homeopathic medicines that could constitute potential safety hazards. Firstly, not all homeopathic medicines are administered at a high dilution. Sometimes, a homeopathic medicine made from source material, such as a mother tincture, is administered in the most concentrated form. Secondly, homeopathic medicines are made from a wide range of natural or synthetic sources: minerals and chemicals, but also plant materials, including

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[1] De Smet P. Herbal medicine in Europe – Relaxing regulatory standards. *New England Journal of Medicine*, 2005, 352:1176–1178.

[2] China Research & Intelligence. *Report of traditional medicine industry, 2009*. Shanghai, China Research & Intelligence (http://www.shcri.com/reportdetail.asp?id=275, accessed 15 September 2009).

[3] *The yearbook of statistics of production by the pharmaceutical industry, 2007* [original in Japanese]. Tokyo, Ministry of Health and Welfare, 2008 (http://www.mhlw.go.jp/topics/yakuji/2007/nenpo/index.html, accessed 13 August 2009).

[4] *WHO traditional medicine strategy 2002–2005*. Geneva, World Health Organization, 2002.

[5] A survey conducted by the Complementary Healthcare Council of Australia, 2008.

[6] ECHAMP. *Homeopathic and anthroposophic medicine in the United Kingdom: ECHAMP Facts and Figures*, 3rd ed. Brussels, ECHAMP, 4 August 2009 (e-pub ahead of print).
ECHAMP. *Homeopathic and anthroposophic medicine in the French Republic: ECHAMP Facts and Figures*, 3rd ed. Brussels, ECHAMP, 4 August 2009 (e-pub ahead of print).
ECHAMP. *Homeopathic and anthroposophic medicine in the Federal Republic of Germany: ECHAMP Facts and Figures*, 3rd ed. Brussels, ECHAMP, 4 August, 2009 (e-pub ahead of print).

[7] Nahin NL et al. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. *National Health Statistics Report*, 2009, 18 (http://nccam.nih.gov/news/camstats/costs/nhsrn18.pdf, accessed 15 September 2009).

roots, stems, leaves, flowers, bark, pollen, lichen, moss, ferns and algae; microorganisms, including fungi, bacteria, viruses and plant parasites; animal organs, tissues, secretions and cell lines. Human materials may include tissues, secretions, hormones, and cell lines. Some of these source materials constitute potential safety hazards, even at high dilutions.

The resolution on traditional medicine adopted by the World Health Assembly (WHA) in May 2009 (WHA62.13),[1] urges Member States to "formulate national policies, regulations and standards, as part of comprehensive national health systems, to promote appropriate, safe and effective use of traditional medicine." It also requests WHO to "continue providing technical guidance to support countries in ensuring the safety, efficacy and quality of traditional medicine." This applies to homeopathic medicines, and this document is a contribution to implementing these recommendations, by identifying potential safety issues related to the production of homeopathic medicines.

At the same time, it attempts to bring some consensus about terminology harmonize definitions of homeopathic medicines, to recommend safe degrees of dilutions of homeopathic preparations and to promote the exchange of information.

In preparing this document, WHO has consulted with more than 400 reviewers from 105 countries, including experts in the fields of homeopathic medicines, herbal medicines, biologicals and pharmaceuticals, members of the WHO Expert Advisory Panel on Traditional Medicine, members of the WHO Expert Advisory Panel on international pharmacopoeia and pharmaceutical preparations and WHO Collaborating Centres for Traditional Medicine, as well as relevant nongovernmental organizations. National regulatory authorities in more than 100 countries have received the drafts of the document for their review and provided additional information, comments and advice.

The document is intended as a support to national regulatory authorities – and to manufacturers of homeopathic medicines - in ensuring the safety and quality of homeopathic medicines. National authorities may want to use it as a reference when establishing appropriate regulatory requirements. The document provides definitions of commonly used technical terms in relation to the quality of homeopathic medicines:. This had been recommended by workshop on homeopathy at the 10th International Conference of Drug Regulatory Authorities (ICDRA) in 2002, held in Hong Kong Special Administrative Region of the People's Republic of China, and should facilitate quality control regulation.

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[1] http://apps.who.int/gb/ebwha/pdf_files/A62/A62_R13-en.pdf

1 Introduction

The term homeopathy is derived from the Greek words ὅμοιος (*hómoios:* similar) and πάθος (*páthos:* suffering, disease). Homeopathy has a holistic approach to healing, with as its central tenet that "like cures like" (in Latin: *similia similibus curentur*). Homeopathy has its own views on illness, and its own diagnostic and treatment principles, as well as products and practices. Established in 1796 by the German physician Samuel Christian Hahnemann, it treats patients with heavily diluted preparations of substances which in their undiluted form are thought to cause effects similar to the symptoms presented. Homeopathic medicinal products are also used in other therapeutic approaches with a different epistemological and methodological status, such as *anthroposophic medicine, homotoxicology/antihomotoxic therapy* and *isotherapy* .

Homeopathy is widely used in all WHO Regions. The national regulatory framework and the place of homeopathy within the health care system differ from country to country, but the use of homeopathic medicines, mostly as non-prescription medicines, is growing in many parts of the world. The exact size of the homeopathic medicines market in economic terms, is not well known, but sales data reveal that homeopathic medicines represent a significant part of medical economies.

Despite the growing use of homeopathic medicines worldwide, few of the WHO Member States regulate these medicines. It is usually taken for granted that the safety of homeopathic medicines should not be a major concern as these medicines are often highly diluted when administered. However, this is not always the case. Moreover, the variety of materials used (medicinal plants, animal and human materials, pathogens as well as minerals and chemicals) and other technical aspects of the production and manufacture of homeopathic medicines may constitute potential risks to their safety.

Adverse events occurring during homeopathic treatment are rarely attributed to the homeopathic medicine itself. However, safety assessment should also consider possible impurities of the source material or contamination and failures of good manufacturing practice. Furthermore, because many homeopathic medicines can be purchased as non-prescription medicines in community pharmacies and health stores, without consultation with a healthcare provider, it has become increasingly important to provide sufficient and accessible information on such medicines. Although homeopathic medicines are generally assumed to be benign, the level of authorization, appropriate labelling and quality assurance should take into consideration its extensive use, also within vulnerable populations such as the elderly, pregnant women and children.

In recent years there have been a number of calls on WHO to support efforts to regulate the safety of homeopathic medicines.

WHO's Traditional Medicine Strategy 2002-2005, as well as that covering the period from 2004 to 2007 have both addressed the safety, quality and efficacy of

traditional medicine (TM) and complementary and alternative medicine (CAM). Developing technical guidance regarding the safety and quality control of herbal medicines and other TM / CAM products was a key element in these Strategies.

The 10th International Conference of Drug Regulatory Authorities (ICDRA) held in Hong Kong Special Administrative Region of the People's Republic of China in June 2002, requested WHO to: "Harmonize definitions of homeopathic medicines; [make] recommendations for safe degrees of dilutions of homeopathic preparations; promote the exchange of information; and provide guidance to governments and [nongovernmental organizations] NGOs training of homeopathic medicines"*(1)*.

Finally, resolution WHA56.31 on traditional medicine, adopted by the 2009 World Health Assembly, requested WHO to provide technical support for developing methodologies to ensure product quality, efficacy and safety.

This technical document is WHO's response to these requests and recommendations, and is a part of the implementation of the WHO Traditional Medicine Strategy and the WHO Medicines Strategy. It aims to provide guidance to Member States on technical aspects of the production and manufacture of homeopathic medicines that potentially have implications for their safety. This is of relevance for establishing national quality standards and specifications for homeopathic medicines, as well as for controlling their quality. The document, however, does not address issues of efficacy or clinical utilization.

Homeopathy uses a specific terminology that is not always used in a consistent way in the monographs and current editions of pharmacopoeias in official use. For the purpose of this document it has been necessary to define key terms unambiguously: without doing so quality control recommendations are difficult to make. The terms used in this document are defined in Annex 2. These definitions enjoy considerable consensus, and are broad enough to encompass homeopathic medicines made and used according to well-established variations to the original philosophy of Hahnemann (such as reference to complex homeopathic medicines and those referred to as homeotherapy). The terminology is used consistently as defined in the annex; this is felt to be necessary for a uniform and explicit regulation of homeopathic medicines.

The document is structured in three parts. First the specificity of homeopathic medicines is reviewed, indicating the type of potential safety problems they may present and the quality control challenges this poses. The next chapter deals specifically with the safety aspects related to the materials and ingredients used in the preparation of homeopathic medicines. The last part reviews regulatory issues related to the manufacturing and marketing processes, and to consumer information. The body of the document is followed by a glossary of technical terminology relevant to the subject, and complementary materials.

2 Challenges for quality control of homeopathic medicines

2.1 Homeopathy and homeopathic medicines

The central tenet of homeopathy is that “like cures like” (in Latin: *similia similibus curentur*), in a holistic approach to the totality of the patient’s symptoms. Homeopathic medicines are based on the principle that high dilutions of potentially active molecules retain a memory of the original substance. Hence, the starting materials, the homeopathic stocks and/or mother tinctures are subjected to a process of serial dilution and succussion in order to potentize the product with an inert carrier material. Originally, Hahnemann employed this process to diminish the toxicity of potentially hazardous substances. The name potentization to characterize this process was given by him later.

From the safety point of view it is important to note first that, although homeopathic treatments often utilize ultramolecular dilutions of the starting material (above Avogadro's number), there are also homeopathic medicines of considerably lower dilution which do contain molecules that may be active in the biochemical sense. Hence, although homeopathic medicines are in general considered to be safe when administered appropriately, toxicological aspects should not be neglected especially when using lower dilutions of unsafe starting material.

Moreover, the amount of starting material present in homeopathic medicines may depend on the method of preparation. Safety issues may arise if these differences in method of preparation are neglected. For example, a comparison of the "identically" entitled pharmacopoeial monographs on *Aconitum napellus* in different pharmacopoeias, e.g. the *Pharmacopoeia française* (Phf) *(2)*, the *German Homeopathic Pharmacopoeia* (GHP) *(3)*, the *Homoeopathic Pharmacopeia of the United States* (HPUS) *(4)* and the *Homoeopathic Pharmacopoeia of India* (HPI) *(5)*, reveals considerable differences (Table 1). *Aconitum napellus* 1X = 1DH prepared according to the *German Homeopathic Pharmacopoeia* is closer to *Aconitum napellus* mother tincture than to the 1X = 1DH, both prepared to according to the *Pharmacopoeia française*. In the case of India the alkaloidal content is not specified because the members of the Homoeopathic Pharmacopoeia Committee (HPC) feel that minor variations in the quantity of physiologically active alkaloids in the end product are of no consequence for the action of the medicine. They consider it acts qualitatively, at a non-physiological level, and its action is qualitative and not quantitative (dose-dependent).

Table 1. The monographs on *Aconitum napellus* in four pharmacopoeias

Characteristic	*Pharmacopoeia française* (Phf)	*German Homeopathic Pharmacopoeia* (GHP)	*Homoeopathic Pharmacopeia of the United States* (HPUS)	*Homoeopathic Pharmacopoeia of India* (HPI)
Alkaloid content expressed in aconitine in the mother tincture	0.02–0.05%	0.08–0.16%	0.025–0.075%	Not described (approximately 0.03%)
Ratio of mother tincture to diluent for obtention of 1X = 1DH	1:9	1:4	1:1	Mother Tincture = 1X
Percentage of the mother tincture in the 1DH dilution	10%	20%	100%	100%
Resulting alkaloid content expressed in aconitine in 1X = 1DH	0.002–0.005%	0.016–0.032 %	0.025–0.075%	N/A

2.2 Potential safety issues

There are two major groups of potential hazards: those related to the source materials, and those related to the procedures used for manufacture of the finished product.

Homeopathic medicines or their stocks / mother tinctures are prepared from natural or synthetic sources that are referenced in pharmacopoeial monographs or other recognized documents. Not considering imponderabilia, the source materials for homeopathic medicines may consist of the following:

- *plant material* such as: roots, stems, leaves, flowers, bark, pollen, lichen, moss, ferns and algae;
- *microorganisms* such as: fungi, bacteria, viruses and plant parasites;
- *animal materials* such as: whole animals, animal organs, tissues, secretions, cell lines, toxins, nosodes, blood products;
- *human materials* such as: tissues, secretions, cell lines and endogenous molecules such as hormones;
- *minerals and chemicals.*

The quality of source materials and of the excipients used in the manufacture of homeopathic medicines is important. Homeopathic medicines may employ material from problematic sources, the use of which is restricted in conventional medicine: nosodes comprise dilutions of pathogenic organs or tissues; causative agents such as bacteria, fungi, ova, parasites, virus particles, and yeast; disease products; excretions or secretions. All materials of animal or human origin are at risk of containing pathogenic agents. Homeopathic medicines may be based on toxic source materials from animals or plants, while others, particularly in their fresh form are prone to degradation processes or microbiological contamination.

Plant materials may be contaminated with pesticides and heavy metals. The content of toxic constituents in plant materials may vary considerably.

Good manufacturing practice (GMP) guidelines covering the manufacturing process, premises, personnel, packaging and labelling apply to homeopathic medicines as well as to conventional pharmaceuticals. Failure to apply GMP may lead to major quality and safety concerns such as misidentification, impurity of starting material, cross-contamination or incidental contamination.

The unique characteristics of the manufacturing of homeopathic medicines has a number of specific implications and demand specially qualified and experienced personnel. These have to handle toxic materials, materials, particularly fresh ones, that are prone to degradation processes and microbial contamination; and homeopathic medicines derived from animals or human sources. The properties of homeopathic medicines can be compromised by accidental or intentional contamination of source materials, excipients or diluents, or by the vessel or bottle in which the dilution is made. Because definitions may vary between pharmacopoeias, and because of the wide range of processing techniques and manufacturing methods in the various pharmacopoeias, the final homeopathic products may show marked variability.

2.3 Quality control challenges

Manufacturers of licensed medicines are required to prove that their products meet basic quality standards and adhere to GMP guidelines. The same goes for licensed homeopathic medicines. Most established manufacturers of homeopathic medicines have already adopted relevant measures for quality assurance procedures and manufacture according to the principles of GMP. This is not always the case in countries where production of homeopathic medicines is not subject to licensing. Beyond adherence to GMP guidelines, the distinctive characteristics of homeopathic medicines have implications for quality control.

First, a number of WHO technical guidelines relating to quality assurance and control of herbal medicines apply *(6, 7, 8–12)*.

Second, the specific nature of homeopathic medicines have as consequence that some of the methods for quality control and some test systems that are mandatory in pharmaceutical regulation, may at times be inapplicable or irrelevant. These include identification and quantification of active substance and toxicological testing of the final homeopathic product. Identification and assay of source materials may not be feasible at high potencies. In such cases the quality should be demonstrated by complete validation of the manufacturing and dilution process.

3 Quality control issues for homeopathic medicines

Homeopathic medicines are often prepared from natural source materials. Two issues are decisive for the quality of homeopathic preparations: determining the authenticity and the origin of the starting materials according to the homeopathic tradition, and defining the manufacturing procedure. As long as the identity and purity of starting materials and the reproducibility of the manufacturing process are given, the natural biological and geographical variation of starting materials are an integral part of quality of homeopathic medicines. Identity and purity testing is usually performed with the starting material and with the least diluted source employed for potentization (e.g. mother tincture). Consistency of product quality is assured by defining appropriate specifications especially for starting materials, and by defining the manufacturing procedures standardized according to official homeopathic pharmacopoeias and other officially recognized documents, and validated according to GMP.

The diverse origin of the raw materials used in the production of homeopathic medicines requires a range of approaches to ensure the safety of the final product. Generally speaking, quality control should perform identification and, if applicable, quantification of materials before processing; using validated techniques and relevant analytical tests on source identity, possible contaminants and toxic constituents. These tests should be of pharmacopoeial or equivalent status *(13 - 15)*.

Raw material used for homeopathic preparations should be characterized to determine, where applicable, the origin, the history and the nature of the starting material:

- if of botanical origin, the scientific name – genus, species, subspecies / variety, authority and name of family (cross-reference to general name); other information as appropriate such as ecotype, chemotype, and phenotype; part employed; the state of material; possible pharmacologically active or toxic constituents; macroscopic and microscopic description;
- if of biological origin, by the physical, anatomical and histological state; and
- if of mineral or chemical origin, by the physical form, structural formula and relative molecular mass.

3.1 Plant material

Where plant material is used, all matter, including parts of plants, exudates or processed materials should comply with the relevant national quality standards and specifications, pharmacopoeial analytical requirements and monographs. In addition to any pharmacopoeial references on quality control and analytical

testing of herbal materials, other relevant guidelines and manuals may also be considered *(6, 7, 8-12, 15-18)*.

Due to the complex and variable nature of plant material, and its possible contamination with microbes, insects, pesticides, heavy metals, fumigants, mycotoxins and radioactivity, adequate control of source material, storage and processing assume particular importance when plant materials are used in the manufacture of homeopathic medicines.

Manufacturers are called to follow exemplary standards and provisions regarding identification of source material, limit tests, and complementary tests. These are listed in Table 2. A clear description of the following characteristics should accompany every batch, or its absence should be justified:

- parts / material of plant used; macroscopic description of plant and plant material;
- microscopic characteristics;
- identity tests;
- purity tests;
- moisture / water content;
- determination of content of toxic constituents (if applicable);
- method for preparation of mother tincture.

Table 2. Provisions regarding quality control of plant material used for the preparation of homeopathic medicines.

Identification of source material	1. scientific name; 2. stage of growth; 3. part of plant used; 4. information about whether materials were cultivated or collected from the wild and the place of cultivation or collection from the wild; 5. comparison, by the manufacturer or by a recognized laboratory, with an illustrated description of an authentic specimen for macroscopic and microscopic characteristics as well as analytical determination of marker substances or standard substances (if applicable).
Limit tests:	1. Limit tests should be performed for: • pesticides (agricultural and veterinary chemicals), • heavy metals (if appropriate, for metals such as lead, mercury, arsenic and cadmium), • fungi, bacteria, mycotoxins (e.g. aflatoxins), and • any other relevant contamination (e.g. by-products of manufacture, radiolytic products derived from sterilization by ionizing radiation, or residues from other decontamination procedures). 2. Limit tests should be done on representative samples at an unprocessed or raw stage (if processed matter has to be used, a sample should be taken before any potentization is done). 3. Limit tests and ranges should comply with pharmacopoeial standards, as limits applicable to food may not be appropriate.

Complementary tests:	Where applicable, tests are performed for: 1. foreign matter; 2. total ash; 3. water content; 4. bitterness value; 5. loss on drying; 6. radioactive contamination.

3.2 Animal or human derived source material

Homeopathic medicines derived from healthy or diseased animals or human sources raise concerns about microbiological and viral contamination. These issues are discussed, particularly with a view of minimizing the risk of exposure to transmissible spongiform encephalopathy (TSE) transmitting agents. The Head of Medicines Agencies Homeopathic Medicinal Products Working Group has reviewed the points to consider on safety of homeopathic medicines of biological origin (Annex 3).

Adequate and validated procedures such as filtering, pasteurization, sterilization or precipitation have to be used depending on the individual raw material, contamination or pathogenic load, especially to establish the first safe preparation. The dilution process alone is not sufficient to establish microbial, viral or TSE safety (Box 1). Therefore, effectiveness of the method used to eliminate pathogenic agents, in addition to dilution, should be assessed and validated by appropriate limit tests. If homeopathic medicines are prepared from raw animal (ruminant) products, all possible transmission of pathogenic agents should be taken into account in the safety procedures. Because animal-derived organs and secretions have different levels of infectivity, tissues can be grouped into corresponding categories *(19-21)*. Only first safe preparations may be distributed as homeopathic medicines or intermediates. These should comply with the principles of minimization of the risk of transmission of pathogenic agents (e.g. sterilization), taking into account the species infection potential other than the homeopathic therapeutic agent. The determination of the "first safe preparation or dilution" ensures the correct definition of viral studies to be applied 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.

Box 1: Managing the risk of transmission of TSE

The use of materials derived from animal resources is essential in certain homeopathic medicines. Currently, there is no evidence that TSE has ever been transmitted by the use of products of animal origin in medicines including homeopathic medicines. However, in response to general safety concerns, the possible risks of TSE and related diseases in animals and humans (e.g. bovine spongiform encephalopathy (BSE), scrapie, Creutzfeld-Jacob Disease (CJD)) should be addressed. The species of the animal and its age constitute important information for a risk assessment. This also concerns carrier materials and excipients, for example, gelatine, collagen, milk and milk-derived products, lecithin, phospholipids, amino acids and protein hydrolysates, glycerol and stearates. Sufficient and accessible information is required for the sponsor and the public, backed up by

regular inspections, strict legislation on international trade and traceability back to the slaughterhouse.

To enable the self-assessment of the processes by the manufacturer and / or sponsor and to minimize the risks of TSE transmission, the following measures should be taken:

- animal species that are not affected by TSE or a non-animal-origin should be preferred;
- use of highly infective tissues must be considered in the context of actual scientific data, and, in particular the age of the animals. The use of such material can be legitimate where adequate documentation on risk assessment is available;
- possible cross-contamination should be avoided through validated cleaning processes;
- preferably, young animals should be used;
- where concerns exist, samples should be submitted for pre-clearance to a recognized laboratory;
- a risk–benefit assessment should be done to consider the quantity of animal material used;
- working procedures and sources of material should be documented to identify products and enable an immediate response in the case of any unexpected event.

Source materials of animal origin should comply with test systems described for:

- contamination with viruses pathogenic to humans (e.g. *European Pharmacopoeia* 6.0 *(22)*, "Homeopathic preparations" describing handling of starting materials of animal origin with a clear distinction between starting materials from healthy animals);
- agents that could transmit animal spongiform encephalopathy (e.g. *European Pharmacopoeia* 6.0 *(22)*, "Minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products").

A clear description of the following characteristics should accompany every batch, or its absence needs to be justified:

- identification of the source of the animal material, including information on whether animals were bred or caught in the wild and the place of breeding or capture in the wild.;
- parts / material of animal used;
- anatomical description of the animal part;
- histological description of the animal part;
- identity tests;
- purity tests;
- moisture / water content;
- determination of content of toxic constituents (if applicable);
- method for preparation of the initial homeopathic preparation (reference to general procedure).

Source material of human origin (tissues, blood or fluids) is a potential source of infection through a variety of known and unknown transmissible agents. Whenever any blood product is to be used, or contamination of blood is possible, raw materials should comply with the relevant national or official guidelines *(3, 23-25)*. Since human-derived materials such as pituitary or liver extracts, albumin, or tonsils may be contaminated by bacteria, virus or CJD transmission, quality control measures should address these issues.

Clear documentation on the donor is a prerequisite for ensuring the safety of homeopathic medicines of human origin. A clear description (from tests and/or documentation of history of the material) of the following characteristics should accompany every batch, or its absence needs to be justified:

- identification of the source;
- material used;
- anatomical description;
- histological description;
- identity tests;
- purity tests;
- moisture/water content;
- method for preparing the initial homeopathic preparation (reference to general procedure).

Nosodes. By definition, nosodes comprise dilutions of pathogenic organs or tissues; causative agents such as bacteria, fungi, ova, parasites, virus particles, and yeast; disease products; excretions or secretions. Nosodes are considered as homeopathic medicines if processed in accordance with a recognized homeopathic pharmacopoeia in official use, or other officially recognized documents. Due to their diverse nature, it is recommended that nosodes be evaluated individually for safety assessment.

Biotechnological source material, i.e. materials derived from biotechnologically manufactured or processed raw materials (e.g. human, animal or plant cell lines, microorganisms, genetically modified organisms or products of fermentation) should comply with relevant guidance *(26-29)*.

3.3 Mineral and chemical material

If minerals or chemicals are used as source materials for the manufacture of homeopathic medicines, analytical tests should be carried out to determine the identity and the source or origin; to detect possible contamination with heavy metals and any other possible toxic constituents. The purification procedure must be described. For minerals and chemicals data must be presented on source material; appearance and description of raw materials; identity tests; purity tests; and determination of content. If these data are absent justification must be provided.

For the first dilution/trituration, details of the following are required, or their absence needs to be justified:

- method of preparation;
- description and characteristics;
- identity tests;
- purity tests;
- determination of content;
- determination of toxic constituents.

3.4 Mother tincture

Mother tinctures for the production of homeopathic medicines should comply with pharmacopoeial specifications and quality requirements in official use, or those of other officially recognized documents.

The following data should be presented, or their absence needs to be justified:

- method of preparation (reference to general procedure);
- appearance and description;
- identity tests;
- purity tests;
- procedure for stability tests;
- determination of content;
- determination of toxic constituents.

3.5 Finished product

Homeopathic dosage forms in the final products should comply with pharmacopoeial requirements and should be tested to determine the following:

- *identity and content* (if applicable); normally the test for uniformity of content is not appropriate either to determine the potency or to demonstrate that the source material or its characteristic constituents cannot be detected;
- *quality of dosage form* (uniformity of mass, hardness and friability for tablets – test for disintegration can only be omitted when justified); test for viscosity or rheology (for ointments);
- *residual solvents, reagents or incidental contamination* as a result of the manufacturing process (e.g. *European Pharmacopoeia* 6.0 *(22)*, "Residual solvents; limiting residual solvent levels in active substances, excipient, and medicinal products";
- *stability;* the stability tests for the dosage form should be the minimum requirement.

3.6 Diluents and excipients

In addition to the evaluation of active substances, safety evaluation should also cover the excipients and diluents used in homeopathic medicines. The manufacturer should ensure that:

- all excipients and diluents included in the final product are listed in the documentation and, if applicable, on the label if required under national legislation;
- excipients and diluents comply with a pharmacopoeia in official use or other officially recognized documents;
- if new excipients and diluents are included, sufficient data on their safety and quality are provided to national health authorities.

Depending on the pharmacological and toxicological nature of the excipient and diluents concerned, risk evaluation should take into account their overall exposure, because any substance might be found potentially toxic after long term or intensive use. In this context, it should be recognized that additional sources or routes of administration of the excipient or diluent from food or concomitant treatments might add to the total daily exposure.

Special attention should be paid to the general labelling and warnings on the package of the final product. For example, ethanol, glycerol and lactose, often used in the preparation of homeopathic medicines, are listed in the EU under the guideline ENTR/F2/BL D (2003) entitled *Excipients in the label and package leaflet of medicinal products for human use (30)* and a threshold is given for the individual substance on a *per dose* basis.

The Food and Drug Administration of the US (US FDA) has set up "maximum concentration limits for alcohol as an inactive ingredient in OTC drug products intended for oral ingestion". However, it should be recognized that "dose" has to be defined more precisely, as a single dose and as a maximum daily dose. It is the actual intake of the excipient or diluent that is relevant, although very low in the case of homeopathic products, and not its percentage in the final product. On the other hand, in homeopathy, small quantities can be used several times a day and such homeopathic medicines may contain high levels of ethanol. In this context, adequate information including warnings, contraindications and adoption of monographs is mandatory when remedies are prescribed to children, women who are pregnant or breastfeeding, or patients with relevant medical histories including liver failure, brain injury, seizures or alcoholism. Other relevant warnings as regards sugars also apply to homeopathic medicines.

3.7 Impurities and contaminants

Quality and safety of homeopathic medicines can also be affected by impurities and incidental constituents, which may be found in the final preparation as a by-product of manufacturing and storage, contamination or low-quality raw materials, or may be formed during the production process. Such constituents include microbial toxins, microorganisms, metals, pesticide residues or degradation products. These impurities may pose a potential risk to patients and therefore need to be minimized. Hence, the manufacturer or sponsor should validate and manage the production, processing and storage practices. Owing to the large range of potential impurities and contaminants and the varying extent of exposure to them over time, no comprehensive list of all impurities and their limits can be presented. However, the manufacturer has an obligation to trace and minimize the presence of impurities and contaminants. The following questions should be considered in setting requirements regarding impurities and incidental constituents:

- what specific impurities and contaminants need to be considered?
- what tests (validated and reproducible limit tests which comply with a pharmacopoeia in official use or other officially recognized documents should be applied?
- what limits should be specified? (If possible, pharmacopoeial references should be used – others have to be justified.)

Therefore, quality control has to determine limits of relevant contaminants for the source material as well as the stock solution or triturate. This aspect is of particular importance, since storage and manufacture may pose an additional risk for accidental contamination of the final product. In principle, the legal standards and limits for the final product should comply with those published in the pharmacopoeia in official use or other officially recognized documents.

To ensure adequate quality and safety of the final homeopathic product, limit and product tests, validation checks and process control represent essential approaches and apply to the source materials, stocks or mother tinctures, starting materials and excipients. Methods, techniques and apparatus necessary for the quality control of homeopathic medicines has to be in accordance with a pharmacopoeia in official use or other officially recognized documents.

4 Regulation regarding homeopathic medicines

The regulatory framework and its requirements for homeopathic medicines differs from country to country. Homeopathic medicines may be subject to similar regulatory control to that applicable to conventional pharmaceutical products, with adaptations to the particular requirements of homeopathic medicines. In some countries they are subject to separate regulatory frameworks.

A number of regulatory authorities already require quality assurance of homeopathic medicines. Manufacturers, packagers, labellers, importers and distributors of finished homeopathic medicines or related raw materials have to meet the relevant requirements including effective process controls, validated analytical methods, adequate buildings, and good storage and sanitary conditions.

4.1 Regulations relating to manufacturing and marketing

The regulatory frameworks expect health authorities to request pre-marketing proof of quality and safety. Typically, manufacturers of homeopathic medicines are expected to prepare documentation describing quality assurance in general, and quality control of specific homeopathic medicines. Raw or source material, mother tincture, diluent or excipient, and final product must all comply with quality standards published in an official pharmacopoeia or documentation of equivalent status and the process of manufacture should conform with the applicable GMP principles (*12*).

While GMP guidelines provide general guidance for medicinal products including homeopathic medicines, they do not necessarily address the special requirements of homeopathic medicines for guidance on, e.g., process validation or quality assessment of the starting material. Theoretically, this could lead to substandard product quality, which may pose a risk to public health and could result in a comprehensive product recall. The relevant documents that define basic principles in quality assurance and control, taking into account the unique characteristics of homeopathic medicines *(4, 6 ,10-12, 31-38)*. These are general guidance references, and may be adapted to meet individual needs. The equivalence of alternative approaches to quality assurance should, however, be validated.

Validation of the manufacturing process is crucial, given the specific nature of homeopathic medicines. It relies heavily on the compliance with the master formula which provides the relevant information on the system of potentization to be adopted (e.g., decimal, Hahnemannian) and the relevant pharmacopoeial method; processing of raw materials (e.g. maceration or percolation); number of succussions during each potentization step; duration of trituration; method of

impregnation; in-process controls; and procedures to be followed for handling of the final product[1].

4.2 Consumer information

Given the conditions under which homeopathic medicines are used, consumer information is a critical issue *(39)*. A particular aspect is constituted by the product label and package leaflet, which represent the first and, in many cases, the only information received by the consumer, it plays a crucial role in safe and rational use of the medicine. Hence, it is important, that labels show the required consumer information about the product. Labelling requirements vary from country to country and may be very detailed, as is the case in Canada (Annex 4).

The list of labelling requirements in Table 3 may serve as orientation for what is generally considered useful and realistic. Local regulatory systems may require additional data, such as lists of contraindications, precautions and side-effects; also special patient groups, such as pregnant or breastfeeding women, children and people with allergies should be addressed. Moreover, there may be a requirement that licensed homeopathic medicines should be sold with a package insert, similar to that of conventional medicines. Some of the information listed above might be presented in the package insert, or on the secondary packaging, according to national provisions.

4.3 Regulatory frameworks

The objectives, scope and approaches of national regulatory frameworks for homeopathic medicines varies considerably from country to country. Even in highly regulated health systems, regulation of homeopathic medicines may still be in an early stage. Annex 5 provides a set of examples from countries with regulatory systems in place. Most divide homeopathic medicines into two or more classes, - with limitations on route of administration and minimal dilution, but also with.simplified authorization procedures for those that are considered harmless and used for self-limiting conditions and over the counter sales. On the whole, however, there is still a dearth of information on the occurrence of safety problems and on whether safety in those counties that have regulatory and quality control regimes safety is actually improved.

There is a need for better documentation and evidence on actual rather than potential safety problems. For example, in a number of countries there are regulatory frameworks that oblige licence holders to report possible adverse reaction after authorization, including events related to quality defects and incorrect labelling. Such pharmacovigilance systems yield information on adverse events. Current global databases, however, document only very few

[1] The “first safe preparation or dilution” should be clearly defined. Depending upon national provisions and legislation, manufacturers or distributors of homeopathic medicines may face restrictions on their distribution of potencies below “first safe preparation”. The first safe preparation should be defined on a case-by-case basis and can be defined at any level of the manufacturing process up to the last removal/inactivation step introduced in the process.

Table 3. Typical labelling requirements for the safe and proper use of homeopathic medicines

- name and address of manufacturer, packager or distributor (with contact telephone number or e-mail address, if appropriate);
- manufacturer's batch number;
- registration number (if applicable);
- net amount (content) of the product in the container;
- common name of dosage form, the traditional homeopathic name commonly used in the geographical area, if applicable;
- statement that identifies the product as homeopathic – e.g. "homeopathic medicine" or "homeopathic medicine for anthroposophic use";
- scientific name of the active substance(s), and / or the traditional homeopathic name of the active substance(s), as given in recognized pharmacopoeias in official use or other officially recognized documents; the degree of dilution / potency; and a reference to the pharmacopoeia that was used for the method of preparation;
- quantity of the active substance(s) in the dosage form;
- excipients, if required by the national regulatory system;
- directions for use and dosage requirements, if applicable;
- indications, in accordance with the national regulatory system;
- storage conditions;
- warnings about alcohol or lactose, if applicable;
- warning that advises the user to consult a doctor or qualified health care professional if the symptoms persist or worsen;
- route of administration;
- expiry date (if required by the national regulatory system).

such events. It is presently unknown whether this is due to underreporting or to a genuine absence of such events.

It is the responsibility of governments to design regulatory frameworks that are adapted to their specific situation. Nevertheless, they can and should take full advantage of experience accumulated across the world. National health authorities that are developing regulatory frameworks may want to adapt WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems *(40)* for their frameworks and pharmacovigilance systems. They may also want to ensure more systematic exchange of experience on the implementation of effective regulation. This document provides a modest contribution to such exchange of experience.

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Annex 1: List of participants in the WHO consultation on quality of homeopathic medicines, Milan, Italy, 25-27 June 2007

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Annex 2: Glossary

The terminology used in this document is commonly used within the homeopathic community, albeit in a sometime inconsistent way. For the purposes of this document an effort was made by the participants of the WHO consultation on quality of homeopathic medicines, held in Milan, Italy in 2007, to agree, by consensus, on the definitions used throughout this document. The definitions in this glossary are not intended to be absolute, but to provide the necessary consistency for a uniform and explicit regulation of homeopathic medicines.

Active substance: Active substances are considered to be source materials processed by one or a sequence of homeopathic manufacturing procedures listed in pharmacopoeias in official use and other officially recognized documents (e.g. mother tinctures, dilutions or triturations).

Contamination *(1):* The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, or of another homeopathic medicine into or on to starting material, intermediate product or finished homeopathic medicines during production, sampling, packaging or repackaging, storage or transport.

Cross-contamination *(1):* The contamination of starting material, intermediate product or finished product with another starting material or product during production.

Diluent: Substance used for the preparation of a stock / starting material or the potentization process and which may also represent the substance of the dosage form. Liquid diluents usually consist of purified water, aqueous solution, glycerol or ethanol of a suitable concentration or for which there is an appropriate monograph. The commonest solid diluent is usually lactose monohydrate.

Dilution: Dilution has two meanings in homeopathy:

- For a product, a dilution is a liquid homeopathic preparation which is potentized as described below (see the definition of potentization). Individual dilutions are also called potencies;
- As a procedure, dilution means the de-concentration process of a liquid or a solid preparation. One part of each stage in the preparation of a homeopathic medicine from its stock or previous dilution (potency) by adding one part of a previous solid or liquid phase to a predetermined weight or volume of the diluent (see Potentization below). Dilution occurs at all stages of production of the homeopathic medicines whether by addition of solid excipient in trituration or the addition of diluent in the liquid phase and succussion.

Dinamization: see potentization

Dosage form: a dosage form in homeopathy complies with any relevant specifications for that dosage form for which an appropriate characterization exists in a pharmacopoeia in official use, or in other officially recognized documents. The most commonly encountered homeopathic dosage form, *the globule (pillule or pellet)*, is a solid spherule which consists of lactose, sucrose or any other suitable vehicle. Usually, preformed globules are impregnated with a dilution or directly by a mother tincture. The homeopathic dosage form *tablet* is a solid preparation which complies with any relevant characterization in the pharmacopoeia in official use (or in other officially recognized documents) for tablets. Homeopathic medicines in tablet form are either prepared by impregnation of preformed tablets or by compression of triturations with the vehicle. The most commonly used *liquid homeopathic medicines* are either alcoholic solutions or oral liquids.

Excipient: Substance needed for manufacturing a dosage form (used after potentization) such as wheat starch and magnesium stearate for tablets. It may also represent the substance of the dosage form.

Foreign matter *(2):* This is material consisting of any or all of the following: parts of the source material or materials other than those named with the limits specified for the homeopathic medicine concerned; any organism, part or product of an organism, other than that named in the specification and description of the homeopathic medicine concerned.

Homeopath: A qualified provider (practitioner) of homeopathic treatment.

Homeopathic medicines: Any medicine prepared in accordance with a homeopathic manufacturing procedure described by a pharmacopoeia in official use or other officially recognized documents. A homeopathic medicine may contain a number of homeopathic preparations.[1]

[1] Note that some countries use terms such as "homeopathic drugs" or "homeopathic preparations". Compare with definitions in:
United States of America: a homeopathic drug is any drug labelled as being homeopathic and listed in the Homeopathic Pharmacopoeia of the United States (HPUS) *(3)*, an addendum to it, or its supplements. The potencies of homeopathic drugs are specified in terms of dilution, i.e., 1x (1/10 dilution), 2x (1/100 dilution), etc. Homeopathic drug products must contain diluents commonly used in homeopathic pharmaceutics. Drug products containing homeopathic ingredients in combination with non-homeopathic active ingredients are not homeopathic drug products. Food and Drug Administration *(4)*.
Canada: homeopathic medicines are products (i) manufactured from, or containing as medicinal ingredients, only substances referenced in a homeopathic monograph in one of the following homeopathic pharmacopoeias, as they are amended from time to time: *Homeopathic pharmacopeia of the United States* (HPUS) *(3); Homöopathisches Arzneibuch* (HAB) or *German Homeopathic Pharmacopoeia* (GHP) *(5); Pharmacopée française* or *French pharmacopoeia* (PhF) *(6); European pharmacopoeia* (Ph.Eur.) *(7); Encyclopedia of homeopathic pharmacopoeia* (EHP) *(8)*; and (ii) prepared in accordance with the methods outlined in one of the homeopathic pharmacopoeias listed above, as they are amended from time to time. Natural Health Products Directorate (NHPD) *(9)*: Evidence for Homeopathic Medicines Guidance Document (2007)
India: homoeopathic medicines include any drug which is recorded in homoeopathic provings or therapeutic efficacy of which has been established through long clinical experience as recorded in authoritative Homoeopathic literature of India and abroad and which is prepared according to the techniques of Homoeopathic pharmacy and covers

Homeopathy: Classical homeopathy is a system of medicine using preparations of substances whose effects, when administered to healthy subjects, correspond to the manifestations of the disorder in the individual patients (see also section 3.1.1).[1]

Homeotherapy: A reference name for all therapeutic approaches that have developed from homeopathic therapy as established by Hahnemann. Homeotherapy comprises, among others: classical homeopathy; clinical homeopathy; homeopathic combination products; anti-homotoxic therapy and

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combination of ingredients of such Homoeopathic medicines but does not include a medicine which is administered by parenteral route. *Drugs and Cosmetics Act 1940, as amended 2005 (10)*.

European Union: homeopathic medicinal products are any 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. Directive 2004/27/EC amending Directive 2001/83/EC *(11)*.

Switzerland: homeopathic medicinal products are medicinal products containing homeopathic active substances that are manufactured exclusively in accordance with the fundamental principles of the homeopathic manufacturing procedures described in the Pharmacopoeia, in the German Homeopathic Pharmacopoeia ("Homöopathischen Arzneibuch" (HAB) *(5)*), in the French Pharmacopoeia ("Pharmacopée Fraçaise (Ph.F.) *(6)*; under "préparations homéopathiques") or in the British Homeopathic Pharmacopoeia (B.Hom.P.) *(12)* and that are used in accordance with the principles of homeopathic therapy. Swiss Agency for Therapeutic Products *(13)*.

In **Australia** Homeopathic preparations are preparations: (a) formulated for use on the principle that it is capable of producing in a healthy person symptoms similar to those which it is administered to alleviate; and (b) prepared according to the practices of homeopathic pharmacy using the methods of: (i) serial dilution and succussion of a mother tincture in water, ethanol, aqueous ethanol or glycerol; or (ii) serial trituration in lactose. Therapeutic Goods Administration *(14)*.

In the **European Union** homoeopathic preparations: are prepared from substances, products or preparations called stocks, in accordance with a homoeopathic manufacturing procedure. A homoeopathic preparation is usually designated by the Latin name of the stock, followed by an indication of the degree of dilution. *European pharmacopoeia*) *(7)*

In **Switzerland** homeopathic single drugs are homeopathic medicinal products with a single homeopathic active substance: mother tinctures, solutions, powders, or liquid or solid homeopathic dilutions. Swiss Agency for Therapeutic Products *(13)*. Homaccords are mixtures of single homeopathic drugs from the same starting material, with varying potencies. Swiss Agency for Therapeutic Products *(13)*. Homeopathic combinations: Switzerland: :mixtures that contain exclusively homeopathic single drugs or homaccords. Swiss Agency for Therapeutic Products *(13)*.

[1] Compare with definitions in:

India: a system of medicine which believes in a specialised method of treatment system of curing natural diseases by administration of potentised drugs which have been experimentally proved to possess the power of producing similar artificial symptoms on healthy human beings. Department of Ayurveda, Yoga & Naturopathy, Unani, Sidda and Homoeopathy *(15)*

United States of America: the practice of treating the syndromes and conditions which constitute disease with remedies that have produced similar syndromes and conditions in healthy subjects. Food and Drug Administration *(4)*.

homotoxicology; isopathy; anthroposophic medicine; biochemic medicine according to Dr Schüssler; spagyric therapy; gemmotherapy; lithotherapy; and resonance homeopathy.

Imponderabilia: Homeopathic medicines prepared from energy, emanating from natural and physical reactions. It means "not weighable", i.e. which have no perceptible weights. They are energy forms such as sunlight (Sol), magnetic fields (Magnetis Polus Australis), radiation (X-ray).

Mother solution (also called solution): the most concentrated solution prepared from a substance of mineral or chemical origin by dissolving it in alcohol or purified water. It may also be prepared by exposing alcohol or purified water to an energy source (see Imponderabilia).

Mother substance: see source material

Mother tincture (also called tincture): The initial homeopathic preparation made from source material that can be further potentized (also called "liquid stock"), sometimes used as homeopathic medicines, is regarded as the most concentrated form of a finished homeopathic medicine. Mother tinctures are obtained classically by maceration or percolation (sometimes also by digestion, infusion, decoction or fermentation) techniques from source materials according to a procedure prescribed by a recognized homeopathic pharmacopoeia. Sometimes a mother tincture corresponds to the first decimal dilution, "1D" or "1X" (10-1), mostly when dry plant material is used as starting material.

Nosodes: Homeopathic medicines prepared from disease products from humans or animals; from pathogenic organisms or their metabolic products; or from decomposition products of animal organs.

Potency: The denominated degree of serial trituration or dilution and succussion that is reached for each homeopathic medicine. The degrees of dilution or potencies are normally indicated by the letters D, DH or X for successive 1 to 10 (decimal) dilutions, the letters C, CH or K or CK for successive 1 to 100 (centesimal) dilutions while Q or LM denote successive 1 to 50 000 (Hahnemannian quinquagintamillesimal) dilutions. Dilution by 1 to 10 denotes 1 part processed with 9 parts of diluent (Hahnemannian decimal), dilution by 1 to 100, 1 part processed with 99 parts (Hahnemannian or Korsakovian centesimal), and so on. The number preceding the letters (e.g. D, C or LM) normally indicate the number of dilution steps employed (Table 1).

As a consequence of different views in various approaches in homeotherapy and because the notion of these terms may depend on the nature of the starting materials, the terms "high potency" and "low potency" cannot be defined unambiguously.

Potentization (also called dinamization)**:** The combined process of serial dilution and succussion or trituration at each step in the manufacture of homeopathic medicines from stocks. (According to the tenet of homeopathy, potentization represents the process by which the activity of a homeopathic medicine is developed.)

Table 1. Potency table

Dilution ratio	*Common designation(s)*	*Examples*
1:10[a]	X	1X, 2X, 3X, etc.
1:10[a]	D	D1, D2, D3, etc.
1:10[a]	DH	DH1, DH2, DH3, etc.
1:100[b]	C	1C, 2C, 3C, etc. C1, C2, C3, etc.
1:100[b]	CH	1CH, 2CH, 3CH, etc. CH1, CH2, CH3, etc.
1:100[b]	CK	1CK, 2CK, 3CK, etc. CK1, CK2, CK3, etc.
1:100[b]	K	1K, 2K, 3K, etc. K1, K2, K3, etc.
1:50 000[a]	LM	1LM, 2LM, 3LM, etc.
1:50 000[a]	Q	Q1, Q2, Q3, etc.

[a] For 1:10 and 1:50 000 dilution ratios only the Hahnemannian method of manufacture (multi-flask method) is used.

[b] For 1:100 dilution ratios a C potency is assumed to use the Hahnemannian method of manufacture (multi-flask method) and can also be denoted as CH. When the Korsakovian method of manufacture (single-flask method) is used, the potency is designated as CK or K.

Raw Material: see source material

Sarcodes: Homeopathic medicines made from healthy animal tissues or secretions. In Greek, sarcode means fleshly.

Source material (raw material, starting material, mother substance): Source material is the original raw material used for the production of homeopathic medicines. This material is obtained from natural sources, e.g. of botanical, zoological, microbiological, mineral, chemical, animal and human origin, or synthetic procedures. Source materials may undergo preliminary treatment in order to be further processed.

Starting material: see source material

Stock: Substances or preparations made from the source materials (e.g. by maceration, succussion or trituration) used as starting points for the production of homeopathic medicines. [1]

Succussion: A procedure of vigorous shaking with impact or elastic collision carried out at each stage of dilution in the preparation of a homeopathic potency.

[1] It should be noted that this term is not used in all homeopathic regulatory systems (it is used in the *French pharmacopoeia (6), European pharmacopoeia (7)*, and European Union Directive 2001/83/EC *(11)*, but not by others). Moreover, in certain homeopathic systems, the stock is the mother tincture or the mother solution whereas, according to others, the stock may also represent the source material itself. In the European Union stocks are defined as substances, products or preparations used as starting materials for the production of homoeopathic preparations. A stock is usually one of the following: a mother tincture or a glycerol macerate, for raw materials of botanical, zoological or human origin, or the substance itself, for raw materials of chemical or mineral origin. *European pharmacopoeia*) *(7)*

In some pharmacopoeias, specific methods for transmitting the impact may be described in other areas of homeotherapy.

Trituration: Trituration has two meanings in homeopathy. For a product, a trituration means a solid homeopathic preparation that has been potentized. As a homeopathic procedure, trituration means the de-concentration process of a solid material with another solid material. It is a stage in the preparation of a solid homeopathic medicine from its stock or previous trituration by adding one part to a prescribed number of parts of diluent (lactose or other diluent as defined in an appropriate pharmacopoeia in official use, or other officially recognized documents.

Vehicle: See Diluent.

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Annex 3: Points to consider on safety of homeopathic medicines from biological origin

Extracted from the document of Heads of Medicines Agencies[1] - Homeopathic Medicinal Products Working Group

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

[1] The Heads of Medicines Agency is a network of the heads of the national competent authorities whose organizations are responsible for the regulation of medicinal products for human and veterinary use in the European economic area

PLAN

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6. Risk assessment of homeopathic medicinal products from biological origin

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 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 2001/82/EC. For parenteral forms, quality and safety should be demonstrated according to

article 16 or 19 of the same Directives, respectively. Nevertheless, safety measures must have equivalent strength as for parenteral forms considering that their intended use may involve application in skin lesions and mucosa.

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.

Annex 4: Examples of national labelling requirements for homeopathic medicines in selected countries

Australia requires the following information on the label *(1, 2)*:

- product name and name(s) of all active ingredients in the goods (i.e. name of active ingredient or the substance from which the dilution was prepared)
- homeopathic potency
- name of dosage form
- quantity of goods
- warning statements – if applicable
- batch number
- expiry date and storage conditions
- directions for use
- name and address of the sponsor or supplier
- statement of the purpose for which it is intended to be used (except where goods are supplied solely to a complementary healthcare practitioner, "For Practitioner Dispensing Only")
- statement: "homeopathic product" or "homeopathic preparation".

Canada requires the following labelling information *(3, 4)* on the inner/outer label, as per the Labelling guidance document and the Evidence for homeopathic medicines guidance document:

- The brand name must appear on the principal display panel.
- The prefix "DIN-HM" followed by an 8-digit number must appear on the principal display panel.
- The dosage form must appear on the principal display panel.
- The word "Sterile" (for sterile products only) must appear on the principal display panel.
- The words "homeopathic medicine", "homeopathic preparation", "homeopathic remedy" or "homeopathic drug" must appear on the principal display panel.
- A list of all medicinal ingredients including proper name and common name, if different.
- The net amount in the immediate container (e.g. 5 ampoules) in terms of weight, measure or number on the principal display panel.
- Product licence holder's name and address including the company name and postal code (or zip code).
- Importer's name and address including the company name and postal code.
- The homeopathic potency (e.g. 5CH) of each medicinal ingredient.
- The metric amount (e.g. 5 g) of each dilution.
- Recommended use or purpose (specific claims must be supported by evidence).

- Recommended conditions of use including recommended dose, route of administration, duration of use, dosage form, directions for use, frequency, subpopulation and risk information (cautions and warnings, contraindications and adverse reactions).
- The term "source:" or "source information:" preceding the website address which provides a link to the NHPD website. A database listing proper and common names of homeopathic medicines as well as complete source information, as found in the accepted homeopathic pharmacopeias, will be published on the NHPD website in the near future.
- A description of source material for each medicinal ingredient as written on the Product Licence Application form. Alternatively, source information can be made available to consumers through a website as an extension of the label. If this alternative is chosen, the label is required to include the term "source:" or "source information:", followed by either the NHPD website (www.hc-sc.gc.ca/dhp-mps/prodnatur/index_e.html) or a company or association website which provides a link to the NHPD website. A database listing proper and common names of homeopathic medicines as well as complete source information, as found in the accepted homeopathic pharmacopeias, will be published on the NHPD website in the near future.
- Recommended storage conditions, as per the *Homoeopathic Pharmacopoeia of the United States* (HPUS) *(5)* requirements for ophthalmic/nasal solutions: statements to the effect of "Protect from light", "Do not touch dropper end" and "Do not use beyond 4 weeks after opening" must be on the label.
- The lot number, preceded by one of the following designations: "Lot number", "Lot No.", "Lot", or "(L)", and the expiry date.
- A reference to the security feature of the product package should appear on the label unless it is self-evident in the product packaging. Examples of security packaging are seals, transparent wrappers and lids that are sealed until opened.
- A list by common name of all non-medicinal ingredients, preceded by the heading 'Non-medicinal ingredients' (to appear on the outer label only).
- The quantity of mercury contained in the product (to appear outer label only) (only required if the product contains mercury or its salts or derivatives as a non-medicinal ingredient).

The European Union requires the following labelling information *(6)*:

- the name "homeopathic product"
- registration number
- scientific name of the stocks
- degree of dilution (making use of symbols of the pharmacopoeia)
- name and address of the registration holder and, where appropriate, the manufacturer
- method of administration
- expiry date
- pharmaceutical form
- contents of the sales presentation
- special storage precautions, if any
- special warning, if applicable
- manufacturer's batch number

- statement: “homeopathic product without approved therapeutic indications”
- warning advising the user to consult a doctor if the symptoms persist during the use of the medicinal product.

India requires the following labelling information *(7):*

- label of innermost container shows the words “Homeopathic medicine”
- name of medicine
- potency of the homeopathic medicine
- name of each ingredient together with the potency and proportion expressed in metric units, in the case of two or more ingredients
- name and address of manufacturer
- alcohol content, expressed as percentage by volume, in terms of ethyl alcohol, except when the total quantity of the homeopathic medicine in container is 30 ml or less
- in the case of a mother tincture additional information is required:
    - a distinctive batch number preceded by the words “Batch No.” or “Batch” or “Lot Number” or “Lot No. or “Lot” or any distinguishing prefix;
    - a manufacturing licence number preceded by the words “Manufacturing Licence Number” or Mfg. Lic. No.” or “M.L.”
- no proprietary name shall be shown, if the homeopathic medicine contains a single ingredient.

Switzerland requires the following labelling information *(8).*

- name of the product (for homeopathic single drugs: common or scientific name of the active substance and potency, for homeopathic combinations: common name of at least one active substances with an addition, e.g. “comp.”)
- addendum “homeopathic medicinal product”
- dosage form
- contents of the retail pack
- qualitative and quantitative declaration of all active substances, declaration of the excipients
- name and address of the registration holder
- manufacturer’s batch number
- facultative statement: “For individual therapy, use and dosage according to the recommendation of the homeopathic expert”
- special risk information (cautions, warnings, contraindications – if applicable)
- expiry date
- storage conditions
- authorization number.

United States of America

The US Food and Drug Administration *(9)* requires the following information

- name and place of business (manufacturer, packer, or distributor)
- directions for use
- statement of identity
- at least one major OTC indication for use
- statement of ingredients (quality and potency the product, e.g. 3x)

- documentation must be provided to support that those products or ingredients which are not recognized officially in the HPUS are generally recognized as homeopathic products or ingredients
- established name (English names are obligatory, Latin names can also be provided)
- container size and net quantity
- warning statement.

The Homeopathic Pharmacopeia of the United States (HPUS) *(6)* requires:

- directions for use
- statement of identity
- potency of the homeopathic medicine
- net contents
- name and place of business of the manufacturer, packer or distributor
- National Drug Code (NDC) number or FDA establishment number
- "Homeopathic" designation (and possibly "HPUS" if made according to an existing HPUS monograph and methods)
- adequate directions for use.

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7. (India) Drugs and Cosmetics Act, 1940, as amended 2005 (Part IX-A).

8. *Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the requirements relating to the authorization of the placing on the market of medicines (AMZV), Annex 1a (homeopathic or anthroposophic products without therapeutic indication).*

9. US Food and Drug Administration, FDA: Act 201 section 502, 503 CFR; FDA/ORA CPG 7132.15

Annex 5: Examples of national regulatory requirements for homeopathic medicines in selected countries

Australia *(1)*

The Australian Commonwealth, and the Government of New Zealand seek to harmonize their regulatory system, creating a new joint Authority will replace Australia's Therapeutic Goods Administration (TGA) and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe).Legislation relating to homeopathic medicines is still being developed.

Currently homeopathic medicines are recognized as low risk medicines, and may only contain ingredients from a published list of permitted ingredients; they may not contain scheduled medicines; do not have to be sterile; and are not intended to be used in the prevention or treatment of a serious disease.

Class I medicines are not required to be evaluated for safety and quality, but comply with certain legislative requirements; contain only substances previously approved and are produced by a licensed manufacturer.

Homeopathic medicines are, with certain exceptions, not required to be listed and are exempt from selected GMP requirements if all ingredients are diluted to greater than a 1000-fold serial dilution of the mother tincture; the preparation is not required to be sterile; and it does not contain ingredients of human origin, or from listed parts of animals.

Canada *(2–5)*

Homeopathic medicines are regulated as natural health products for over-the-counter use. Regulation covers manufacture, packaging, labelling, storage, importation, distribution, sales and clinical trials. Ingredients must be listed in at least one of the homeopathic pharmacopoeias accepted by the NHPD:

- *Homeopathic Pharmacopeia of the United States (6)*
- *Homöopathisches Arzneibuch or German Homeopathic Pharmacopoeia (7)*
- *Pharmacopée française or French Pharmacopoeia (8)*
- *European Pharmacopoeia (9)*
- *Encyclopedia of Homeopathic Pharmacopoeia (10).*

There are criteria for drugs that are not accepted as homeopathic: drugs administered by puncturing the dermis; drugs derived from substance in Schedules I to IV of the Controlled Drugs and Substances Act (narcotic ingredients); and drugs derived from substances in Schedule C of the Food and Drugs Act (radiopharmaceuticals).

Homeopathic medicines have to comply with GMP specifications. For all homeopathic medicines, licensing has to be proved by an eight-digit identification number preceded by the letters DIN-HM. Applicants for product licences must provide information on all ingredients of the product, on safety of the product and on the text of the proposed label and the recommended conditions of use.

European Union *(11).*

Homeopathic medicinal products are regulated according to Directive 2001/83/EC, which applies to industrially produced medicinal products for human use – special provisions are applicable to homeopathic medicinal products with regard to a simplified registration procedure and proof of therapeutic efficacy. Homeopathic medicinal products are divided into two categories:

- homeopathic medicinal products registered under the "simplified procedure" are for oral or external use, bear no therapeutic indication on the label and the preparations present a dilution of at least 1:10 000 of the mother tincture; such products come under Article 14 of Directive 2001/83/EC (simplified registration procedure); No proof of therapeutic efficacy is needed for these products.
- all other homeopathic medicinal products that do not comply with the criteria listed for eligibility for the simplified procedure; are less diluted than 1:10 000; are not intended for oral or external use; or are marketed for a particular indication as self-care products; are covered by Article 16 of Directive 2001/83/EC (marketing authorization procedure).

Quality and safety of source material, mother tincture and authorized homeopathic medicinal products must comply with European legislation for medicinal products and with the standards of the *European Pharmacopoeia.* Quality and safety standards of homeopathic medicinal products are warrant by legislation and guidelines on good manufacturing practice (Directive 2003/94/EC), inspection and supervision, labelling and leaflet design, and wholesale.

India *(12–15)*

Homeopathy is accepted as one of the National Systems of Medicine in India. The *Homoeopathic pharmacopoeia of India (16)* covers: principles and standards for manufacture; tests for identity, quality and purity; a homeopathic pharmaceutical codex; and monographs of homeopathic medicines.

The Homoeopathic Pharmacopoeia Laboratory sets standards and performs testing, as a national laboratory, on identity, purity and quality of homeopathic medicines.

Objectives of good manufacturing practice cover special aspects of premises, staff, plant and equipment for the manufacture of homeopathic medicines.

Homeopathic medicines shall only be purchased from a dealer or manufacturer licensed under the Drugs and Cosmetics Rules 1945. Homeopathic medicines containing more than 12% alcohol v/v (ethyl alcohol) shall not be packed and sold in packages or bottles of more than 30 ml, but it may be sold to hospitals or dispensaries in packages or bottles of not more than 100 ml.

Switzerland *(17)*

The homeopathic medicinal products are regulated according to their specific characteristics and risks.

- The simplified authorisation for products with therapeutic indications requires a complete dossier including proof of quality, safety and efficacy.
- The simplified authorization for products without therapeutic indications is subdivided into three categories:
    1. Simplified authorization for products with fantasy/brand names and/or with dosage: complete dossier including proof of quality,

safety and clinical tolerance, but without documentation of efficacy.

2. Simplified authorization with a reduced dossier: in addition to the general documentation (including basic information) a reduced documentation specific for the preparation must be submitted.
3. Formal application procedure (applicable in most cases):
    - submission of a basic company dossier containing the summarized information and confirmations relating to the manufacturers and to the medicinal products;
    - electronic submission of an individual notification for each substance and dosage form with basic information, i.e. mention of manufacturing method and starting material;
    - additional documentation is only required in the case of certain substances of animal or human origin, or for medicinal products administered parenterally or applied on or in the eye: single joint submission of master dossiers for all medicinal products concerned.

There is an extensive positive list for starting materials and active substances (*Liste homöopathischer und anthroposophischer Stoffe* (list HAS)) that defines which of the procedures is applicable to the particular medicinal product without indication. The list contains those substances for which the Agency has proof that their use can be seen as traditional within homeopathy (or anthroposophic medicine). It also contains those potencies for the substances for which safety has been proven to the extent that all or at least certain items of documentation on quality and security do not need to be submitted. The list is regularly revised and can be expanded.

The basis for the quality is the guidelines on good manufacturing practice (Directive 2003/94/EC *(18)*), inspection and supervision. Accepted standards are the *European Pharmacopoeia* (Ph Eur) *(9)*, the *Swiss Pharmacopoeia (19)*, the *German Homeopathic Pharmacopoeia* (GHP) *(7)*, the homeopathic chapter of the *French Pharmacopoeia* (Phf) *(8)*, some specific manufacturing methods of the *British Homeopathic Pharmacopoeia* (BHP) *(20)* and, in some cases, substance monographs of the *Homoeopathic Pharmacopoeia of the United States* (HPUS) *(6)*.

United States of America *(21, 22)*.

Official homeopathic products are classified as drugs and must have a monograph in the *Homoeopathic Pharmacopoeia of the United States* (HPUS) *(6)* as opposed to non-official homeopathic drugs, which may be marketed if ingredients are generally recognized as homeopathic. The FDA distinguishes between official (HPUS-listed ingredients) and non-official homeopathic drugs both of which are legal. Eligibility for inclusion in the HPUS requires that the homeopathic product is proven to be safe, effective and prepared according to HPUS provisions.

Homeopathic products must meet the standards for quality and purity set out in the HPUS. The presence of the initials HPUS on the label of a product assures that legal standards of strength, quality, purity and packing are respected.

Homeopathic products intended solely for self-limiting disease conditions amenable to self-diagnosis and treatment may be marketed as over-the-counter (OTC) drugs. Homeopathic products for conditions not amenable to OTC use must be marketed as prescription products.

Homeopathic products must be manufactured in conformity with GMP, but are exempt from provisions for expiration dating, tablet imprinting, and laboratory determination of identity and strength. Requirements for stability must be met by

a written assessment on compatibility of ingredients and excipients and on possible disintegration during expected period of use.

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