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Current concepts on integrative safety assessment of active substances of botanical, mineral or chemical origin in homeopathic medicinal products within the European regulatory framework

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ABSTRACT

For active substances of botanical, mineral or chemical origin processed in homeopathic medicinal products for human use, the adequate safety principles as with other human medicinal products are applied in line with the European regulatory framework. In homeopathy, nonclinical safety assessment is facing a particular challenge because of a multitude and diversity of source materials used and due to rarely available toxicological data. Thus, current concepts applied by the national regulatory authority in Germany (BfArM) on integrative safety assessment of raw materials used in homeopathic medicinal products involve several evaluation approaches like the use of the Lowest Human Recommended Dose (LHRD), toxicological limit values, Threshold of Toxicological Concern (TTC), data from food regulation or the consideration of unavoidable environmental or dietary background exposure. This publication is intended to further develop and clarify the practical use of these assessment routes by exemplary application on selected homeopathic preparations. In conclusion, the different approaches are considered a very useful scientific and simultaneously pragmatic procedure in differentiated risk assessment of homeopathic medicinal products. Overall, this paper aims to increase the visibility of the safety issues in homeopathy and to stimulate scientific discussion of worldwide existing regulatory concepts on homeopathic medicinal products.

1. Introduction

According to Article 1 of the Directive of the European Parliament and of the Council (Directive 2001/83/EC, 2001), homeopathic medicinal products represent "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 my contain a number of principles". As a form of complementary and alternative medicines, homeopathic remedies have a centuries-long tradition and their availability and application is nowadays widespread world-wide. According to homeopathy's central principle "like cures like", in Latin *similia similibus curentur*, a substance in small or even minuscule amounts is thought to alleviate those symptoms in the patient that are caused by its large doses in the healthy individual (Briggs, 2012; World Health Organization, 2009). Homeopathic remedies are subject to regulatory control in several regions, e.g. in the European Community (Directive 2001/83/EC, 2001), in the US (http://www.hpus.com/regulations.php, http://nccam.nih.gov/health/homeopathy), in Canada (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/ehmg-nprh-eng.php), or in Australia (http://www.tga.gov.au/industry/cm-basics-regulation-overview.html). In the U.S., homeopathic medicines are regulated by the U.S. FDA (Food and Drug Administration). They are classified as drugs under the terms of the enabling legislation FDCA (Federal Food, Drug and Cosmetic Act). "*Conditions Under Which*

Abbreviations: ADI, Acceptable Daily Intake; D, Decimal (1/10) homeopathic potency, Decimal Hahnemannian dilution; FSD, First Safe Dilution; GHP, German Homeopathic Pharmacopoeia; HMA, Heads of Medicines Agencies; HMPWG, Homeopathic Medicinal Products Working Group of HMA; LHRD, Lowest Human Recommended Dose; NOAEL, LOAEL, no (lowest) observed adverse effect level; NQ, Naphthoquinones; PDE, Permitted Daily Exposure; Ph. Eur., European Pharmacopoeia; PtC, Points to Consider; RfD, Reference Dose; TDI, Tolerable Daily Intake; TTC, Threshold of Toxicological Concern.

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Homeopathic Drugs May be Marketed" are described in the FDA's Compliance Policy Guide (CPG 7132.15). Homeopathic remedies may be marketed using the option to refer to standards and monographs defined by HPCUS (Homeopathic Pharmacopoeia Convention of the United States). These remedies require to meet defined criteria, as stated in the Homeopathic Pharmacopeia of the United States (HPUS; i.e. listed active ingredients, legal standards e.g. for strength, quality, purity, packaging or label requirements; http://nccam.nih.gov/health/homeopathy). Their safety and efficacy is not assessed by the FDA but is determined by the HPCUS and required for HPUS inclusion (Borneman and Field, 2006). In Canada, the legal requirements in this context include a Product Licence Application, assessed for safety, efficacy and quality by the Natural Health Products Directorate (NHPD).

Here we focus on the European regulatory framework and assessment practice applied by the national regulatory authority in Germany (BfArM). Homeopathic preparations are precisely defined by the manufacturing process according to the provisions of official pharmacopoeias, in Europe the European Pharmacopoeia, Ph. Eur., as well as several national pharmacopoeias, e.g. the German Homeopathic Pharmacopoeia, GHP, and the French Homeopathic Pharmacopoeia). More than a decade ago, the Council of the European Communities by Directive 92/73/EEC (1992) (replaced by Directive 2001/83/EC, 2001) made provisions for and later established a special simplified registration procedure for homeopathic medicines that comply with certain criteria (Article 14 of Directive 2001/83/EC, 2001). Of particular importance is that raw materials of botanical, mineral or chemical origin (Ph. Eur., Monograph 1038, 1995) conventionally used in homeopathic remedies are basically regulated according to the same non-clinical safety principles as applied to other human medicinal products (Directive 2001/83/EC, 2001). In 2007, a European guidance document on safety has been adopted by the EU Heads of Medicines Agency (HMA), outlining the general framework and practical approach of safety assessment regarding homeopathic medicinal products (Points to Consider, PtC, on Non-Clinical Safety, 2007). Within the context of European harmonisation the recently introduced concept of the so-called First Safe Dilutions (FSD) is considered a general approach in safety assessment of homeopathic medicinal products providing distinctly conservative overall FSD potencies related to 10 g or 10 ml of homeopathic medicinal products, as described in the "*Introduction to the List of First Safe Dilutions*", adopted by Heads of Medicines Agencies (HMA) in (2010), and in the PtC on Non-Clinical Safety (2007).

In contrast to centuries-long experience and publićs perception of safe use, relevant comprehensive toxicological data for the vast majority of homeopathic remedies are usually scarce if not even lacking. Homeopathic medicines can be derived from almost any starting substance, thus an appropriate safety evaluation for a multitude and diversity of homeopathic ingredients represents a specific challenge. These raw materials may be of botanical origin, either individual substances or multicomponent mixtures, chemically defined substances (of organic or inorganic origin), environmental materials (contaminants, residues, biocides), food additives, metals, metalloids, starting materials of biological origin e.g. micro-organisms preparations (fungi, bacteria etc.).

In the present publication, the current regulatory perspectives on integrative safety assessment of raw materials of botanical, mineral or chemical origin processed in homeopathic medicinal products including evaluation approaches are elaborated, like application of the Lowest Human Recommended Dose (LHRD), of toxicological limit values (e.g. Acceptable Daily Intake, ADI; Tolerable Daily Intake, TDI; Reference Dose, RfD; Permitted Daily Exposure, PDE), of the Threshold of Toxicological Concern (TTC), of data from food regulation, and furthermore the consideration of unavoidable environmental/dietary background exposition. This publication aims to further develop and clarify the criteria, principles and recommendations for the safety evaluation of raw materials processed in homeopathic medicinal products by exemplary application of the different assessment routes on selected homeopathic preparations. Considering the world-wide and long-standing tradition of complementary therapy, the limited safety information in view of the current regulatory requirements, and because the assessment routes elucidated here are based on general toxicological principles and regulatory concepts, this publication may be of interest not only for a European but for a broader audience.

2. Principles and practice

2.1. Principles of evaluation approaches for safety assessment

Homeopathic medicinal products comprising substances of botanical, mineral or chemical origin of high diversity can be evaluated by allocation to selected, different approaches: LHRD, toxicological limit values, TTC, food regulation data or consideration of unavoidable background exposure. Principles and practices of safety evaluation in this context are summarized in Table 1. If two or more different assessment routes are applicable, each approach should be taken into consideration and the respective outcomes should be compared, discussed and evaluated.

2.1.1. Assessment via LHRD

Referring to the Directive 2001/83/EC (2001) on the community code relating to medicinal products for human use (Article 14), the LHRD/100 in mg/day as 1/100th of the smallest dose used in allopathy (with regard to active substances present in an allopathic medicinal product under prescription) is considered to be harmless in homeopathy.

As in the mentioned PtC, merely the brief term "LHRD/100 mg/day" is used, the following more specific considerations emerging from the evaluation practice are particularly worth mentioning:

(a) For LHRD/100 calculation the relevant LHRD value is the lowest adult daily dose. Questions of maintenance versus loading doses, of single doses, of therapeutic versus prophylactic doses, require expert judgement and hence are a matter of case-by-case decisions.
(b) Usually, contraindications of the allopathic medicines are considered covered by the safety margin of 100 as per Directive 2001/83/EC, Art. 14. Using expert judgement and on an exceptional case-by-case basis, specific toxicological concerns, allergy notes, coverage of sensitive subgroups, long-term, short-term use should be discussed with regard to the question if allopathic medicinal product contraindications may be transferred.
(c) Regarding the use in pediatric patients the lowest existing LHRD for the relevant age group is recommended. If pediatric posologies are lacking, assessment might be based on considerations such as: (1) the lowest adult daily dose may be adapted to the average body weight (bw) of the neonate age group (adult LHRD in terms of mg/kg/d, divided by 100, multiplied with 3 kg for neonates bw, unless there is special concern, particular severity or justified exclusion, or (2) assessment considering TTC principles i.e. threshold of 0.15 μg/person per day (related to 60 kg bw; according to Kroes et al., 2004; European Food Safety Authority, EFSA, 2012; see Section 2.1.3 in this publication).
(d) According to the PtC on Non-Clinical Safety, 2007, the LHRD is considered applicable also for herbal medicinal products, although the majority are non-prescription medicines. In