HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP

(HMPWG)

QUESTIONS AND ANSWERS DOCUMENT ON REGULATORY AND LEGAL ISSUES CONCERNING HOMEOPATHIC MEDICINAL PRODUCTS IN THE EUROPEAN FRAMEWORK

Discussion at HMPWG	Completed: 21 November 2019
Consultation with EC	Comments received: 10 May 2020
Response from HMPWG to EC	29 June 2020
Final confirmation from EC	29 July 2020

QUESTIONS AND ANSWERS DOCUMENT ON REGULATORY AND LEGAL ISSUES CONCERNING HOMEOPATHIC MEDICINAL PRODUCTS IN THE EUROPEAN FRAMEWORK

Introduction

This guidance document addresses a number of legal and regulatory questions in relation to the regulation of homeopathic medicinal products (HMPs) for human and veterinary use by European Union legislation. It provides an overview of the Homeopathic Medicinal Products Working Group's ("HMPWG") position on issues which typically arise in connection with the implementation of the applicable EU rules governing HMPs for human and veterinary use. However, the interpretation provided by this document is without prejudice to:

- the binding nature of the relevant legislation; or
- any legal interpretation given by the Court of Justice of the European Union.

In accordance with the above, this document has been produced for guidance only. It is neither intended to lay down rules in itself nor is it intended to override the relevant provisions in force. It should be read in conjunction with all applicable legislation and "*The Rules governing Medicinal Products in the European Union, Volume 2, Notice to Applicants*".[1] In case of discrepancies between the text and any provisions of applicable legislation, the latter shall prevail.

References throughout this document to legislative provisions must be read as references to the legislative acts containing such provisions as last amended, unless it is otherwise expressly stated. It is important to note as regards veterinary medicinal products that Regulation (EU) 2019/6[2] has entered into force on 28 January 2019; however, its provisions will only be applicable after a transitional period of 3 years, as of 28 January 2022. Accordingly, this document does not yet include specific references to the provisions of Regulation (EU) 2019/6 as it refers to the currently applicable rules.

References of this document extend to Iceland, Liechtenstein and Norway by virtue of the EEA agreement in accordance with the explanations of Section 2 of Chapter 1 (Marketing Authorisation), Volume 2A of the European Commission's Notice to Applicants on "The rules governing medicinal products in the European Union" (hereinafter: "Notice to Applicants").[3]

This guidance is not applicable to centralised marketing authorisation procedures governed by Regulation (EC) No 726/2004.

[1] The Rules governing Medicinal Products in the European Union, Volume 2, Notice to Applicants (available here)
[2] Regulation (EU) 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC (available here)
[3] Chapter 1, Volume 2A of Notice to Applicants is available here

Table of Contents

1. What is the definition of Homeopathic Medicinal Products ("HMPs") and Homeopathic Veterinary Medicinal Products ("HVMPs)"?

Human

According to Article 1(5) of *Directive 2001/83/EC on the Community code relating to medicinal products for human use* homeopathic medicinal product ("**HMP**") is 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.

Veterinary

As regards veterinary medicinal products, *Article 1(8) of Directive 2001/82/EC on the Community code relating to veterinary medicinal products* provides an almost identical definition. Accordingly, a homeopathic veterinary medicinal product ("**HVMP**") is any veterinary 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 Member States. A homeopathic veterinary medicinal product may contain a number of principles.

2. Marketing authorisation/registration of HMP/HVMPs

2.1. What are the different routes of authorisation/registration applicable to HMP/HVMPs?

In accordance with Article 13(1) of Directive 2001/83/EC and Article 16(1) of Directive 2001/82/EC HMP/HVMPs manufactured and placed on the market within the European Union shall be registered or authorised in accordance with the rules of these Directives, except where such medicinal products are covered by a registration or authorisation granted in accordance with national legislation *on or before* 31 December 1993.

Directive 2001/83/EC and Directive 2001/82/EC provide a **special, simplified registration procedure** for those HMPs and HVMPs which satisfy all conditions set forth in Article 14(1) of Directive 2001/83/EC or Article 17(1) of Directive 2001/82/EC, respectively. As regards the scope of products eligible for simplified registration and the requirements of this registration procedure, please see Questions 2.2 and 2.3.

If a HMP or HVMP does not satisfy all conditions set forth in the above referenced provisions, and therefore it is not eligible for simplified registration procedure, it shall be authorised through a **marketing authorisation procedure** in accordance with Articles 8, 10, 10a, 10b, 10c and 11 of Directive 2001/83/EC or Articles 12, 13a, 13b, 13c and 14 of Directive 2001/82/EC, as appropriate.[4] For further details on the rules of marketing authorisation procedure in the context of HMP/HVMPs, please see Question 2.6.

[4] As this is explicitly provided in Article 16(1) of Directive 2001/83/EC and Article 19(1) of Directive 2001/82/EC.

For a Homeopathic Application Form applicable to applications for marketing authorisation/registration of a HMP for human use submitted under either a centralised, national, mutual recognition procedure (MRP) or decentralised procedure (DCP) please see *Volume 2B of the European Commission's Notice to Applicants on the 'Presentation and content of the dossier',* Homeopathic Application Form.[5]

2.2. Which HMP/HVMPs may be subject to special, simplified registration procedure? [6]

Human

In the case of human medicines, Article 14(1) of Directive 2001/83/EC states that only those HMPs which satisfy all of the following conditions may be subject to special, simplified registration:

- they are administered orally or externally,
- no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto,
- there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

Veterinary

As regards veterinary medicines, Article 17(1) of Directive 2001/82/EC establishes similar criteria for HVMPs to be eligible for simplified registration procedure. Accordingly, only those HVMPs may be subject to simplified registration, which satisfy all of the following condition:

- they are administered by a route described in the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in Member States,
- no specific therapeutic indication appears on the labelling of the veterinary medicinal product or in any information relating thereto,
- there is a sufficient degree of dilution to guarantee the safety of the medicinal product (in particular, the medicinal product shall not contain more than one part per 10 000 of the mother tincture).

2.3. What are the requirements of a special, simplified registration of HMP/HVMPs?

Human

In the case of HMPs eligible for simplified registration, Article 15 of Directive 2001/83/EC requires that in the application for simplified registration the pharmaceutical quality and the batch-to-batch homogeneity of the products concerned shall be demonstrated. The documents to be provided by the applicant are conclusively listed in Article 15 of Directive 2001/83/EC. Accordingly, the following documents shall be included in the application for simplified registration of an HMP:

[5] Available at https://ec.europa.eu/health/documents/eudralex/vol-2_en

[6] In relation to this question see also Section 3.3 of Chapter 1 (Marketing Authorisation), Volume 2A of the Notice to Applicants; and as regards HVMPs Section 3.3 of Chapter 1 (Marketing Authorisation), Volume 6A of the Notice to Applicants.

- scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered,
- dossier describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic use, on the basis of an adequate bibliography,
- manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentization,
- manufacturing authorization for the medicinal product concerned,
- copies of any registrations or authorizations obtained for the same medicinal product in other Member States,
- one or more mock-ups of the outer packaging and the immediate packaging of the medicinal products to be registered,
- data concerning the stability of the medicinal product.

An application for simplified registration of HMPs may cover a series of medicinal products derived from the same homeopathic stock or stocks.[7]

As regards combination products it is clear from the above list of Article 15 of Directive 2001/83/EC that only the homeopathic stock or stocks from which the combination is derived must be well-known and not additionally the combination itself. Accordingly, additional data in order to justify the homeopathic use of the combination is not necessary to be provided. The second indent of the list requires a dossier to be lodged describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic use, on the basis of an adequate bibliography. However, a bibliography showing that the effects of the homeopathic medicinal product itself have been identified is not required.[8]

Article 14(1) of Directive 2001/83/EC provides that the classification for the dispensing of the HMP shall be determined by the concerned Member State at the time of the registration. In addition, the Directive requires that the criteria and rules of procedure provided for in Article 4(4), Article 17(1), and Articles 22 to 26, 112, 116 and 125 shall apply by analogy to the special, simplified registration procedure for HMPs, with the exception of the proof of therapeutic efficacy.[9]

For a Homeopathic Application Form applicable to applications for marketing authorisation/registration of a HMP for human use submitted under either a centralised, national, mutual recognition procedure or decentralised procedure please see *Volume 2B of the European Commission's Notice to Applicants on the 'Presentation and content of the dossier', Homeopathic Application Form.*[10]

Veterinary

In the case of HVMPs eligible for simplified registration, Article 18 of Directive 2001/82/EC establishes similar requirements and this article provides a conclusive list of the documents to be provided by the applicant. Accordingly, in the application for simplified registration the pharmaceutical quality and the

[7] Article 15 of Directive 2001/83/EC

[8] See: Judgement of the Court of Justice in *Meta Fackler KG v Bundesrepublik Deutschland*, C-444/03, EU:C:2005:288, paragraph 20, available at: http://curia.europa.eu/juris/liste.jsf?language=en&num=C-444/03.

[9] Article 14(2) of Directive 2001/83/EC

[10] Available at https://ec.europa.eu/health/documents/eudralex/vol-2_en

batch-to-batch homogeneity of the products concerned shall be demonstrated, and the following documents shall be included:

- scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered,
- dossier describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic nature, on the basis of an adequate bibliography (in the case of HVMPs containing biological substances, a description of the measures taken to ensure the absence of pathogens),
- manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentisation,
- manufacturing authorization for the medicinal products concerned,
- copies of any registrations or authorizations obtained for the same medicinal products in other Member States,
- one or more mock-ups of the outer packaging and immediate packaging of the medicinal products to be registered,
- data concerning the stability of the medicinal product,
- proposed withdrawal period together with all requisite justification.

An application for simplified registration of HVMPs may cover a series of medicinal products derived from the same homeopathic stock or stocks.[11]

As regards combination products it is clear from the list of Article 18 of Directive 2001/82/EC that only the homeopathic stock or stocks from which the combination is derived must be well-known and not additionally the combination itself. Accordingly, additional data in order to justify the homeopathic nature of the combination is not necessary to be provided. The first sentence of the second indent of the list requires a dossier to be lodged describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic use, on the basis of an adequate bibliography. However, a bibliography showing that the effects of the homeopathic medicinal product itself have been identified is not required.

According to Article 17(1) of Directive 2001/82/EC the classification for the dispensing of the HVMP shall be determined by the concerned Member State at the time of the registration. In addition, the Directive requires that the criteria and rules of procedure provided for in Chapter 3 (with the exception of Article 25[12]), shall apply by analogy to the special, simplified registration procedure of HVMPs, with the exception of the proof of therapeutic effect. [13]

It is important to highlight that the provisions of *Regulation (EC) No 470/2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin* and *Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically*

[11] Article 18 of Directive 2001/82/EC

[12] Article 25 of Directive 2001/82/EC contains rules on the summary of product characteristics. In this regard, please see Question 4.1.

[13] Article 17(2) of Directive 2001/82/EC

active substances and their classification regarding maximum residue limits in foodstuffs of animal origin shall be respected in the case of HVMPs subject to simplified registration procedure as well.

2.4. How is the mutual recognition or decentralised procedure applicable to HMP/HVMPs subject to special, simplified registration procedure?

In relation to the simplified registration of HMP/HVMPs, Article 13(1) of Directive 2001/83/EC and Article 16(1) of Directive 2001/82/EC require that the provisions on mutual recognition and decentralised procedure (MRP/DCP) shall apply. (In particular, Article 28 and Article 29(1) to (3) of Directive 2001/83/EC, and Article 32 and Article 33(1) to (3) of Directive 2001/82/EC). It follows that if an HMP/HVMP is intended to be registered through the simplified procedure in more than one Member States, the use of mutual recognition or decentralised procedure, as appropriate, is mandatory.

In this regard, it should be mentioned that it will only be the principles of the procedure which will apply by analogy. The application should be assessed by one of the Member States, and the other Member States which are included in the procedure should recognise the assessment done by the Reference Member State ("RMS"). On the other hand, the requirements on the particulars and documents which must accompany an application for a marketing authorisation will not apply. Instead, the requirements provided under the simplified registration procedure will define the particulars and documents to be provided by the applicant.

The objective of MRP/DCPs is to facilitate free circulation of medicinal products by ensuring that Member States do not duplicate assessment of applications already conducted by the RMS, and at the same time safeguard public health. In order to maintain these objectives also after a simplified registration is granted to an HMP/HVMP, the above-mentioned procedural principles of MRP/DCPs must apply by analogy also to variations to HMP/HVMPs registered through the MRP/DCP. Consequently, the request for a variation should be assessed by the RMS and recognised by the Concerned Member States in accordance with the requirements following from the simplified registration procedure for HMP/HVMPs.

It is important to clarify that pursuant to Article 39 of Directive 2001/83/EC and Article 43 of Directive 2001/82/EC, the rules of referral procedures do not apply to HMP/HVMPs subject to simplified registration procedure. Consequently, if a Member State cannot approve the assessment under the simplified registration procedure conducted by RMS, on the grounds of potential serious risk to public health, and the Member States fail to reach an agreement in the coordination group, the case will not be submitted to EMA for arbitration. Each Member State will therefore take its own decision.[14] The detailed steps of the procedures in such situation are the following.

In case a Member State cannot approve, within the timeframe given in the legislation[15], the assessment report and the product information on the grounds of potential serious risk to public health, the RMS will refer the points of disagreement to the coordination group (CMDh or CMDv, respectively). If no agreement could be reached at the end of such 'coordination group-referral' between the Member States concerned by the procedure, the issue will not be forwarded to EMA for arbitration. As no further information is given in the legislation how to conclude the national phase of the registration, the Member States and the European Commission have agreed in the spirit of the legislation on the following interpretation: It is a national decision - taking into account the assessment report of the RMS and the

[14] See also Section 3.3 of Chapter 1 (Marketing Authorisation), Volume 2A of the Notice to Applicants, as well as Section 3.3 of Chapter 1 (Marketing Authorisation), Volume 6A of the Notice to Applicants as regards HVMPs.
[15] Article 28 (4) of Directive 2001/83/EC and Article 32(4) of Directive 2001/82/EC

discussion at the coordination group - of each Member State concerned by the procedure to issue a registration for this homeopathic medicinal product or not.

2.5. How many application forms are necessary to submit in case of an application in MRP/DCP involving several potencies (dilutions and/or triturations) of a homeopathic stock?

In the case of several dilutions of a homeopathic stock a separate application form per each pharmaceutical form of medicinal products derived from this homeopathic stock is needed.

The individual potencies (dilutions and/or triturations) have to be listed in the application form. The application for a registered homeopathic medicinal product in MRP/DCP is characterised by the normal MRP/DCP-numbering system (CC/D/nnnn/sss/X/vvv[16]) in which 'n' is the specific number (4 digits) for the actual medicinal product which equals to the homeopathic stock and is further characterised by 's' (sequential speciality number) for the individual potencies (dilutions and/or triturations). No sub-numbering system is in place if the same final dilution is the result of a series of potencies (dilutions and/or triturations): C' or 'CH' (centesimal), D', 'DH' or 'X' (decimal), 'LM'.

Further characterisation of the potencies (dilutions and/or triturations) of a homeopathic stock by a different numbering system may exist in Member States.

2.6. How can HMP/HVMPs other than those subject to simplified registration obtain a marketing authorisation?

Human

As regards human medicines, Article 16 of Directive 2001/83/EC provides that HMPs which are not eligible for simplified registration shall be authorised (and labelled) in accordance with Articles 8, 10, 10a, 10b, 10c and 11 of that Directive. Nevertheless, in accordance with Article 16(2), a Member State may introduce or retain in its territory specific rules for the pre-clinical tests and clinical trials of such HMPs subject to marketing authorisation in accordance with the principles and characteristics of homeopathy as practised in that Member State.[17] In the case of products concerned by such specific rules, the mutual recognition or decentralised procedure, as well as referral procedures (as provided in Articles 28 to 34 of Directive 2001/83/EC) shall not apply.[18] This means that if a Member State introduced or retained specific rules for the pre-clinical tests and clinical trials of HMPs (as permitted by Article 16(2) of Directive 2001/83/EC), the products subject to the national marketing authorisation of this Member State under such specific rules cannot be involved in mutual recognition or decentralised procedures, even if their marketing authorisation is applied for or already granted in another Member State.

For a Homeopathic Application Form applicable to applications for marketing authorisation/registration of a HMP for human use submitted under either a centralised, national, mutual recognition procedure or decentralised procedure please see *Volume 2B of the European Commission's Notice to Applicants on the 'Presentation and content of the dossier', Homeopathic Application Form.*[19]

Veterinary

[16] See Section 7 of Chapter 2 (Mutual Recognition), Volume 2A of the Notice to Applicants on the numbering system for the procedures for mutual recognition and decentralised procedure

[17] See also Section 3.3 of Chapter 1 (Marketing Authorisation), Volume 2A of the Notice to Applicants

[18] Article 39 of Directive 2001/83/EC

[19] Available at https://ec.europa.eu/health/documents/eudralex/vol-2_en

In the case of veterinary medicines, Directive 2001/82/EC provides comparable rules for HVMPs. According to Article 19, HVMPs other than those subject to simplified registration shall be authorised in accordance with Articles 12, 13a, 13b, 13c and 14 of Directive 2001/82/EC. Article 19(2) further states that a Member State may introduce or retain in its territory specific rules for the safety tests and pre-clinical and clinical trials of HVMPs intended for pet species and non-food producing exotic species (and not subject to simplified registration), in accordance with the principles and characteristics of homeopathy as practised in that Member State. [20] In the case of products concerned by such specific rules the mutual recognition or decentralised procedure, as well as referral procedures (as provided in Articles 32 to 38 of Directive 2001/82/EC) shall not apply.[21] Accordingly, similarly as in the case of human medicines, if a Member State introduced or retained specific rules for the safety tests and pre-clinical and clinical trials of HVMPs (as provided by Article 19(2) of Directive 2001/82/EC), the products subject to the national marketing authorisation of this Member State under such specific rules cannot be involved in mutual recognition or decentralised procedures, even if their marketing authorisation is applied for or already granted in another Member State.

2.7. Are the requirements of the European Medicines Regulatory Network (HMA) eSubmission Roadmap applicable to HMP/HVMPs?

General information on the HMA eSubmission Roadmap and the eSubmission Expert Group documentation may be found in the following website:
http://esubmission.ema.europa.eu/tiges/cmbdocumentation.html

Further documentation developed, approved or maintained by the eSubmission Expert Group and its key user groups may be found on dedicated sites, for example related to 'Veterinary eSubmission'[22] or 'Human eSubmission'[23] and further websites linked from these sites.

Human

In relation to the implementation of mandatory use of eCTD format for Human regulatory submission, Annex 2[24] of the HMA eSubmission Roadmap states that for registrations according to Articles 14 or 16a of Directive 2001/83/EC (i.e. simplified registration procedure either for HMPs or traditional herbal medicinal products), the timelines of the eSubmission Roadmap are considered optional. This interpretation is reiterated in the 'Q&A on how to handle ongoing procedures in relation to mandatory eCTD format'.[25] Accordingly, regarding the applicability of the HMA eSubmission Roadmap requirements and timelines to HMPs subject to simplified registration it is recommended to refer to guidance of the Member States.

On the other hand, this clarification of Annex 2 of the HMA eSubmission Roadmap and the above referenced Q&A only address simplified registration. As regards HMPs other than those subject to simplified registration the general requirements and timelines of the HMA eSubmission Roadmap apply depending on the particular authorisation procedure followed (e.g. in case of national authorisation procedures the respective provisions apply).

[20] See also Section 3.3 of Chapter 1 (Marketing Authorisation), Volume 6A of the Notice to Applicants.
[21] Article 43 of Directive 2001/82/EC
[22] http://esubmission.ema.europa.eu/tiges/vetesub.htm
[23] http://esubmission.ema.europa.eu/whatisesubmission.htm
[24] http://esubmission.ema.europa.eu/tiges/docs/Annex 2 on eCTD v3.2.2_update nov 2018_adopted.docx
[25] http://esubmission.ema.europa.eu/tiges/docs/QA on how to handle ongoing procedures in relation to mandatory eCTD format update Jan 2019.pdf

Veterinary

As regards the applicability of HMA eSubmission Roadmap to HVMPs no harmonised approach is currently available. Accordingly, with regard to eSubmission of HVMPs both subject to simplified registration or authorisation, it is recommended to refer to regional guidance of the Member States.

3. Legal and regulatory matters concerning all type of HMP/HVMPs

3.1. What are the requirements applicable to the labelling and package leaflet of HMP/HVMPs?

According to Article 68 of Directive 2001/83/EC and Article 64(1) of Directive 2001/82/EC, HMPs and HVMPs must be labelled in accordance with the applicable provisions of the directives on '*Labelling and Package Leaflet/Package Insert*', i.e. Title V of Directive 2001/83/EC and Title V of Directive 2001/82/EC.[26] In addition, they shall be identified by a reference on their labels, in clear and legible form, to their homeopathic nature. As regards HVMPs the legislation explicitly requires the use of the words "*homeopathic medicinal products for veterinary use*". In relation to HMPs other than those subject to the simplified registration procedure, Article 16 of Directive 2001/83/EC further clarifies that they shall be labelled in accordance with Articles 8, 10, 10a, 10b, 10c and 11 of that Directive.

In the case of HMP/HVMPs subject to simplified registration procedure, Article 69 of Directive 2001/83/EC and Article 64(2) of Directive 2001/82/EC establish special requirements in addition to the general principles and rules applicable to them under Title V of Directive 2001/83/EC and Title V of Directive 2001/82/EC.

Human

For HMPs which are subject to the simplified registration procedure, in addition to the clear mention of the words "*homeopathic medicinal product*", the labelling and (where appropriate) the package insert shall bear no other information than those mentioned in Article 69(1) of Directive 2001/83/EC. Furthermore, Article 69(2) allows Member States to adopt additional requirements regarding the use of certain types of labelling in order to show the price of the medicinal product and the conditions for refunds by social security bodies.

As regards excipients to be listed on the labelling of HMPs, Volume 2C of the Notice to Applicants on the "*Guidelines on excipients in the labelling and package leaflet of medicinal products for human use*"[27] provides detailed explanation about the applicable rules. Regarding HMPs subject to simplified registration procedure, the Guidelines state that even though they are not specifically addressed in the document, information in its Annex may be used if they are relevant for such simplified procedures.

Veterinary

In the case of HVMPs subject to simplified registration procedure, the scope of information exclusively permitted for use is stated by Article 64(2) of Directive 2001/82/EC and the words "*homeopathic veterinary medicinal product without approved therapeutic indications"* shall be included in the labels of these products. For additional information on packaging requirements concerning HVMPs in different

[26] See also Section 3.3 of Chapter 1 (Marketing Authorisation), Volume 2A of the Notice to Applicants, as well as Section 3.3 of Chapter 1 (Marketing Authorisation), Volume 6A as regards HVMPs.

[27] Available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/guidelines_excipients_march2018_en.pdf

Member States please see Volume 6C of the Notice to Applicants on the *Guideline on the packaging information of veterinary medicinal products authorised by the Community*[28].

3.2. What are the pharmacovigilance requirements applicable to HMP/HVMPs?

Human

With regard to human medicines, Article 16(3) of Directive 2001/83/EC states that the pharmacovigilance requirements of the Directive, i.e. Title IX on Pharmacovigilance shall apply to HMPs, with the exceptions of those subject to the special, simplified registration procedure (i.e. those referred to in Article 14(1) of Directive 2001/83/EC).[29]

Therefore, marketing authorisation holders of HMPs shall comply with the general pharmacovigilance requirements applicable to human medicinal products. In contrast to this, holders of simplified registrations of HMPs are not subject to reporting obligations for suspected adverse reactions, and they are not required to submit Periodic Safety Update Reports ("PSURs"), unless one of the cases provided for in Article 107b(3)(a) or (b) of Directive 2001/83/EC is applicable, i.e. such requirement is laid down as a condition in the marketing authorisation or requested by a competent authority. It must be also noted that national competent authorities may impose additional conditions for HMPs subject to simplified registration procedure pursuant to Articles 22, 22a and 107b(3) of Directive 2001/83/EC. In addition, pursuant to Article 23(4) of Directive 2001/83/EC, the national competent authority may at any time ask the marketing authorisation (registration) holder to forward data demonstrating that the risk-benefit balance remains favourable.

Registration holders of HMPs should use alternative mechanisms such as signal management and emerging safety issues channels to communicate relevant new safety information to regulatory authorities (see GVP Module VI[30] and Module IX[31]). In addition, the product information of such products should be kept up to date by the registration holder by submitting the appropriate variations taking account of the latest scientific knowledge or conclusions of assessments and recommendations made public by means of the websites of the European Medicine Agency and national competent authorities.[32]

In the case of HMPs subject to simplified registration procedure, there is no need for the medicines data submission using the electronic format referred to as Article 57 format or extended EudraVigilance Product Report Message (XEVPRM) format under Article 57 of regulation (EC) No 726/2004. However, registration holders of these HMPs can submit such data on a voluntary basis as the system allows for this. In accordance with Article 1(2) of *Regulation (EU) No 658/2014 on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use* HMPs registered in accordance with Article 14 of Directive 2001/83/EC shall be excluded from

[28] Available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-6/c/vol6c_packaging-guideline_bluebox2008_en.pdf

[29] See also *Traditional herbal medicinal products and simplified registrations for homeopathic medicinal products: pharmacovigilance requirements and EudraVigilance access,* available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/03/WC500222351.pdf

[30] *Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2)* available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232767.pdf

[31] *Guideline on good pharmacovigilance practices (GVP): Module IX – Signal management (Rev. 1)* available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/10/WC500236408.pdf

[32] See previous footnote.

the scope of the Regulation. Therefore, no fees will be charged for submission of data in the Article 57 database concerning HMPs registered through the simplified procedure.

Veterinary

In the case of veterinary medicines, Directive 2001/82/EC does not establish distinct pharmacovigilance requirements applicable to HVMPs with marketing authorisation and those subject to simplified registration procedure. On the contrary, Article 20 of Directive 2001/82/EC generally states that the provisions of Title VII (i.e. the pharmacovigilance requirements of the Directive) shall apply to HVMPs.

3.3. Is Regulation (EC) No 1901/2006 on medicinal products for paediatric use applicable to HMPs for human use?

With regard to its scope on certain types of products, *Regulation (EC) No 1901/2006 on medicinal products for paediatric use* ("Paediatric Regulation"), Article 9 of the Regulation explicitly states that *"Articles 7 and 8 shall not apply to products authorised under Articles 10, 10a,* ***13 to 16*** *or 16a to 16i of Directive 2001/83/EC."* (Emphasis added.) It follows that a paediatric investigation plan (or a deferral or a waiver) is not required in the case of HMPs with marketing authorisation or HMPs subject to simplified registration procedure.

On the other hand, HMPS are not excluded from the scope of Articles 45 and 46 of the Paediatric Regulation requiring that paediatric studies and other studies involving the use of a medicinal product in paediatric population shall be submitted to competent authorities. The purpose of Articles 45 and 46 of the Paediatric Regulation is to improve the information available on the use of medicinal products in the paediatric populations. Companies holding such data should submit them to be assessed by the competent authorities so that information could be included in the products information, if appropriate. Therefore, given the wording of the provisions, marketing authorisation holders for HMPs should submit studies according to Article 45 and 46 of the Paediatric Regulation.

3.4. Is Regulation (EC) No 1234/2008 ("Variations Regulation") applicable to HMP/HVMPs?

According to Recital (2) of *Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products* ("Variations Regulation"), for reasons of proportionality, homeopathic and traditional herbal medicinal products which have not been granted a marketing authorisation but are subject to a simplified registration procedure should remain excluded from the scope of the Regulation. Furthermore, according to Article 1(1) the Variations Regulation *"lays down provisions concerning the examination of variations to the terms of all* ***marketing authorisations*** *for medicinal products for human use and veterinary medicinal products* ***granted in accordance with*** *Regulation (EC) No 726/2004,* ***Directive 2001/83/EC, Directive 2001/82/EC****, and Council Directive 87/22/EEC".* (Emphasis added.)

It follows from the above that the Variations Regulation does not apply to HMP/HVMPs which are subject to a simplified registration procedure under Article 14(1) of Directive 2001/83/EC or 17(1) of Directive 2001/82/EC in case of HVMPs. Correspondingly, the Variations Regulation does not apply to HMP/HVMPs which are covered by a registration or authorisation granted in accordance with national legislation on or before 31 December 1993.[33] Accordingly, it will be for each Member State to adopt its own national practices with regard to variations of HMP/HVMPs in accordance with the obligations following from Article 23 of Directive 2001/83/EC and Article 27 of Directive 2001/82/EC.

[33] As provided by Article 13(1) of Directive 2001/83/EC and Article 16(1) of Directive 2001/82/EC

On the other hand, the Variations Regulation does apply to HMP/HVMPs for which a marketing authorisation was granted in accordance with the legislation quoted above.

For more information on variations to HMP/HVMPs registered through MRP/DCP please see Question 2.4 above.

3.5. Is Regulation (EU) 2017/852 on mercury ("Mercury Regulation") applicable to HMP/HVMPs or homeopathic manufacturing procedures?

Regulation (EU) 2017/852 on mercury ("Mercury Regulation") introduces - among others - certain restrictions on the trade, manufacturing and use of (new) mercury-added products and new manufacturing processes involving the use of mercury or mercury compounds. In order to understand whether the restrictions introduced by the Mercury Regulation are applicable to HMP/HVMPs or homeopathic manufacturing procedures, it should be clarified whether they fall under the definition of 'mercury-added product', 'new mercury-added products' or 'new manufacturing processes'.

According to Article 2(4) of the Mercury Regulation, **'mercury-added product'** ("MAP") means a product or product component that contains mercury or a mercury compound that was intentionally added. It follows that HMP/HVMPs with mercury or mercury compounds intentionally added, e.g. as active ingredient, intermediate solution or starting material, fall under the definition of MAPs within the meaning of the Mercury Regulation, regardless of the mercury content of the finished product.

Specific restrictions of the Mercury Regulation concern new uses of Mercury. Accordingly, the provisions concerning **'new mercury-added products'** and **'new manufacturing processes'** seek to discourage the emergence of new products or industrial processes in which the mercury or mercury compound fulfils a novel function.[34]

According to Article 8(1) of the Mercury Regulation 'new mercury-added products' are those MAPs that were not being manufactured prior to 1 January 2018. A MAP qualifies as new under this provision when the function fulfilled by mercury or mercury compounds in the product (e.g. active ingredient, intermediate solution or starting material in HMP/HVMPs) or the way mercury or mercury compounds fulfils its function in the product would be new. Hence, as long as mercury or mercury compounds would be used in HMP/HVMPs as active ingredient, starting materials or other intermediate solutions, those products will not qualify as a 'new mercury-added product' within the meaning of Article 8(1) of the Mercury Regulation. However, it is important to highlight that existing MAPs may fall under the definition of new MAPs when technical improvements or redesign affect the function of the mercury/mercury compound or the way it is used to fulfil its function in the product and this does **not** lead to less mercury being used in the product.[35]

In accordance with Article 8(7) of the Mercury Regulation, the European Commission shall make publicly available on the internet an inventory[36] ("Inventory") of

- manufacturing processes involving the use of mercury or mercury-compounds that were used prior to 1 January 2018,
- mercury-added products that were being manufactured prior to 1 January 2018, and

[34] Point 1 of the Explanatory Text of the *Inventory of existing mercury-added products and manufacturing processes involving the use of mercury or mercury compounds* ("Inventory"); available here: https://circabc.europa.eu/w/browse/b0a3ddc3-464e-4e57-9601-55a8315c529e

[35] Point 1 of the Explanatory Text of the Inventory

[36] The Inventory is available here: https://circabc.europa.eu/w/browse/b0a3ddc3-464e-4e57-9601-55a8315c529e

- any applicable marketing restrictions.

In line with the above, Section V.2) of Part A of the Inventory lists among existing MAPs "*Homeopathic medicinal products containing mercury or mercury compounds used as active ingredient, intermediate solution or starting material*". The list of products and processes included in the Inventory is non-exhaustive and will be regularly updated when additional information is available or when related legislative changes are adopted.[37]

According to the 2nd subparagraph of Article 8(2) of the Mercury Regulation, the restrictions on '**new manufacturing processes**' shall not apply to processes manufacturing or using mercury-added products that are not new (i.e. which were manufactured prior to 1 January 2018). In light of this 2nd subparagraph of Article 8(2), the Inventory does not list processes manufacturing or using MAPs where mercury or mercury compounds do not exert a function in the manufacturing process itself in addition to the function exerted in the MAPs.[38] Mercury or mercury compounds used in HMP/HVMPs do not exert a function in the manufacturing process; therefore these products are classified as MAP. It follows from this that homeopathic manufacturing processes do not fall under the definition of new manufacturing process within the meaning of Article 8(2) of the Regulation.

3.6. What are the restrictions of Regulation (EU) 2017/852 on mercury ("Mercury Regulation") that may concern HMP/HVMPs?

Since the definition of mercury-added products (see Question 3.5) include HMP/HVMPs to which mercury or mercury compounds were intentionally added, these products may be concerned by the restriction that the export, import and manufacturing of mercury-added products listed in Annex II of the Mercury Regulation are prohibited as of the date stated in the annex.[39] (It bears noting that certain types of products, including products for research, for calibration or instrumentation, or for use as a reference standard are exempted from this prohibition.[40]) Among others, Part A on mercury-added products of Annex II of the Mercury Regulation includes *'8. Pesticides, biocides and topical antiseptics'*. Accordingly, to the extent that any mercury-added HMPs are intended as topical antiseptics, their export, import and manufacturing will be prohibited from 31 December 2020.

As explained in Question 3.5, it appears that in general HMP/HVMPs do not fall under the definition of 'new mercury-added products'. However, if any new mercury-added HMP/HVMPs were developed that could not be exempted from the definition based on the interpretation above, such new mercury-added HMP/HVMPs could not be manufactured or placed on the market without a specific authorisation provided by the European Commission in accordance with the procedure set forth in Article 8 of the Mercury Regulation.

In addition, HMP/HVMPs may be concerned by the export and import restrictions on mercury and certain mercury compounds and mixtures of mercury, as provided in Articles 3 and 4, and Annex I of the Mercury Regulation.

[37] Explanatory Text of the Inventory
[38] Point 3.1 of the Explanatory Text of the Inventory
[39] See Article 5(1) of the Mercury Regulation
[40] See Article 5(2) of the Mercury Regulation

4. Legal and regulatory matters concerning HMP/HVMPs subject to special, simplified registration procedure

4.1. Is a Summary of Product Information ("SmPC") required in case of HMP/HVMPs subject to special, simplified registration procedure?

In relation to HMP/HVMPs that are eligible for the simplified registration procedure Article 15 of Directive 2001/83/EC and Article 18 of Directive 2001/82/EC conclusively list the documents that shall be included in the application for simplified registration (see Question 2.3). If the product is eligible for the simplified registration (see Question 2.2 above) Member States are not allowed to introduce other requirements than the ones following from Articles 14 and 15 of Directive 2001/83/EC or Articles 17 and 18 of Directive 2001/82/EC.

In addition, it follows from Article 14(2) of Directive 2001/83/EC and Article 17(2) of Directive 2001/82/EC that those articles of the Directives[41] which provide further rules on the approval of SmPCs are not applicable to HMP/HVMPs subject to simplified registration. These provisions, i.e. Article 21 of Directive 2001/83/EC and Article 25 of Directive 2001/83/EC, would otherwise require – among others – that when the marketing authorisation is issued, the competent authority shall inform the holder of the SmPC as approved by it.

It follows from the above that in the case of HMP/HVMPs eligible for the simplified registration, applicants are not required to submit a SmPC with the application for simplified registration.

In accordance with the above, with regard to HMP/HVMPs subject to simplified registration, no SmPC is adopted by the competent authorities in the sense of Article 11 of Directive 2001/83/EC or Article 14 of Directive 2001/82/EC. In line with this, Article 14(1) of Directive 2001/83/EC and Article 17(1)(b) of Directive 2001/82/EC explicitly provide that no specific therapeutic indication may appear in any information relating to such products. Besides, any information and advertising related to such products shall be in full compliance with Title VIII and VIIIa of Directive 2001/83/EC.

4.2. Are Braille requirements applicable to HMPs subject to special, simplified registration procedure authorised via mutual recognition or decentralised procedure?

Human

As explained in Question 3.1 above, HMPs shall be labelled in accordance with the general labelling and package leaflet requirements applicable under Directive 2001/83/EC, while as regards HMPs subject to simplified registration, certain additional rules apply.

As regards human medicinal products, Article 56a of Directive 2001/83/EC requires that the name of the medicinal product, as referred to in Article 54 point (a), must be expressed in Braille format on the packaging. In addition, the marketing authorisation holder shall make available the package leaflet in formats appropriate for the blind and partially sighted at any time upon on request from patients' organisations. Since there is no waiver from this Braille requirement with regard to HMPs subject to simplified procedure, both of the requirements stated in Article 56a (i.e. Braille format and formats appropriate for the blind and partially sighted) apply to these products. As these requirements shall be read in conjunction with the special rules set forth by Article 69(1) it follows that the scientific name of the stock or stocks followed by the degree of dilution should be put in Braille format on the packaging of

[41] Article 21 of Directive 2001/83/EC and Article 25 of Directive 2001/83/EC

the products. If the scientific names of the stocks on the labelling are supplemented by an invented name, this should also be put in Braille format.[42]

For further guidance related to Braille requirements please consult the national provisions of Member States.

Veterinary

As regards veterinary products, Directive 2001/82/EC does not establish mandatory Braille requirements.

4.3. Are HMPs subject to special, simplified registration procedure included in the public list of the European Medicinal Agency ("EMA") on refused, revoked, or suspended products?

According to Article 123(4) of Directive 2001/83/EC the European Medicines Agency shall publish a list of human medicinal products for which marketing authorisation have been refused, revoked or suspended in the Union, whose supply has been prohibited or which have been withdrawn from the market, including the reasons for such action.

The legal requirements for 'withdrawn products' nationally authorised are stated in Article 23a and Article 123(2) of Directive 2001/83/EC which provide the obligation for the marketing authorisation holder to notify the relevant competent authorities of temporary or permanent action taken on their products and the reason for such action, in particular whether it is taken on any safety/ efficacy/ quality grounds as set out in Article 116 or Article 117(1) of Directive 2001/83/EC.

For human HMPs subject to simplified registration procedure Article 14(2) of Directive 2001/83/EC states that *"the criteria and rules of procedure provided for in Article 4(4), Article 17(1) and Articles **22 to 26**, 112, 116 and 125 shall apply by analogy to the special, simplified registration procedure for homeopathic medicinal products, with the exception of the proof of therapeutic efficacy"*. (Emphasis added.) It follows that the notification obligation stated under Article 23a is applicable to HMPs. On the other hand, the applicability of Article 123 of Directive 2001/83/EC – and, in particular, the notification obligation of Article 123(2) and the publication obligation under Article 123(4) – is not established by Article 14(2) of Directive 2001/83/EC.

Therefore, the list provided in Article 123(4) of Directive 2001/83/EC should not include HMPs subject to special, simplified registration procedure.

As regards veterinary products, Directive 2001/82/EC does not establish the requirement of a public list to be published by the European Medicinal Agency on refused, revoked, or suspended products.

5. Additional considerations

5.1. How to submit a request for opinion of the HMPWG on regulatory and scientific matters concerning HMP/HVMPs in the European Union?

Requests for opinion on issues falling under the mandate of the HMPWG may be submitted by written procedure to the Chairperson or the Secretariat, through HMPWG-Secretariat@hma.eu. The scope of the HMPWG mandate under which requests are discussed is defined in the HMPWG Rules of Procedure available on the HMA website.[43] A request for opinion should include reasoning for the question(s) raised,

[42] See also Section 3.3 of Chapter 1 (Marketing Authorisation), Volume 2A of the Notice to Applicants.
[43] http://www.hma.eu/380.html

an explanation of the scientific and regulatory background as well as any other important information concerning the issue. A template format to be used for submission of a request to the HMPWG may be found in the HMA website.

In case a request for opinion falls within the remits of HMPWG, it is discussed within the group with the aim to adopt a final position. In case the request is of relevance for HVMPs, the CMDv will be invited to comment.

5.2. Is the legal/regulatory framework regulating HMPs applicable to Anthroposophic Medicinal Products as well?

Anthroposophic Medicinal Products fall within the definition of 'medicinal products' laid down in Article 1(2) of Directive 2001/83/EC, since they are presented as 'medicinal products' prepared on the basis of principles of anthroposophic medicine.[44] It follows that such products have to be completely in accordance with the European legislation on pharmaceuticals. Most importantly, they may be marketed in the European Union only on condition that they have been authorised under one of the procedures referred to in Article 6 of Directive 2001/83/EC. [45]

Recital (22) of Directive 2001/83/EC further clarifies with regard to Anthroposophic Medicinal Products that in case such products are described in an official pharmacopoeia and prepared by a homeopathic method, then they are to be treated, as regards registration and marketing authorisation, in the same way as homeopathic medicinal products.

In light of the above, the legal/regulatory framework governing the *registration and marketing authorisation* of HMPs is applicable only to those Anthroposophic Medicinal Products which are prepared 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. Therefore, if such products also fulfil the requirements to be eligible for simplified registration (see Question 2.2 above), they can be registered through the simplified procedure.

However, Anthroposophic Medicinal Products which are not described in an official pharmacopoeia and not prepared by a homeopathic method shall be authorised in accordance with one of the other legal basis referred to in Article 6 of Directive 2001/83/EC, i.e. any other legal basis of the Directive other than registrations for HMPs or in accordance with Regulation (EC) No 726/2004.

[44] See Judgement of the Court of Justice in *Antroposana and Others*, C-84/06 EU:C:2007:535, paragraphs 32-33.
[45] See Judgement of the Court of Justice in *Antroposana and Others*, C-84/06 EU:C:2007:535, paragraph 43 and the operative part of the judgment.