01 October
Guidance on module 3 of the homeopathic medicinal products dossier_rev.1 as released for public consultation on 25-26 June 2024 until 4 October 2024

Template for submission of comments on draft document

Written procedure decided by the HMPWG	**30 May 2013**
Adoption by written procedure	**15 September 2013**
Report of the outcome of the written procedure	**21 November 2013**

Submission of comments on draft document

Table 1: Origin of comments

Guidance on module 3 of the homeopathic medicinal products dossier rev.1 as released for public consultation on 25-26 June 2024 until 4 October 2024

Organisation or individual	Contact details (e-mail address, telephone number, name of contact person)
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Interested parties are invited to send
comments together with a copy of the cited references.
This will facilitate the assessment of comments, suggestions and corresponding justifications.

When the reference consists of a book chapter, the copy must include
the page of the book showing the year of publication.

Comments without copies of the supporting literature will not be considered.

Comments should be sent electronically and in Word format (not pdf).

Comments and the identity of the sender will be made public
unless a justified objection is received at the time of the submission.

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Please submit comments on each document separately.

Table 2: Comments

GENERAL COMMENTS ON DRAFT DOCUMENT

Interested party	Comment and Rationale	Outcome
ECHAMP	Inclusion of precise definitions as well as appropriate and detailed examples for the following terms (and all cases) would be appreciated: Raw materials, Starting material for... etc. (botanical origin, zoological or human origin, chemical and mineral origin). Example for “botanical origin” = plants, fungi, algae (fresh- or seawater) and lichens. E.g. for mineral origin: unprocessed mineral piece = raw material, mineral powder 100% = starting material, D1 trituration from a mineral powder 100% = homeopathic stock (HMA List of terms used in homeopathy should be taken in to consideration).	
ECHAMP	Experience with a wording like “...should be considered, if appropriate (e.g., ...) or “...if relevant..” often leads to a misinterpretation of authorities i.e. assessors: they often request information according to exact wording of the guidance (including the given examples in brackets) without taking into account if there is a relevant scientific rationale for the request in the specific case. The justification for an irrelevant request does unnecessarily cost resources and is opposed to the demand for less bureaucracy.	
ECHAMP	In order to avoid the increase of administrative burden for both industry and agencies inclusion of redundant information in the dossier should be avoided. Reference to pharmacopeial monographs and methods should be sufficient without the obligation to copy the text.	
ECHAMP	Raw materials should be differentiated from stocks, as this would also be in line with GMP (where stocks are also APIs, depending on the registration status in a country), as APIs are assessed more strictly.	

Interested party	Comment and Rationale	Outcome
ECHAMP	In general mineral substances and chemical substances should be considered separately. They are often covered together in one point with information that do not fit exactly for both cases (e.g. lines 350-358). The distinction between organic and inorganic within the chemical substances would be important, due to the different spectrum of impurities.	
ECHAMP	The wording in the current guideline of 3.2.P.8 stability should be transferred to the new draft.	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
181 - 184 372 - 373	ECHAMP	The following should be added as an important alternative approach: "Alternatively, information on intermediates up to the final dilutions can be included in module 3.2.P with a reference to it placed in module 3.2.S." Rationale: If the identical homeopathic stock is used in different preparations, the same S-file can be used for it, remarkably reducing workload for both, competent authorities and companies.	
270 - 273	ECHAMP	Add "If applicable " Rationale: Only applicable to the main toxic constituents, such a remark should be added. Not applicable to herbal raw materials, where not every characterisation can be attributed to one or few ingredients, which then must be characterised exactly as stated above. This might be feasible for toxic ingredients - but there are often ingredient groups that are determined or sums of e.g. bufadienolides. 'If applicable' should be clearly presented for the entire text passage. The Guide for the elaboration of monographs on Hom. Preparations is a state of the art and should be considered.	
274	ECHAMP	**Text to be added:** Physical, anatomical and histological description**, if relevant**. Rationale: For some materials of zoological origin, as insects, e.g. a histological description might not be required and/or suitable.	

169, 170, 298, 300 and in general	ECHAMP	Include precise definitions for raw material, starting material, homeopathic preparations and stock (homeopathic stock). E.g. mineral piece = raw material, mineral powder 100% = starting material, D1 mineral trituration = homeopathic stock (HMA List of terms used in homeopathy). E.g. for chemical substance: Natrium sulfuricum (starting material) e.g. from sodium carbonate (=raw material) and sulfuric acid (=raw material), Natrium sulfuricum D1 = homeopathic stock	

98-299	ECHAMP	Delete this section. ~~RAW MATERIAL~~ ~~The name, address, and responsibility of each manufacturer and supplier should be provided.~~ Rationale: Flexibility in changing suppliers and reduction of administrative burden without affecting GMP and GACP, is possible while maintaining constant quality. This flexibility is of high importance for supply of the medicinal products. There is a wide variety of materials concerned (herbal, animal, mineral, chemical or biological origin). Therefore, a large number of suppliers is needed and difficult to change per substance. Defining suppliers results in high efforts and is difficult in case of rare plant material (crop failure) and small batch sizes. For fresh plant material which is often used as starting material there is only a narrow time of harvest and supply. For minerals, the quality of the mineral is never determined by the suppliers. One supplier can offer one mineral gained from different mines and even countries. The supplier cannot be the “manufacturer” of a mineral, he is only a distributor of the mineral, that does not intervene in its quality by performing any kind of treatment. Some minerals are very rare and precious. It´s not possible to define a permanent supplier for minerals and this case should be treated differently as in the case of herbals. The quality of the mineral is defined in different pharmacopeias and a reference to it, including a mineralogical assessment should be sufficient without fixing suppliers. See also comments made for line 352. Information on several suppliers (in the past) should be possible without the need of presenting batch analysis results for each supplier since the specifications of materials do not change with a new supplier.	

306 - 311	ECHAMP	Reference to pharmacopoeia monographs should be sufficient.for inorganic chemical substance: Rationale: When inorganic chemical substance is purchased, detailed information on the manufacturing of raw materials, starting material or stocks itself is not made available to homeopathic manufacturers. There are no organic impurities in the mineral inorganic substances; only the natural elements can occur. Toxic elements are adequately assessed and regulated by ICH Q3D. The quality of inorganic substances can be fully verified by analysis (content and purity). The synthesis route is not relevant.	
316	ECHAMP	Delete “region”. Rationale: It is not practicable to give more detailed information other as the country to keep certain flexibilities which is necessary to avoid supply problems. Furthermore, specific plants can only grow in specific environmental condition. Therefore, there is no additional value to give more detailed information. Geographic location could be given as an example only for the certified raw material batches.	
325	ECHAMP	Information on storage time could be given as an example only for the certified raw material batches. Rationale: This information is highly depending on the used material	

328	ECHAMP	Botanical: delete batch size Rationale: Plant suppliers normally deliver plant / raw material to different stock manufacturers. This means that the originally harvested amount of plant material can be much bigger than the material received by the manufacturers and used for further processing. This means that it is not relevant how much plant material was harvested in total/ how big the batch size is. The stock manufacturer orders and receives the amount of plant material necessary for the intended batch size of the stock. So, the relevant data is the batch size of the stock.	
335	ECHAMP	Geographic location to be given only as an example for the certified raw material batches. Rationale: The geographical origin of a zoological or human material is not associated to the quality of the material, especially considering animal breeding, which can take place anywhere, and the worldwide distribution of mankind.	
344	ECHAMP	Delete ~~Assessment of the risk of infectivity.~~ Rationale: Double information to inactivate infectious agents and for specifications of the raw material. This information is already given in 3.2.A.2.	

352	ECHAMP	Delete requirement for mineral substances Rationale: the quality of a mineral does not depend on the geographical source and is not dependent on the different kind of suppliers (no added treatment by suppliers). The locality of the mineral is a criterion, which reveals what kind of natural formation processes this mineral has undergone e.g. millions of years ago. But even within one mine, the quality of the mineral (crystal form, crystal size, purity, trace elements …) may vary. Important is, that the mineral meets the individual specification. The only method for getting a quality statement of the mineral consists in its mineralogical and analytical testing, which is always performed by the manufacturer of the homeopathic stocks of mineral origin.	
355 - 356		Delete requirements for minerals Rationale Purification stage not applicable in case of minerals. Rationale: Batch size of mineral/ chemical substance: when chemical substance purchased, the supplier does not communicate the batch size of the substance supplied. The synthesis pathway including the batch size is not the quality determining criterion, but the chemical analysis of the substance. See comments for line 357.	

357	ECHAMP	The manufacturing process should only be required for the first homoeopathic preparation and in the case of minerals include “if applicable” or exclude minerals. Rationale: Manufacturing of the first homoeopathic preparation is the first GMP-relevant step in the manufacturing process. This would be in line with all other type of raw materials. Mineral substances are normally only comminuted and sieved. There is no synthesis pathway with purification stages. There are no organic impurities in the mineral inorganic substances; only the natural elements can occur. Toxic elements are adequately assessed and regulated by ICH Q3d. The quality of inorganic substances can be fully verified by analysis (content and purity). The synthesis route is not relevant. For substances where there is a Ph. Eur. Monograph, the reference to Ph. Eur. should be sufficient.	
376	ECHAMP	It should be possible to provide this information in the P-Part of CTD Module 3 as an alternative. Rationale: This strategy is already accepted by many competent authorities in Europe. It would allow preparing one S-Part per stock instead of one S-Part per potency. S-Part per potency would multiply the number of required S-Parts, as companies often use the same material in different potencies. The information on potencies would not be lost but simply be presented in a different part of the CTD.	

380	ECHAMP	List of stored potencies: should be a matter of GMP, not a regulatory requirement. Rationale: Stored potencies may vary vastly throughout time and are controlled by GMP requirements. Fixing the stored potencies would highly influence the production planning and the ability of companies to properly react to market needs by. unnecessarily increasing the number of variations.	
394-395	ECHAMP	Delete requirement. Rationale: Confirmation of GACP for each supplier: is a matter of GMP, not a regulatory requirement to be included in the dossier.	
396-397	ECHAMP	Delete this requirement. Rationale: Generally, the certification of ecological cultivation was foreseen for food production. If HMPWG wants to extend this certificate to plant specific certification for medicinal plants, it should address this requirement to the EU entity responsible for the EU ecological certification form (Certificate pursuant to Article 35(1) of Regulation (EU) 2018/848 on organic production and labelling of organic products). A plant specific certificate for Demeter, Bioland and Naturland cultivation is not foreseen from these associations, because - contrary to Eu-Eco.... - they certificate the whole farm / agronomic enterprise.	
411-412	ECHAMP	Add “if applicable”. Rationale:For methods described in the Ph. Eur, this section is not applicable.	
414 - 426	ECHAMP	Information should only be required for non-standard processes	

		Rationale: Normally, the manufacturing of homeopathic active substances is a standard process of the pharmaceutical technology described in several pharmacopeias. According to the Guideline on process validation for finished products EMA/CHMP/CVMP/749073/2016 Scope, information on validation of the manufacturing process is not required in the dossier, see scope of the guideline.	
445	ECHAMP	Add “if relevant”. Rationale: only in the case of toxic plants it is necessary to address the toxic plant constituents as given in annex 1 of directive 2001/83/EC where for homeopathic medicinal products . This is also reflected in the EDQM “Guide for the elaboration of monographs on homeopathic. preparations, Edition 2022”	
446, 451	ECHAMP	Images of chromatographic profiles could be provided if applicable only for the certified raw material batches. As an alternative the schematic chromatograms of the substance-specific monographs could be depicted here. Rationale: Fresh plants have to be processed immediately after harvesting (within 24 hours), because of their perishable character. Therefore TLC (Thin-layer-chromatography) is not practicable due they would last several days. It is not foreseen by the official Ph. Eur. Monographs for fresh plants and therefore not applicable for fresh plants.	

		The same applies for zoological raw materials.	
454 - 455	ECHAMP	Requirements to be applicable to organic substances only. Rationale: Chemical analysis is completely sufficient. The requirements listed are disproportional to the outcome. The listed methods are only useful for organic substances, but not for inorganic chemical substances and minerals.	
481	ECHAMP	Delete example. Rationale: there are no requirements for bromine	
495-497	ECHAMP	Delete line. Rationale: Impurities of the vehicle are evaluated during testing of the vehicle.	
500	ECHAMP	Add if applicable. Rationale There is no differentiation between raw materials as fresh plants or from zoological origin. The requirements are only applicable in the case of dried herbal material and chemical substances. Add “if appropriate” for final dilutions	
473 - 475	ECHAMP	Double information for microbial and viral contamination. This information is already given in 3.2.A.2.	
546-550	ECHAMP	Add “if applicable”	

		Rationale: Depending on type of material , for example sulphated ash only for herbals (and in some cases for organic chemical substances), not appropriate for inorganic chemicals and minerals.	
516	ECHAMP	Amend text as follows : Assay of toxic stable compounds ~~or, if applicable, of the main constituent or analytical markers (e.g., for stored dried herbal drugs)~~ Rationale: the requested data should remain in line with the Eu Pharmacopoeia.	
575 - 585	ECHAMP	Include group validations as alternative Rationale: Group validations as e.g. for contaminants such as pesticides should be acceptable since they are state of the art. This is also usual within the food industry. Specific validation of hundreds of substances such as pesticides are not appropriate nor affordable. Grouping validations using methods as in the food industry should be sufficient. The testing of suitability methods of Ph. Eur. within the company is a matter of GMP and is always being proven and evaluated by inspections. This information should not be given in a regulatory dossier. Further, it should not be necessary to include validation reports of analytical procedures for pharmacopeia methods.	
599-602	ECHAMP	Delete this new requirement or add "**unless otherwise justified."** Rationale: if the manufacturing method and release specification for homeopathic stock(s) are identical then this requirement does not add any quality or safety related benefit to the dossier.	

		According to the applicable Pharmacopoeia, manufacture and release specification of the homeopathic active substance are (in contrast to chemical active substances of non-homeopathic medicinal products) in general identical regardless of the manufacturer. As long as the manufacture and the release specification of homeopathic stock(s) are according to the same methods and requirements described in the European Pharmacopoeia or, in the absence thereof, an official Pharmacopoeia of a Member State, there is no practical benefit of such a submission. All batches of the homeopathic stock(s) must be released according to the specification, which always verifies the adherence to the manufacturing method according to the applicable Pharmacopoeia – regardless of the manufacturing site/supplier/manufacturer. For example, the specification for Achillea millefolium according to HAB 2020 (Homöopathisches Arzneibuch) must be pursuant to provision HAB 3a: mother tinctures and liquid dilutions, which is equivalent to manufacturing method 1.1.5 of the Ph. Eur. monograph (2371) on methods of preparation of homoeopathic stocks and potentisation (see Ph. Eur. 2371 and HAB monograph of Achillea millefolium). Moreover, analytical procedures are already described in section 3.2.S.4.2 and the manufacturers are listed in section 3.2.S.2.1. The compliance of manufacturers of active substances with good manufacturing practice is verified by audits (Art. 46 (f), Art. 53 Directive 2001/83). A declaration by the Qualified Person that each active substance is manufactured in compliance with the principles and guidelines on good manufacturing practice is provided in Module 1, section 2.5.4.	

		From a practical perspective, manufacturers of homeopathic medicinal products often purchase only small batches of homeopathic stock(s) and procurement of some rare plants is infrequent. The requirement to submit batch analyses of all suppliers/manufacturers of homeopathic stock(s)would be disproportionate as it causes extra workload and administrative effort for the applicants without adding a real benefit neither to the clear description of the quality nor to the assessment by the national authorities. These results would only have an added value for the dossier, if the manufacturing procedure and/or the release specification applied in a specific case differ between the manufacturers. Therefore, the scope of the guidance regarding batch analyses from each manufacturing site/supplier/manufacturer for homeopathic stock(s) should foresee the possibility of exceptions, analogous to the wording in lines 597-598 regarding batch analyses of raw materials.	
635	ECHAMP	Raw materials should be deleted. Rationale: this requirement is not in line with current stability guidelines. Stability data for raw materials is part of GMP and not to be included in the dossier. There is no justification to increase the documentation level for inorganic and mineral substances when compared to allopathic medicines. Stability data for raw materials is established by the manufacturer and has to comply with ICH conditions (see GMP principles…) . Minerals are known to be stable due to their long formation processes in nature .	
665	ECHAMP	Delete this line.	

		Rationale: the container closure system is described in detail in section 3.2.P.7, redundant information should be avoided	
759-760	ECHAMP	**Text to be added:** If more than one batch size is indicated, the batch formula for each of the batch sizes should be given. **If a batch range is given, the batch formula for the smallest and the largest batch size should be provided.** Rationale: Batch size depends on the actual demand. A batch size range with minimum and maximum batch size should therefore be acceptable. The batch formula should be given for the smallest and the largest batch size.	
811 - 813	ECHAMP	Holding time validation should only applicable to non-standard manufacturing procedures. Add text : For non-standard manufacturing processes the validation of the maximum, holding time…. Rationale: For standard manufacturing procedures this is covered by GMP principles, and the information should not be part of the registration dossier.	
869	ECHAMP	Replace as follows: “As a minimum, the stability specifications should include all the stability indicating parameters of the batch release specification.” Rationale: for example identity tests included in the release specification are only needed at start in the shelf-life specification. The right storage under ICH conditions is ensured by compliance with GMP	

		principles. An identity testing during stability does not provide information on the quality of the product throughout the storage time.	
878	ECHAMP	*Add the following **text** "Assay of the main characteristic constituents of the drug substances, if applicable":* **In case of instable toxicological compounds limit tests are sufficient.** Rationale: Assay **o**nly applicable for stable toxicological relevant substances, see 2003/63/EC.	
892	ECHAMP	Include "(plastic containers)" after extractables	
907 – 908, 912	ECHAMP	Delete lines Rationale: Suitability tests are a matter of GMP and controlled by inspections. This is adequately addressed in 5.26 Implementation of Pharmacopoeical Procedures	
920	ECHAMP	Replace three with two Rationale: Analytical results of at least two batches should be sufficient and would enable a better flexibility. There is no reasonable need to increase the requirements as currently established.	
960-963	ECHAMP	Amend the text as follows: A tabulated summary of the data, clearly indicating the number and types / sizes (Prodution, pliot or experimental) of batches, packaging material, storage conditions and storage period, ~~and manufacturer of the active substance with their batch numbers, should be included for each finished product manufacturer.~~ Rationale: The requirement to indicate the manufacturer of the homeopathic active substance is not in line with requirements for other types of medicinal products. Also, according to the variation	

		classification guideline (EC) No 1234/2008 a change in API manufacturer has not to be supported by stability data. The requirement to provide data on the manufacturer of the homeopathic active substances with their batch number also in Section 3.2.P.8.1 is redundant, if the manufacturing method and release specification for homeopathic stock(s) are identical. As mentioned above in our comments to section 3.2.S.4.4: According to the applicable Pharmacopoeia, manufacture and release specification of the homeopathic active substance are (in contrast to chemical active substances of non-homeopathic medicinal products) in general identical regardless of the manufacturer. Furthermore, all batches must be released according to the specification, which always verifies the adherence to the manufacturing method according to the applicable Pharmacopoeia. If manufacturing method and release specification are identical regardless of the manufacturer, specifying the manufacturer of the homeopathic active substances with their batch number is redundant information causing additional administrative burden for the applicants without adding a benefit to the quality assessment. This information would only have an added value for the dossier, if the manufacturing procedure and/or the release specification applied in a specific case differ between the manufacturers. Therefore, exceptions of this requirement should be possible in justified cases, i.e. when manufacture and/or release specification of the homeopathic active substance are identical for all manufacturers.	

973	ECHAMP	Replace three with two " A stability commitment for the first **two** industrial-scale batches..." Rationale: "Thee batches should only be required for for non-standard pharmaceutical forms.	