14 May 2018

Questions and Answers Document on the Quality of Homeopathic Medicinal Products (Q 4-7)

as released for public consultation on 26 February 2018 until 31 May 2018

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

Questions and Answers Document on the Quality of Homeopathic Medicinal Products (Q 4-7)
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Organisation or individual	Contact details (e-mail address, telephone number, name of contact person)
ECHAMP ECHAMP E.E.I.G. – European Coalition on Homeopathic and Anthroposophic Medicinal Products	Rue Washington 38-40 B-1050 Brussels Tel: +32 2 649 94 40 amandine.oset@echamp.eu

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	Formal Comment: In its title the document refers to Questions 4 – 7 (*Q 4-7*) which is correct because in 2016 the HMPWG released Questions 1 – 3 (not on the HMPWG website anymore). The questions and answers themselves start with *Question 3* instead with *Question 4*	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
Question ~~3~~ 4 What is the "appropriate number" of reference products deemed acceptable for the transferability of stability data of homeopathic medicinal products?	ECHAMP	**Comment**: Clarification of this topic is very helpful in order to implement stability concepts accepted by all member states.	
Question 5 Where are the intermediate dilutions	ECHAMP	***Comment:*** We do not understand the necessity to repeat this purely formal point in a Q&A document on Quality, since it is already defined by the HMPWG *Guidance on Module 3 of the*	

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reported within the CTD dossier (3.2.S or 3.2.P section)?		*Homeopathic Medicinal Products Dossier*. Nevertheless, there are strong arguments that it should be left to the decision by the applicant to include information on the preparation of dilutions/triturations in the Module 3.2.S or 3.2.P section. **Proposed change:** *According to the Guidance on Module 3 of the Homeopathic Medicinal Products dossier, under Drug substance (section 3.2.S) information on the starting material, including raw material(s), homeopathic stock(s), and intermediate(s) up to the final dilution(s) or trituration(s) to be incorporated into the finished product should be provided. Alternatively, the intermediate and final dilution(s) or trituration(s) can be placed in the corresponding sections of 3.2.P instead.* **Rationale:** Since 2006 when the Guidance was written, in practice it has been experienced that for many products and companies' product portfolios it is more useful to describe the dilution process and final dilutions in the Module 3.2.P section (3.2.P.3). The latter solution facilitates the regulatory work for companies and agencies since an identical S-file for distinctive stocks can be used and submitted for different single and complex products, as in many cases different final dilutions from the same homeopathic stock are used for different finished products. In other cases, it may be more suitable to have the information on intermediates up to the final potency in the S-Part. Example: Atropa belladonna Ø used in 6 different homeopathic complex medicinal products in 6 different potencies: 1. Dilutions placed in 3.2.S: Number of different 3.2.S: **6** (whereas in each the information on Ø is identically repeated 6 times) Number of 3.2.P: **6** (1 per product)	

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		2. <u>Dilutions placed in 3.2.P:</u> Number of 3.2.S: **1** (Ø only) Number of 3.2.P: **6** (1 per product) For a homeopathic manufacturer with 300 different stocks in an average of 4 different potencies / finished products, the number of 3.2.S parts would be 1.200 if the dilution information would be obligatory in 3.2.S compared to 300, in case of placing it into 3.2.P. In the view of the general aim of reducing the regulatory burden both for industry and for agencies this information should not be neglected. In some member states the 3.2.S part in terms of information on the homeopathic stock serves as a reference document for all products which use this stock. There, for Art. 14 registrations with the same stock it is even not necessary to resubmit the file itself for each next product, pure reference is enough. This highly efficient regulatory concept would not be viable anymore if there was an obligation to include the dilutions in the same 3.2.S part. It is also remarked that a former version of the current valid HMPWG guidance allocated the documentation of dilutions/triturations into the P-part, so it can be seen that there is room for different arguments. Finally, the important thing is that the relevant information is included in the dossier, but not if it is placed in the S- or P-part. Since the time the guidance was published the placement of the information on homeopathic dilutions / triturations into 3.2.P or 3.2.S has been accepted in registration procedures by the regulatory agencies of Austria, Belgium, France, Germany, Latvia, Lithuania, Netherlands, Poland, Switzerland, United Kingdom, including the only one finalised mutual recognition procedure for homeopathic medicinal products. Moreover, it is common practice that with justified reasons a requirement of a guidance can be resolved otherwise. In the case of the formal topic regarding the place of the	

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		description of the intermediate dilutions in the CTD there is no scientific reason to follow the guidance literally. On the contrary, more than 10 years of experience with CTD registrations prove that the approach chosen by various manufacturers is reasonable and viable. For these reasons, we would like you to reconsider this topic and accept the CTD dossier structure as presented by the respective applicant.	
Question 6 In HMP CTD dossier (section 3.2.P.3.5), is the process validation always required?	ECHAMP	**Comment**: If a manufacturing process is justified as a standard process, a common exemplary validation valid for identical galenic forms (dosage forms) for a specific manufacturing site and process should be acceptable. Moreover, a manufacturing process validation does not appear to be relevant in the context of a standard procedure described in the pharmacopoeia. It is to be considered that the HAB/Ph.Eur. methods of preparation of final potencies are in use for decades with much experience gained on it. A pharmaceutical development as expected for new medicinal products according to actual guidelines has not taken place in most of the cases. Therefore, for these standard processes it should be sufficient to prove the validity of the process by submitting the in-process control results of three consecutive production batches. For standard manufacturing processes, it should also be acceptable that no validation scheme is given in the dossier, since this is a matter of GMP verified by the supervisory authority. **Rationale**: In homeopathic products the concentration of chemically detectable drug substances is often very low. Therefore, the specification of the finished product contains only parameters of the dosage form, and no product-specific tests. In these cases, any influence of the drug substances on the quality of the finished product can be excluded. From the chemical view the products are identical when produced with the same qualitative and quantitative composition of excipients resulting in the same	

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		pharmaceutical form. The subject of validation should be considered in the same way as the stability of finished products, where data are transferable in certain conditions. For a harmonised view which manufacturing processes can be considered as standard or non-standard with regard to process validation, the *Guideline on process validation for finished products – information on data to be provided in regulatory submissions* (EMA/QWP/BWP/70278/2012-rev1) is of relevance. Annex II to this Guideline states several conditions, which can be considered to define a process as non-standard. For example, as non-standard are seen specialised pharmaceutical dose forms, new technologies, complex processes, non-standard methods of sterilisation. Manufacturing validation in the first line is a matter of GMP and not of registration procedures. **Proposed change:** *Yes, a process validation or alternatively an evaluation may be ~~is~~ required.* *A common exemplary validation valid for identical galenic forms (dosage forms) for a specific manufacturing site and process should be acceptable* *Complete data should be provided in the dossier for non-standard products or processes (e.g. aseptic processing). The process must be validated when an unconventional manufacturing method is used or when its implementation is decisive for the quality of the product.* *It is possible for the applicant to justify that the product process can be considered as a standard procedure for a manufacturer/site. In this case, for these standard processes it should be sufficient to prove the validity of the process by submitting the in-process control results of three consecutive production batches.~~ ~~at least the process validation scheme (as described in Annex I of EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr. 1 guideline) should be provided, and the applicant commits on performing the validation on production scale batches prior to 19 marketing of the product.~~ "Validation of viral safety should be included in Part 3.2.A.2" **Comment:** Generally, a risk assessment should be sufficient for proof of viral safety. A validation should be demanded only in exceptional cases. **Rationale**: Risk assessments describe the manufacturing method, the nature and origin	

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		of raw materials, as well as the deducted risk of contaminations. In addition, specifications can further minimise the risk of contamination by specific viruses. Validations only should be required if questions stay open.	
Question 7 How many batches are required in 3.2.S.4.4 (Batch analysis) section? <u>a. Raw material</u> Certificates of analysis (CoA) of at least two batches of the raw material(s), should be provided. In case of more than one supplier, at least one CoA for each supplier should be provided, unless otherwise justified. <u>b. Stock/Mother tincture</u> Certificates of analysis (CoA) of at least two batches should be provided. In case of more than one supplier/manufacturer, at least one CoA for each	ECHAMP	**General comment:** The term *CoA – Certificate of Analysis* is not applicable in the context of a CTD dossier. In order to maintain correct and consistent wording with EMA and HMPWG regulatory guidance on CTD the term *batch analyses* and *results of batch analyses* is to be used here. **Proposed change:** Replace *Certificate of analysis (CoA)* with *Results of batch analysis* <u>a. Raw material</u> - The following answer should be read in the context with Questions 2 and 3 of the HMPWG Q&A document of 2016 and the corresponding comments from the industry. **Comment:** We propose to submit 2 batch results of the most frequent supplier, if available. **Proposed change:** *a. Raw material* ~~*Certificates of analysis (CoA*~~*) Results of analyses of* ~~*at least*~~ *two batches of the raw material(s) should be provided.* ~~*In case of more than one supplier, at least one CoA for each supplier should be provided, unless otherwise justified*~~*.* **Rationale:** In many cases, especially in the case of fresh herbal plants, it is not realistic to supply 2 batch results per supplier. For the manufacture of medicinal products with active substances of herbal origin it is of vital importance to have the possibility to quickly switch between different qualified raw material suppliers. This is especially relevant for homeopathic medicinal products where	

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supplier/ manufacturer should be provided, unless otherwise justified. <u>c. Dilutions</u> Certificates of analysis (CoA) of at least two batches of intermediate dilutions (if stored or purchased), should be provided. [...] In any case, the certificates should not be older than three years, unless appropriately justified.		several hundreds of different (often fresh) herbal raw materials are used in often very small amounts. The quality and availability of medicinal plants depend on natural variables such as climatic conditions, pests, harvests, seasonal differences etc. Crop failure or very slow plant growth may occur. These conditions can lead to sudden and frequent changes in the suppliers. If the manufacturer does not have the possibility to quickly fall back on another plant supplier, he will not be able to produce the product or to maintain the given quality in compliance with the respective requirements of the pharmacopoeia and/or other relevant specifications. Therefore, the possibility of a short-termed change of plant suppliers is needed on the one side due to the above mentioned unforeseeable events and on the other side this is even a measure of quality management. This situation leads to the practical fact that in the moment of dossier submission results of 2 batches of the same supplier, or even of one batch of a future replacement supplier do not exist. <u>b. Stock/Mother tincture</u> *In case of more than one manufacturer / supplier the analysis of batch results of one manufacturer / supplier is sufficient.* *Rationale:* *The results of batch analysis are exemplary. All manufacturers / suppliers of mother tinctures are listed in the dossier and deliver according to the same specification, in the majority of cases according HAB.* *Often, the purchased batches are really small, because the mother tinctures produced thereof are highly diluted, so that only a small amount of the mother tincture is required. Moreover, often rare plant species used in homeopathy. Unfavourable weather conditions can cause crop failures. All these conditions lead to frequent changes in the suppliers of the mother tinctures. In order to maintain the broad spectrum of homeopathic products, and therewith meet the demands of the homeopathic therapy, flexibility in the purchase of mother tinctures is absolutely necessary. At the time of submission it is infeasible to have*	

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		certificates of all possible manufacturer / supplier of mother tinctures. c. Dilutions **Comment:** We propose to delete this new requirement. **Rationale:** There is no legal basis for this requirement. Neither EU Directive 2001/83/EC Art. 15 nor EU Directive 2003/63/EC, which is the basis of the requirements for a CTD dossier, especially taking account of the specific manufacture and indicating the requirements for homeopathic medicinal products, foresee that analyses of batch results for intermediate potencies are submitted in a registration dossier. Also, according to the HMPWG guidance on module 3 of the homeopathic medicinal products dossier no analyses of batch results of intermediate dilutions are required in the dossier. Therefore, this demand should be deleted from the Q&A document. This requirement is a new requirement which after more than a decade of submitting CTD dossiers to European agencies has arisen now without an evident reason in terms of safety of the public. The production of intermediate dilutions is regulated by the homeopathic manufacturing methods and GMP. As a principle, dossiers should contain only relevant information as foreseen by relevant guidances to limit the workload for both, authorities and companies (e.g. by variations). Unnecessary expanding of information should be avoided in the frame of good regulatory praxis. *Requirement results of batch analyses not older than 3 years* **Comment:** This request should be erased. This request is regarded as not appropriate and not realistic due to the large order cycle of a particular stock. Also, batch analyses of raw materials and homeopathic stocks may be older than three years due to proven shelf life and rare production.	

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		Moreover, the legal basis of this request is unknown, even in other kind of medicinal products.	