11. November 2016
QUESTIONS AND ANSWERS DOCUMENT ON
HMPWG QUALITY OF HOMEOPATHIC MEDICINAL PRODUCT (Q 1-3)

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**

All instruction notes (in green) must be deleted before finalising the overview of comments.

Submission of comments on draft document

Table 1: Origin of comments

QUESTIONS AND ANSWERS DOCUMENT ON QUALITY OF HOMEOPATHIC MEDICINAL PRODUCT (Q 1-3) as released for public consultation on 11.11.2016 until 28.02.2017

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	The registration dossier, granted by the competent agency, is the model in which the production processes, specifications and quality control methods are fixed. Any batch documentation is given in as an example in the dossier. Appropriate specifications in the dossier together with the fulfilment of GACP / GMP requirements provide a sufficient framework to ensure the quality and safety of the medicinal product. Based on recent experiences with national registrations, the homeopathic manufacturers see the tendency that requirements made for marketing authorisation dossiers for new chemical entities or requirements for herbal medicinal products are imposed to dossiers for simplified registration of homeopathic medicinal products. This approach does not take into account the particularities of homeopathic manufacturing – in this context with the different steps between a raw material and a homeopathic active substance – and without taking into account that the legislator was conscious about these particularities resulting in the dossier requirements of Art. 15 of EU Directive 2001/83 as well as resulting in special considerations made in the EC regulation No 1234/2008 on variations with regard to variations of registrations of homeopathic medicinal products. Since decades homeopathic medicinal products are marketed and registered in the EU based on simplified dossiers. To our knowledge there was no case of potential risk to public safety because of the fact that the raw material supplier was not defined in the registration dossier or because of a change of a raw material supplier without notifying the regulatory agencies. Raw material suppliers are known and qualified by the homeopathic manufacturers according to company internal quality management systems. GMP inspectors have access to all these data.	*Leave blank (it will be completed by the Rapporteur).*

Interested party	Comment and Rationale	Outcome
	In 2015, ECHAMP sent its position paper on the topic of Question 2 and 3 to HMPWG. As we see now in the answers given by HMPWG on Questions 2 and 3, none of the concerns raised in the position paper was taken seriously by HMPWG.	
Add rows as appropriate.		

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
Question 2 Are suppliers of raw materials reported within the CTD dossier of HMP? Under which section? **Answer** Yes, according to the HMPWG guidance on Module 3 of HMP dossier, all suppliers of raw material have to be listed at the date of submission. Therefore, all information on suppliers should be clearly indicated: - in Module 1 under the section 2.5.5 "source/manufacturer of the	ECHAMP	Please amend the answers on the questions with the following proposals written in **bold** letters: The EMA reflection paper on "minor deviations" recommends "*… to minimize future occurrence of deviations that are caused by unnecessary detail. It should be noted that details that fall within the scope of GMP are inappropriate for inclusion in submissions…*". GMP documentation includes the name of the raw material supplier used as starting material for each active substance. In this context and with special emphasis on the particularities of homeopathic medicinal products with their high number of raw materials used in small amounts as starting material for homeopathic	

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raw material" - in Module 3 under the section 3.2.S.2 Manufacture / 3.2.S.2.1 Manufacturers		preparations, where the raw material is never the homeopathic active substance but various production steps take place between raw material and homeopathic potencies, the relevant questions are: - How meaningful is the name of the raw material supplier <u>in the registration dossier</u> for the assessment of the quality and safety of the product? - What is the impact of the change of a raw material supplier for the assessment of the quality and safety of the product? We think that the answers to these questions depend on the type of raw material used for homeopathic preparations. Raw material of <u>animal origin</u>: We agree to **indicate the suppliers for raw material of animal origin in the registration dossier.** In case of inorganic raw material of <u>chemical or mineral origin</u> we think that the naming of the supplier of the raw material should only take place considering as supplier the establishment in which the first GMP relevant step which allows to start with	

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		the homeopathic manufacturing method is performed. **Based on a case by case decision taking into consideration the production steps between raw material and starting material for the first homeopathic manufacturing step, we agree to indicate the starting material suppliers <u>exemplarily</u> for material of chemical origin.** Nevertheless, in the case of raw material of immediate <u>mineral origin</u> it is clear that the trader from whom the mineral is purchased has no influence at all on the quality of the mineral. Other information on the mineral, e.g. geographical origin, may have greater importance for its quality. So, the name of the raw material supplier in this case would only be a formality, in other words an administrative burden without pharmaceutical relevance. Therefore, we do think that **the naming of the supplier for a raw material of mineral origin in the registration dossier is not appropriate.** In the case of raw material of <u>herbal origin</u> an	

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		approach is needed which on one hand guarantees the consistency of product quality and on the other hand is a technically feasible. Most herbal raw materials used for homeopathic preparations are used in fresh state. This means it has to be processed within hours. If there is a lack of delivery from a given supplier replacement has to be found at once because the harvesting period is restricted, and storage – so to say use of a batch from another year - is not an option. Also, the quality of a plant material even from the same supplier can be completely different in two subsequent seasons. That means that the quality of the plant material is actually more influenced by natural variables and growing conditions than by the supplier. Some special plants used in homeopathy are fairly uncommon and have only a very limited availability on the market as they grow exclusively in a special geographic region or do not have any importance on the international markets for herbal products. For suppliers it is often not feasible to keep plants in their product range, if they are sold in a low frequency and in low amounts (e.g. 1-2 kg). It is therefore difficult to reach long-term engagements with these suppliers. This difficult situation is aggravated when crop	

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		failures occur e.g. due to climatic conditions which mean that prompt changes of the suppliers are essential within the short individual time frame of the harvesting season for that specific herbal material. It is a reality that flexibility for a variety of suppliers is especially important for the manufacturing of homeopathic active substances from herbal origin. This situation is not comparable to any other group of medicinal products, even not to herbal medicinal products. Therefore, we propose to **indicate the names of the suppliers for raw materials of herbal origin <u>exemplarily</u>, confirming that the quality management system in place guarantees consistent product quality independently from the supplier.** We also reference to the attached position paper with detailed rationale.	

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	ECHAMP	Comment According to the HMPWG document on Module 3 http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/HMPWG/2007_11_HMPWG_dossier_guidance_mod3.pdf the names and addresses of the raw material suppliers are to be given in section 3.2.S.2.3 Control of Materials, and not in 3.2.S.2.1. Manufacturer. We agree to the statement of this Q & A paper that the suitable place for this information in Module 3 is 3.2.S.2.1. Please adapt the Module 3 Guidance document accordingly. Rationale HMPWG Guidance and Q & A documents should not contain contradictory information.	

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Question 3 Do variation procedures apply to the suppliers of raw material? **Answer** Yes, changes affecting suppliers should be notified through variation procedures. For any modification regarding a supplier, the applicant should apply for a variation application, by analogy with variations procedures pursuant to Commission Regulation (EC) 1234/2008 as amended, as: - A.4. "Change in the name and/or address of a manufacturer ....". in case a change in the name/address of the supplier occurs; - B.I.a.1.z. "Change in a manufacturer of a starting material ...". The presentation as "unforeseen variation (z)" is needed since the category of this variation could be a type IB or type II on a case-by-case basis (e.g. depending on the nature of the raw material or in case of consequent substantial changes in	ECHAMP	EC regulation No 1234/2008 on variations to the terms of marketing authorisations states: *"...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 <u>should remain excluded from the scope of the Regulation</u>."* It is therefore not in the meaning of the legislation to establish rules which go beyond this Commission Regulation. In fact, in practice most national competent agencies are following this stipulation of the regulation and do have national rules in place for the handling of variations for registered homeopathic medicinal products which take into account this principle of proportionality. In consequence, the HMPWG answer concerns only marketing authorisations of homeopathic medicinal products. Please amend your answer accordingly. In consequence to our proposals on Question 2, the question if variations are applicable in the case of changes of raw material suppliers depend on the type of raw material applied: **In cases where the specific suppliers are defined in the registration dossier, such as for raw material of**	

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the manufacturing process).		**animal origin, a variation should be submitted.** Only qualified suppliers are accepted. Quality and safety of raw material from animal parts is ensured by complete documentation within a consistent quality assurance system of animal origin, if applicable breeding, slaughter, veterinary control and viral safety assessment. Processing is in line with GMP. Specifications of the raw material and homeopathic stocks have to be fulfilled for each batch in compliance with the registration dosser. Therefore the supplier of the animal material himself has no or a minimal impact on the quality, safety or efficacy of the medicinal product. **This means that in case of marketing authorization a notification procedure of type IA, and for simplified registrations a notification within 12 months following the implementation of the variation shall be submitted.** **For raw material of mineral origin naming of raw material supplier makes no sense towards the quality or safety of the medicinal product therefore the question of a variation is not applicable.** **As consequence** of our proposal **to name the suppliers of raw material of herbal origin exemplarily only, a variation in case of changes of the supplier is not applicable.** HMWPG proposes a variation type IB for changes of	

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		suppliers. Apart from the fact that this classification is only applicable for marketing authorisation procedures, the application of an IB variation is not feasible in daily practice in the case of herbal raw material. The reasons for this fact are given in the answer to Question 2. Since in most cases fresh plants and not dried drugs are used in homeopathic medicines it is not possible to wait for approval by the agency. In practice, if a given supplier is changed to another one new plant delivery is purchased by the MAH from a new supplier. The new supplier is qualified according to the company's quality management system which includes that GACP is fulfilled, the plant batch is only released if compliant with the specification in the registration dossier. If between plant supply and batch release a variation procedure including authorisation by the agencies (mostly more than one country is concerned) needs to be performed which means a process taking a time period of some months, the (fresh) plant would not be suitable for use anymore. Moreover, in case of rejection the harvest season would have passed to purchase another plant delivery from a third supplier. Also, since all processes and specifications remain the same, except the identity of the –qualified - supplier, the competent agency in its assessment of the variation would not do anything else than the manufacturer is doing according to his quality management and GMP requirements: check if the batch from the new supplier fulfils the existing specification.	

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		We kindly ask HMPWG to explain the reasons for their classification of Type IB or even Type II and why Type IA was not considered at all. Formal reasons would neither be in the meaning of the legislation to fulfil the principal of proportionality nor helpful to decrease the administrative burden on the European agencies and applicants in the view of the Commission's principal of Better Regulation. In this context, it is to mention that the fees which some competent agencies require are much higher than the yearly turnover of many products. In some countries the variation fees even equal the fees for a new marketing authorisation. Such fees combined with too detailed dossier requirements creating future variations are an administrative obstacle for the maintenance of homeopathic medicinal products and cannot be in the interest of any stakeholder .	

Annex:

- ECHAMP Position paper on raw material supplier