TEMPLATE FOR SUBMISSION OF COMMENTS

Submission of comments

2015-04-09
HMPWG – Points to consider on safety of homeopathic medicinal products from biological origin as released for public consultation

Table 1: Origin of comments

Organisation or individual	Contact details (e-mail address, telephone number, name of contact person)
ECHAMP E.E.I.G.	ECHAMP E.E.I.G. Rue Gray, 100 B-1040 Brussels Contact person: Amandine Oset Tel.: +32 2 649 94 40 e-mail: 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.

.

Please submit comments on each document separately.

Table 2: Comments

GENERAL COMMENTS ON DRAFT DOCUMENT

Interested party	Comment and Rationale	Outcome
ECHAMP	ECHAMP welcomes the revision of this PtC, especially the inclusion of the decision tree. Nevertheless in our opinion the following amendments are necessary.	
ECHAMP	This PtC should neither repeat nor exceed requirements given in the European Pharmacopoeia or relevant existing guidances for biological starting material.	
Add rows as appropriate.		

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
1 Introduction	ECHAMP	"*Regarding viral safety, viral validation studies related to the species of origin should be addressed."* Should be replaced by the following: "*Regarding viral safety,* ***a risk assessment figures out the necessity of viral validation studies. If a need is identified****, viral validation studies related to the species of origin should be addressed.*" Reason: The risk assessment is a strong tool to determine relevant risks and infectious agents, so it should be used to figure out the necessity of viral validation studies (see Ph. Eur.	*Comment was not accepted.*

Section number and heading	Interested party	Comment and Rationale	Outcome
		5.1.7.) Viral validation studies are not reasonable in every raw material.	
2. Scope Second sentence	ECHAMP	"*Their intended use may involve application to skin lesions and mucosa, therefore* ***safety measures must have equivalent strength as for parenteral forms****"* Should be replaced by the following: "*Their intended use may involve application to skin lesions and mucosa. Therefore* ***quality*** *measures* ***being in line with corresponding pharmacopoeial provisions related to Pharmaceutical Dosage Form in conjunction with Route of Administration are essential***." Reason: The text "equivalent strength as for parenteral forms" leaves it unclear, which concrete requirements are meant.	*Comment was not accepted.*
2 Scope Last sentence	ECHAMP	"*Concerning fungi, only macroscopic fungi are considered of plant origin and therefore fall outside this document – microscopic fungi are to be considered together as microscopic organisms and shall comply with this document."* Should be replaced by the following: "*Concerning fungi, only macroscopic fungi fall outside this document – microscopic fungi* ***and bacteria*** *shall comply with this document* ***with the exception of viral safety studies when this is justified by a risk assessment.****"* Reason: In general, microscopic fungi and bacteria are not	*Comment was not accepted.* *The first part of the sentence "Concerning fungi, only macroscopic fungi are considered of plant origin and therefore fall outside this document" was cancelled.*

Section number and heading	Interested party	Comment and Rationale	Outcome
		host cells for human- or animal pathogenic viruses because of differences in cell walls/membranes, specific receptors as well as enzymes for replication of nucleic acids and biosynthesis of viral proteins. During the fermentation process (production of microbial biomass in a closed system), the growing of human- or animal host cells is not possible because of extreme differences in growth time and culture media requirements. Note: In Ph. Eur., viral risks are only defined for “materials of human or animal origin” [Ph. Eur. 5.1.7: Viral Safety] and “for raw materials of zoological or human origin“ [Monograph Homeopathic preparations, Praeparationes homeopathicae, Ph. Eur.1038]. In these chapters microorganisms (microscopic fungi and bacteria) are not mentioned.	
4.1 Sourcing of biological starting material 4.1.1 Animal origin 4th indent	ECHAMP	*“The manufacturer of the stock or homeopathic medicinal product should ensure that animal materials come from documented and recorded sources and should perform regular audits of the suppliers. The supplier of animals should be subject to routine legal supervision by a competent veterinary authority. Any exception to these should be justified.“* Should be replaced by the following: ***“Applicants should provide for adequate information about the origin of the human or zoological raw material and the precautions taken to minimize the risk of contamination with micro organisms and compile a***	*Comment was not accepted.*

Section number and heading	Interested party	Comment and Rationale	Outcome
		comprehensive documentation in this regard. *"* Reason: The assumption that regular supplier audits all over the world could be performed is unrealistic. Usually it should suffice to submit information about the source of origin and the precautions taken to prevent or minimize contamination.	
4.1 Sourcing of biological starting material 4.1.1 Animal origin 7th indent.	ECHAMP	*"When animal species of higher order are sourced, a regular health monitoring system should be in place ensuring that the animals are subject to continuous and systematic veterinary and laboratory monitoring to ensure freedom from infectious agents. This should include constant monitoring of the animal herd by the veterinarian, routine pathological examination of randomly selected animals, serological analysis for a range of virus, bacteria and parasites and examination of the health status."* Should be replaced by the following: "*When **bred** animal species of higher order are sourced, a regular health monitoring system should be in place ensuring that the animals are subject to continuous and systematic veterinary and laboratory monitoring to ensure freedom from infectious agents, **which are classified as relevant by the risk assessment**. This should include monitoring of the animal herd by **a** veterinarian **within an overall risk assessment framework**, **reasonable** routine pathological examination of **fallen or diseased** animals and examination of the health status. Serological analysis for a range of virus, bacteria and parasites **classified as***	*Comment was not accepted.*

Section number and heading	Interested party	Comment and Rationale	Outcome
		relevant in view of risk assessment. Reason: "*When bred animal species of higher order are sourced…"* The mentioned point is not applicable to wild animals. "…*to ensure freedom from infectious agents,* ***which are classified as relevant by the risk assessment****."* *"****Serological analysis for a range of virus, bacteria and parasites, which are classified as relevant by the risk assessment*** *could be performed as appropriate* " Freedom from <u>any</u> infectious agent is not possible. The risk assessment is a strong tool to determine <u>relevant</u> infectious agents. *"…monitoring of the animal herd by a veterinarian service,…"* The former formulation sounds as if a single veterinarian is responsible for the monitoring. *"…reasonable … examination of fallen or diseased animals…"* Randomly selected animals is misleading because it includes healthy animals. In order to monitor infectious agents (which are classified as relevant by the risk assessment) it is more useful to subject selected fallen or diseased animals to pathological examination.	
4.1.1 Animal origin 8th indent.	ECHAMP	*"The manufacturer of the homeopathic medicinal product should ensure that newly emerging serious veterinary diseases in the animal species supplied, are immediately reported to the competent authorities. "* Should be deleted.	*Comment was not accepted.* *The sentence was changed to "Newly emerging serious veterinary diseases in the animal species supplied should be immediately reported to the competent authorities."*

Section number and heading	Interested party	Comment and Rationale	Outcome
		Reason: The obligation to report diseases is the governed by the diseases legislation. The notification of veterinary diseases does not fall under the pharmaceutical manufacturers' responsibility.	
4.1.1.1 Viral and microbial contamination	ECHAMP	Should be deleted. Reason: See chapter „general comments" See Ph. Eur.: General chapters 5.1.4, 2.6.12, 2.6.13, and 5.1.7 General chapter „Viral safety", referring to CPMP/BWP/268/95 as cited in the PtC	*Comment was not accepted.*
4.1.1.2 + 5.4 Transmission of TSE	ECHAMP	Should be deleted. Reason: See chapter „general comments" See Ph. Eur. Monograph 1483 Products with risk of … TSE; 5.2.8 General chapter: Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products = Note for Guidance: Minimising the risk ... EMA/410/01 rev. 3, final, 2011.	*Comment was not accepted.*
4.1.2 Medicinal products	ECHAMP	Should be deleted. Reason: See chapter „general comments"	*Comment was not accepted.*

Section number and heading	Interested party	Comment and Rationale	Outcome
		See Ph. Eur. Monograph 1038 Homoeopathic Preparations: „Raw materials comply with any requirements of the relevant monographs of the Ph. Eur." Therefore the monograph 0084 "Immunosera for human use, animal" is compulsory if the situation arises	
4.1.3 + 5.3 Human origin	ECHAMP	Should be deleted. Reason: See chapter „general comments" See Ph. Eur. Monograph 1038 Homoeopathic Preparations:"-for materials of human origin, the donor follows the recommendations applicable to human blood donors and to donated blood (see Human plasma for fractionation (0853), unless otherwise justified and authorized." Therefore the monograph 0853 is compulsory if the situation arises. The monograph explicitly quotes the Commission directives 2004/33/EC of 22 March 2004 implementing directive 2002/98/EC of the Council as regards certain technical requirements for blood and blood components.	*Comment was not accepted.*
4.1.4 Products derived from human, animal and microbial cell lines	ECHAMP	Should be deleted. Reason: The requirements of Note for Guidance CPMP/ICH/294/95 and corresponding guidelines are not applicable for homeopathic preparations currently on the market. We therefore see no need for such a section. However a risk assessment concerning the TSE risk is required anyhow.	*Comment was not accepted.*

Section number and heading	Interested party	Comment and Rationale	Outcome
5.1 First safe preparation 3rd indent.	ECHAMP.	*"For manufacturing of human and/or animal derived homeopathic medicinal products, obtained from both pathogenic and* ***non-pathogenic raw materials****, an adequate determination of what shall be considered as the first safe preparation, for each stock is essential. This determination ensures the correct definition of virus validation studies to be applied in order to evaluate putative infectivity. Comparable preparations – defined on the basis of zoological taxonomy of animal species and the type of tissue, the manufacturing method and the used vehicle and physical treatment of raw materials - can be used to perform virus validation studies* ***when healthy animal materials are used****."* In analogy to the first part of he section the part of the sentence saying …„*when healthy animal materials are used".* should be replaced by *„****when non-pathogenic (non-nosode) raw*** *materials are used*"- Reason: "*healthy animal materials*" is misleading because only animals alive can be health or not, materials, however, can only be free of pathogenic agents. The focus should lie on the material itself instead of the animal. Change of the wording in the last sentence of the cited chapter would lead to full congruency to the wording at the beginning.	*Comment was not accepted..*

Section number and heading	Interested party	Comment and Rationale	Outcome
5.2 Manufacture of the homeopathic medicinal product and first safe preparations 1st indent.	ECHAMP.	*"Dilutions alone and per se do not ensure biological safety of the first safe preparation."* Should be replaced by the following: „***For potencies up to D15/C8,*** *dilutions alone and per se do not ensure biological safety of the first safe preparation."* Reason: The study: Evaluation of the viral safety level for the manufacturing process of homeopathic pharmaceutical products from animal origin conducted by the Pasteur Institute in Paris demonstrated that the homeopathic potentisation procedure is reducing the concentration of four selected model viruses by the factor 10^{-1} per potency. Therefore a certain endpoint does exist, after which the concentration of potential pathogens is zero. Since the concentration of microbes may not exceed 10^{10}, in homeopathic potencies higher than D10 or C5 no microbes are present anymore. Even after including another safety margin, potencies higher than D12/C6 are free of any infectious agents. Consequently, virus validation studies are inappropriate for potencies above D12/C6.	*Comment was not accepted.* *The part "There should be strong assurance that potential adventitious agents have been effectively removed and/or inactivated during the manufacturing process. This should be demonstrated by performing appropriate validation studies or referring to appropriate homeopathic manufacturing procedures described by the European Pharmacopoeia or, in the absence thereof, by the Pharmacopoeias currently used officially in the Member States." was added.*
5.2 Manufacture of the homeopathic medicinal product and first safe preparation *1st indent.*	ECHAMP.	*"Virus validation studies should be performed on the production of the first safe preparation."* Should be replaced by the following: *"**A risk assessment, considering all factors that may influence the potential transmission of infectious agents should be carried out. If the assessment finds a need for further** Virus validation studies **these** should be performed on the production of the first safe preparation."* Reason: As stated in comment 1 'Introduction' the risk	*Comment was not accepted.*

Section number and heading	Interested party	Comment and Rationale	Outcome
		assessment is a strong tool to determine possible transmission of infectious agents. Viral validation studies are not useful in any case.	
5.5 Products derived from Biotechnology	ECHAMP.	Should be deleted. Reason: The requirements of Note for Guidance CPMP/ICH/139/95 and corresponding guidelines are not applicable for homeopathic preparations currently on the market. We therefore see no need for such a section.	*Comment was not accepted.*

Add rows as appropriate.			