8 November 2010
EMA/CHMP/BWP/551725/2010
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Procedural advice on the submission of variations for annual update of human influenza inactivated vaccines applications in the centralised procedure ' (EMA/CHMP/BWP/99698/2007 Rev. 1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EVM (European Vaccines Manufacturers)
2	
3	

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1. General comments – overview

Stakeholder no.	General comment	Outcome
1	**1. Flexibility regarding submission and review timelines for annual strain update as well as for variations critical for season supply.** EVM considers the draft guideline should be adapted to introduce flexibility regarding submission and review timelines for annual strain update as well as for variations critical for season supply. For example, following scenarios should be allowed on a case by case upon agreement with EMA: - The possibility to submit strain changes and any other variations outside the recommended deadlines when necessary (e.g. at any time during the month) and to have a guarantee for fast-track review and approval for all these variations (and not only for the strain update); - if some variations come late, the possibility of a parallel submission/review of the (technical) variations and the annual strain updates; - for the first year of Life Cycle, the possibility of a submission/review of the critical technical variations right after the CHMP opinion of the first Marketing Authorisation Application, without waiting for the official grant of the formal Marketing Authorisation (Commission Decision). **2. Use Core SPC and PIL of Trivalent Influenza Vaccines for CP-authorised influenza vaccines.** Although it is not within the scope of the guideline, EVM would like to propose that the Core SPC and Package Leaflet for Trivalent Influenza Vaccines could be used for CP-authorised influenza vaccines. The	1. Partly accepted. - The Agency publishes every year a recommended target annual deadline. This is not an absolute deadline and Companies are recommended to discuss with the PTL their needs. For all other variations Marketing Authorisation Holders should comply with published deadlines. Exceptions can be discussed/agreed on a case-by-case basis with Rapporteurs and EMA. There is no need to revise the text of the guideline. -Parallel submissions of other (technical) variations are strongly discouraged. -The official submission of variations before the issue of Commission Decision is not possible. 2. Partly accepted. The core SPC for trivalent influenza vaccines (issued by the CMDh) is already followed by the Marketing Authorisation Holders and this is currently an acceptable approach for

Stakeholder no.	General comment	Outcome
	resulting harmonisation would greatly simplify the management of these texts by manufacturers having both CP and MRP-authorised influenza vaccines. **3. Application of EMA expedited process for issuing Certificates of Medicinal Products (CPP) to change the vaccine strain composition in accordance to the Southern Hemisphere recommendations** Today, the EMA has an expedited process in place for issuing CPPs. However, this is only applicable to variations for the strain composition of the flu vaccines for Northern Hemisphere. Indeed, there is no formal variation submission foreseen in Europe to change the vaccine strain composition in accordance to the Southern Hemisphere recommendations. The timely availability of Certificates of Medicinal Products (CPP) is critical for worldwide supply in both hemispheres. Relevant CPPs covering Southern Hemisphere are critical for the supply in a large number of international countries. EVM Members would like to clarify whether and how the EMA process for issuing relevant CPPs could apply in such cases.	vaccines authorised via the centralised procedure (the core SPC is listed in the reference section). There is no need to revise the text of the guideline. 3. Not accepted. The Agency can only issue Certificates of Medicinal Products for centrally authorised products.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 144	1	**Comment:** EVM understands that, according to the standard procedure/timelines, any technical variation critical for the season supply (e.g. changes in manufacturing processes, sites for ancillary manufacturing activities such as filling, packaging, etc.) cannot be submitted before the initial MA is granted, and will have to be approved before submitting the strain update variation. The time window between the expected MA approval and the start of the vaccination season will therefore be quite narrow, and the probability of having the necessary variations and the annual strain update approved in due time to be ready for the season supply appears extremely small if the "standard" review procedures/timetables are to be followed. A greater flexibility should be foreseen to allow smooth and timely review and approvals of the modifications needed before the launch and subsequent season supplies, hence an access to the vaccine without any delay for the patient. **Proposed change (if any):** EVM would like to add the following paragraph below the flow chart: "A flexible approach to handle the strain change variations (and other related critical variations for seasonal influenza vaccines) can be agreed on a case	Partly accepted. See also outcome to general comment 1. - Official submission of variations before the Commission Decision is not legally possible. For submission of the annual strain update (and other technical variations) applicants are advised to discuss any deviations from official timelines with EMA and Rapporteurs well in advance of the submissions. **Proposed wording added at line 144:** "MAHs are advised to liaise with the Agency (i.e. PTL and Rapporteur) in advance of the submission of the variation, especially in view of possible deviation from the recommended deadlines."

		by case with the Agency, depending on the availability of the relevant data and provided a valid justification (e.g. related to public health needs) is submitted by the applicant. The applicant is advised to liaise with the Agency (i.e. PTL and Rapporteur) in advance of the submission of the variation."	
Line 145 (Flow chart fast-track procedure)	1	**Comment:** The fast-track procedure should allow submission of strain update variations and any other critical variations outside the Agency published submission deadline when necessary (to be discussed with PTL and Rapporteur). **Proposed change (if any):** EVM suggest adding a footnote to the flow-chart: "Submission Variation application (Quality)(the Agency to publish yearly submission deadlines*)" * When necessary, submission of strain update variations and any other critical variations outside the Agency published submission deadlines can be agreed with PTL and Rapporteur.	Partly accepted. The Agency recommends every year a target deadline. This is not an absolute deadline and Marketing Authorisation Holders are advised to discuss any deviations with the PTL and the Rapporteurs. For all other variations Marketing Authorisation Holders should comply with published deadlines. Exceptions can be discussed/agreed with Rapporteurs and EMA on a case-by-case basis. Submissions of other (technical) variations in parallel to the annual strain update are strongly discouraged. See also the outcome to the comment above (line 144). No further change to the wording of the guideline is deemed necessary.
Lines 148-149	1	"Only changes related to the new strains used may be introduced. No other changes are allowed to be processed via the 'fast track' procedure." **Comment:** It is essential that the procedure also allows for a fast-	Not accepted. The fast track procedure is specific for annual strain updates and cannot include other technical variations. Those variations have to be submitted as separate variations. Deviations from the published timetables for these variations will need to be

		track processing of variations that are critical for the season supply, and which are submitted either prior to the strain update or together. **Proposed change (if any):** "In principle, only changes related to the new strains used may be introduced. No other changes are allowed to be processed via the 'fast track' procedure except for variations that are critical for season supply. This should be agreed on a case by case with EMA (PTL and Rapporteur)."	discussed on a case-by-case basis (see outcome above). Please note that, as stated above, submissions of other (technical) variations in parallel to the annual strain update are strongly discouraged.
Line 161	1	**Comment:** Due to dependence from WHO labs MAHs cannot guarantee submission of all data at the published submission date. Therefore, EVM would recommend introducing some flexibility. **Proposed change (if any):** EVM would like to add the following paragraph: "MAHs are requested to submit the full quality documentation by the day published every year together with the EU Annual strain(s) recommendations. It is however recognised that MAHs are dependent on the provision of SRD reagents by WHO collaboration centers (e.g. NIBSC). In these exceptional circumstances, due to the nature of Annual Updates, there should be a possibility to submit limited additional data (e.g. data depending on the SRD-reagents and SRD calibration values) after the cut-off date."	Partly accepted. The proposed approach is discouraged. However, exceptions based on a valid justification from the Marketing Authorisation Holder can be discussed/agreed with EMA and Rapporteurs in advance of the submission. There is no need to revise the text of the guideline.
Line 166	1	"**1.1** Comprehensive Table of Contents (not required if	Not accepted.

		submitted in eCTD format)" **Comment**: The provision of a comprehensive Table of Contents is a requirement associated with paper application. This is not necessary for eCTD submissions. **Proposed change (if any):** Delete this line. ~~"**1.1** Comprehensive Table of Contents (not required if submitted in eCTD format)"~~	The existing wording already states that a Table of Contents is not needed for eCTD submissions.
Line 185	1	"**2.1** CTD Table of Contents (Module 2 – 3)" **Comment**: The provision of a comprehensive Table of Contents is a requirement associated with paper application. This is not necessary for eCTD submissions. **Proposed change (if any):** Delete this line. ~~" **2.1** CTD Table of Contents (Module 2 – 3) "~~	Partly accepted. To harmonise the wording of the guideline the following modification is introduced: "**2.1** CTD Table of Contents (Module 2 – 3) (not required if submitted in eCTD format)"
Lines 197 - 207	1	"**3.2.S.2** Manufacture - seed lots: history: - passage level - characterisation of Haemagglutinin and Neuraminidase - analytical protocols (including test results on seed lots)* - monovalent bulks: - manufacturing process strain specific changes - validation of critical manufacturing steps (new strain) 1. inactivation	Accepted.

		2. splitting efficiency **3.2.S.2.3** Control of Materials **3.2.S.2.4** Control of Critical Steps and Intermediates" **Comment**: 1. EMA agreed with one of the current marketing authorisation holders to provide the seed lot history data in section 3.2.S.2.3 Control of materials. 2. EMA agreed to provide the data on Monovalent bulks in section 3.2.S.2.5 **Proposed change (if any):** EVM would suggest moving information on seed lots into section 3.2.S.2.3. and moving information on monovalent bulks into section 3.2.S.2.5 "**3.2.S.2** Manufacture ~~- seed lots: history:~~ ~~- passage level~~ ~~- characterisation of Haemagglutinin and Neuraminidase~~ ~~- analytical protocols (including test results on seed lots)*~~ ~~- monovalent bulks:~~ ~~- manufacturing process strain specific changes~~ ~~- validation of critical manufacturing steps (new strain)~~ ~~1. inactivation~~ ~~2. splitting efficiency~~ **3.2.S.2.3** Control of Materials - seed lots: history: - passage level - characterisation of Haemagglutinin and Neuraminidase - analytical protocols (including test results on seed	

		lots)*" **3.2.S.2.4** Control of Critical Steps and Intermediates **3.2.S.2.5** Process validation monovalent bulks: - manufacturing process strain specific changes - validation of critical manufacturing steps (new strain) 1. inactivation 2. splitting efficiency	
Lines 225 - 226	1	"**3.2.P.5.3** Validation of analytical procedures; validation of SRD test for new strains (either using trivalent bulk or drug product)" **Comment**: EVM considers that the SRD test for new strain on the trivalent bulk or the drug product has little added value, knowing that this is already done on monovalent bulks. If the EMA keeps this requirement, this might affect manufacturers' ability to provide the data in time to submit this variation for review during the July CHMP meeting. A written procedure will have to be initiated to evaluate the variation application. A validation on the trivalent bulk or the drug product can only be initiated after production of a first clinical batch, the availability of the NIBSC reagent and the validation of the SRD test on monovalent bulks. Proposed change (if any): EVM would propose to only request validation of the SRD test on monovalent bulks and suppress this requirement for trivalent bulk.	Not accepted. The validation of the SRD test should be carried out on trivalent bulk or drug product, including adjuvant in case of adjuvanted vaccines, in order to cover any potential interaction between the strains that may impact the SRD test. This approach is considered to generate the most accurate and valuable information.

		~~"**3.2.P.5.3** Validation of analytical procedures; validation of SRD test for new strains (either using trivalent bulk or drug product)"~~	
Line 240	1	**"1.1** Comprehensive Table of Contents" **Comment**: The provision of a comprehensive Table of Contents is a requirement associated with paper application. This is not necessary for eCTD submissions. **Proposed change (if any):** Delete this line. ~~**" 1.1** Comprehensive Table of Contents "~~	Partly accepted. To harmonise the wording of the guideline the following modification is introduced: **"1.1** Comprehensive Table of Contents (not required if submitted in eCTD format)"
Lines 241-242	1	**"1.2** Revised Application Form (from European Variation Application Form as published in the NTA, Volume 2C)" **Comment:** With the current version of the variation application form, there will be no update of the application form associated with the clinical submission with the current version of the variation compared to the application form in the quality submission. A resubmission would not have any added value, especially as the clinical submission is a follow-up to complete the initial quality submission. **Proposed change (if any):** Delete this line. ~~**"1.2** Revised Application Form (from European Variation Application Form as published in the NTA, Volume 2C)"~~	Partly accepted. The following modification is introduced: **"1.2** Revised Application Form (~~from European Variation Application Form as published in the NTA, Volume 2C~~ if not revised a cross-reference in the cover letter to the previously submitted Application form is sufficient) "
Lines 243 - 248	1	**"1.3** Product Information **1.3.1** SPC, Labelling and Package Leaflet	Not accepted.

		Note: No product information is expected to be submitted; if so, exceptionally details of the proposed changes and their justification should be clearly details with their rational in the cover letter and the clinical overview." **Comment**: the note on this section states that no product information is expected to be submitted during the second step. If Sections 1.3 and 1.3.1 are listed in the application contents this could result in validation issues if the list is used for dossier verification by the EMA. **Proposed change (if any):** ~~**"1.3** Product Information~~ ~~**1.3.1** SPC, Labelling and Package Leaflet~~ **Note: No product information is expected to be submitted; if so, exceptionally details of the proposed changes and their justification should be clearly details with their rational in the cover letter and the clinical overview.**"	The existing text is sufficiently clear.
Line 255	1	**"2.1** CTD Table of Contents (Module 2 – 5)" **Comment**: The provision of a comprehensive Table of Contents is a requirement associated with paper application. This is not necessary for eCTD submissions. **Proposed change (if any):** Delete this line. ~~**" 2.1** CTD Table of Contents (Module 2 – 5) "~~	Partly accepted. To harmonise the wording of the guideline the following modification is introduced: **"2.1** CTD Table of Contents (Module 2 – 3) (not required if submitted in eCTD format)"

Line 257	1	"**2.3** Quality Overall Summary (revised to first addendum to Quality Overall Summary, in case needed)" **Comment**: No information on Quality is expected to be submitted during the second step. If Section 2.3 is listed in the application contents this could result in validation issues if the list is used for dossier verification by the EMA. **Proposed change (if any):** Delete this line. ~~"**2.3** Quality Overall Summary (revised to first addendum to Quality Overall Summary, in case needed)~~ Note: No Quality Overall Summary is expected to be submitted. A Quality Overall Summary will be submitted only in case of submission of stability data. "	Not accepted. The current text is sufficiently clear.
Line 267	1	"**5.1** Table of Contents of Module 5 " **Comment**: The provision of a comprehensive Table of Contents is a requirement associated with paper application. This is not necessary for eCTD submissions. **Proposed change (if any):** Delete this line. ~~" **5.1** Table of Contents of Module 5 "~~	Partly accepted. To harmonise the wording of the guideline the following modification is introduced: "**5.1** Table of Contents of Module 5 (not required if submitted in eCTD format)"

Lines 281 - 284	1	**"Finally, applicants are encouraged to include the following PSURs in the clinical data package:** **PSUR covering the period 1 September- 30 April of the previous season** **PSUR covering the period 1 May - 31 August of the last but one season. "** **Comment**: EVM is surprised by this statement as the PSURs requested here are already provided prior to the submission of the clinical part of the variation. Their submission is mandatory within 2 months of the end of the period covered. A re-submission in the clinical application would not be in line with the management principle of the eCTD, which does not allow for duplicate submissions of the same information.	Accepted. The following clarification will be added: **Finally, applicants are encouraged to include the following PSURs in the clinical data package** *(for eCTD submissions, a cross reference to the eCTD sequences of the previous PSUR submissions is sufficient)*: • **PSUR covering the period 1 September- 30 April of the previous season** • **PSUR covering the period 1 May - 31 August of the last but one season.** "