01 June 2015
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Overview of comments on 'Guideline on influenza vaccines – submission and procedural requirements' (EMA/56793/2014)

Comments from:

Name of organisation or individual
Vaccines Europe

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Vaccines Europe thanks EMA for the opportunity to provide comments on the EMA draft Guidance on 'Guideline on influenza vaccines – submission and procedural requirements' (EMA/56793/2014) Our general comments: • Requirements in the 'Guideline on influenza vaccines – submission and procedural requirements' should be aligned with the 'Guideline on Influenza Vaccines – Quality Module'. • Need to clarify whether the quality supporting documentation described in Annex I to be provided in case of seasonal strain change would also apply to zoonotic and pandemic strain change. Due to the numerous different types of Influenza, seasonal-pandemic, but also, whole virion, LAIV, subunit, adjuvanted etc. and manufactured using new technologies, a general text followed by specific annexes to the various products would help to make the guideline more easy to understand and to respect	Section 3.2.S.3 have been aligned in Annex I Quality requirements described in Annex I apply only in the framework of the annual seasonal update.

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	Also, as this procedural guideline will be applicable to influenza vaccines in the centralised procedure, as defined in the scope, Vaccines Europe wonders whether CMDh will have a similar guidance for seasonal influenza vaccines in the MRP/DCP procedure, for manufacturers using this procedure.	CMDh has agreed to not develop a similar guidance for nationally authorised medicinal products besides the already existing CMDh BPG Chapter 9 (annual strain update). The proposed EMA guidance is besides the annual strain update focused on specific procedures mainly applicable for centrally authorised medicinal products. The changes in the CMDh will focus on adaption to the dossier requirements of CMDh BPG (Chapter 9) – see published CMDh minutes October 2014

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 88-89 ***Seasonal*** *4.1.1. Requirements for MAA*		Comment: It is written that for "reverse genetics, the use of centralised procedure is mandatory". Vaccines Europe would like to emphasise that most of the seasonal influenza vaccines are registered by MRP/DCP, and that with the current law the limitation to CP in case of reverse genetics strain would therefore impact the timely availability of most of the vaccines	This paragraph applies to new Marketing Authorisation Application. MAHs are invited to liaise with the relevant competent authorities in case reverse genetic technics are intended to be used for existing national MAs.
Line 117 ***Seasonal*** *4.1.2. Requirements for applications to change vaccine composition (seasonal strain update)*		Comment: Vaccines Europe proposes to add one paragraph stating that in case of no strain change, the variation application will be submitted as a Type IB variation	Section 4.1.2 and more generally the aim of the guideline is to describe the requirements and procedure in case of change to vaccine composition. Where no change to the strain is foreseen but only changes in labelling, the MAHs are invited to discuss the appropriate procedure with the competent authorities, e.g. in the framework of the annual BWP Ad Hoc Influenza Working Group meeting
Lines 128 – 129		Comment: Sentence to be modified by removing "Union". Proposed change: The scope of the variation to be mentioned in the variation application form is "annual update of Union human	Comment accepted. 'Union' to be deleted.

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		influenza vaccine strain(s)".	
Line 133-136 ***Seasonal***		Vaccines Europe has some comments concerning the "two-step" approach procedure described for seasonal strain update, as follows:	
		Comment #1: In the Reg. COMMISSION REGULATION (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products a two steps procedure for the annual update of the seasonal Influenza vaccines was described (quality dossier review and further submission of clinical dossier). However, the Regulation 1234/2008 of 24 November 2008 has been amended by Regulation n° 712/ 2012 (the name of the 2008 Regulation has been unchanged, but this version is now applicable). In this Regulation, amended, a one step procedure is described with the possibility to the agency to request additional data to complete its assessment in case of need. Concern raised: Vaccines Europe would like to emphasise that the "two-step" procedure is not in line with the amendment of new regulation which describes only one step procedure as mentioned above. Clarification on the 2 steps procedure described in the document: - In the past (from 1998 till 2013), a two steps procedure has	Comment 1: Article 18 of Regulation (EC) No 1234/2008 as amended by Regulation (EC) No 712/2012 was implemented in the '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. 2 which is in force since May 2013. The proposed document is based on this procedural advice. Whilst the procedure may lead to an opinion within 45 days ('first step') from the validation, additional data may be requested ('second step'), in line with Regulation (EC) No 712/2012. Article 18 was revised in Regulation (EC) No 712/2012 for adding flexibility to the annual update procedure (timelines were too rigid leading to non-compliance by MAHs) and to speed up the procedure where possible. EMA and EC interact well in advance of the variation submission for the annual update ; MAHs are advised to liaise in advance with the Agency to discuss their submissions (in particular where deviations with the

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		been used due to obligation to submit a quality dossier and later the clinical trial update part. - With the new European Commission regulation, a single one step procedure is now described. Please note that for the CP, previously the EC was informed about the future approval of the annual update after the first step (quality) in order to be able to anticipate the preparation of the EC decision that was thus granted very quickly after step two. With the one single step described in the current EC regulation, the EC is potentially alerted about the annual update at the end of the assessment only which means no potential anticipation and potential delay on the publication of the final EC decision (officially two months after adoption of the CHMP opinion). Vaccines Europe proposes that EMA could inform in advance the EC about potential future approval of the annual update (for example at the beginning of the procedure) in order to give the opportunity to the Commission to anticipate the preparation of EC decision. Comment #2: - Vaccines Europe would appreciate some clarification on what kind of additional data can be requested, with some concrete examples - In very exceptional cases where EMA would ask for clinical	standard requirements/timeline for submission are intended) to provide the most updated information. This allows streamlining the procedure, in particular the decision-making process. Comment 2: Examples of the type of additional data that could be requested will be clarified in the the non-clinical/clinical module. The EMA acknowledges the need for MAHs to know as soon as possible whether additional clinical data are required. The EMA whenever possible will communicate information on the annual update prior to the submission of the annual update application (e.g. during the 'annual strain selection' meeting with stakeholders or pre-submission meeting,…) Please also refer to 'the overview of comments' for EMA/CHMP/BWP/99698/2007 Rev. 2 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142545.pdf The request for supplementary information is intended to provide further clarification/data within the first step of the procedure in an attempt to adopt an opinion

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		trial data as « additional data »: EMA would need to inform the manufacturers very early, with a clear rationale - Vaccines Europe would like EMA to clarify the differences between "request for additional data", and "request for supplementary information (RSI)" Comment #3: Sentence to be modified by replacing "of" by "after" and by adding a dot. Proposed change: • within 45 days ~~of~~ after the validation, the CHMP adopts an opinion to approve or refuse the variation application or CHMP suspends the procedure (clock stop) by adopting a request for additional data. A request for supplementary information (RSI) without suspending the procedure may be issued at D30.	within 45 days from the validation. If substantial additional data is required or if the applicant needs additional time to answer to the questions, a request for additional data suspending the active time of the procedure ('clock-stop') will be adopted. Comment 3: Comment accepted.
Line 146		Comment: In the flow chart it states that D30 would be ideally by July CHMP** if possible. Proposed change: To add some flexibility: ** if possible or in another ad hoc session of CHMP. - Other comment: there is a discrepancy between the flow	Comment 1: Comment rejected. Due to time schedule and the fact that no plenary session in August, the proposed wording is not retained. Comment 2: comment rejected Line 133: the CHMP may adopt an opinion within 45

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		chart and text on the procedure, with respect to D30: ○ (the text mentions D30 for RSI only, and the flow chart mentions D30 for CHMP Opinion or RSI or request for additional data)	days. An opinion can therefore be adopted at D30.
Line 187-188 **Pandemic** 4.3.1. Marketing authorisation granted prior to the recognition of a pandemic situation ('pandemic preparedness vaccine')		Comment: It is indicated that « the marketing authorisation application should be supported by a 'core pandemic dossier' including data on the potential pandemic strain(s)". Vaccines Europe would like to have clarification whether it means that such core dossier can include multiple sub-type strain information (e.g. data from H7N9 on top of H5)?	Data on other subtypes may be submitted to support the potential pandemic strain of the dossier if justified. This may be relevant, e.g. for the manufacturing development to gather experience and provide insight into the effect of strain-specific process adaptations.
Line 193-195		Comment: It is indicated that « 'Pandemic preparedness vaccines' are indicated for immunization against potential pandemic strain(s) once an official pandemic declaration in the EU has been recognized and after that the variation to include the declared pandemic strain has been authorised".	A link to the official declaration of a pandemic is needed to apply the derogative framework foreseen in article 21 of Regulation (EC) No 1234/2008.

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		Proposed change: Vaccines Europe suggests adding a paragraph related to the indication on the pandemic strain variation itself, to not restrict it for usage in a officially declared pandemic, but provide broader indication (« Prophylaxis of influenza caused by XXX virus"), in order to allow further use of vaccine regardless of whether or not the current WHO pandemic phase is maintained or altered • This is based on past experience where H1N1 licenses were switched to normal licenses with broad indication at the end of official pandemic phase. The approach proposed by Vaccines Europe would give flexibility if needed for usage after pandemic (in Europe but also to support as source country usage in International countries)	
Line 229-231 **Pandemic** 4.3.1.2. Requirements for applications to change vaccine composition (pandemic strain change) during a		Comment: It is indicated that « As per Article 21 of Regulation (EC) No 1234/2008, it may be exceptionally and temporarily acceptable that certain non-clinical or clinical data are missing. In the latter, the MAH will have to submit the missing non-clinical and clinical data within the time limit set in the marketing authorisation." Proposed change: Vaccines Europe suggests adding a distinction whether it is same strain subtype or not. A paragraph should be added that in case of same strain subtype, technical information only should be sufficient.	Wording to be revised to state that the missing data concerns the strain subject of the pandemic strain change. *"As per Article 21 of Regulation (EC) No 1234/2008, it may be exceptionally and temporarily acceptable that certain non-clinical or clinical data on the declared pandemic strain are missing. In the latter, the MAH will have to submit the missing non-clinical and clinical data within the time limit set in the marketing authorisation."*

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pandemic situation			In case of submission the same strain subtype, data to be submitted may be broader than technical information only, the comment is therefore rejected. This Module has to be read in conjunction with the Quality Module and the Clinical Module where the scientific requirements are defined.
Line 278		Comment: Numbering of the annex (Annex 1) to be aligned with the text how it is referenced in section 4.1.2.2 (Annex I) Proposed change: 5. Annex I- Seasonal strain change ("Annual update")	Comment accepted.
Line 285 – 289		Comment #1: Propose to add "unless justified". Comment #2: Potential flexibility on the submission date is proposed in case of need. Proposed change: Vaccines Europe proposes updated paragraph wording as follows: "In case of a type II variation to be used, the variation should be submitted as stated in the guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and should contain the documentation described below (unless justified), if possible by the Agency recommended target annual deadline for centralised procedure, which will be published every year together	Comment rejected - proposal outside the scope of this Annex. In case of potential deviation, applicant is invited to liaise in advance with the Agency (lines 144-145).

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		with the EU Annual strain(s) recommendation. If not possible to submit at recommended target annual deadline, EMA and the company will discuss to find an alternative for submission date."	
Line 293-294		Comment: Reports are not always provided but a comprehensive set of data in the narrative section is provided. In addition, some sections may not be necessary. Vaccines Europe proposes to re-introduce the respective sentence from the previous guideline dated April 2013. Proposed change: Any absence of a study/test data requires a justification in the appropriate summary/overview. All sections not felt to be necessary should however be justified adequately in summary/overview.	Paragraph reworded as follows: *"Any absence of a study/test ~~report~~ requires a justification in the appropriate summary/overview."*
Line 295		Comment#1: The submission concerns also the administrative data in addition to quality data Comment#2: A single one step procedure (see Comment #1 for lines 133-136) Proposed change: 5.1.1 ~~First step submission – quality~~ Submission of the variation application 5.1.2 ~~Second step submission –additional data requested~~ Submission	Comment partially agreed. Titles reworded: *"5.1.1 First step ~~submission – quality~~ Submission of the application* *5.1.2 Second step ~~submission –additional data requested~~ Submission of additional data (if requested)"*

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		of additional data (if requested)	
Line 292 - 298		Comment: Line 293: Any absence of a study/test report requires a justification in the appropriate summary/overview. Lines 297-298: Any deviation (absence of data or additional data) should be justified and discussed with the competent authorities before the submission of the application. Vaccines Europe requests more clarification on the requirement – do we have to discuss with the authorities first and then write the agreed justification in the summary/overview? Proposed change: for lines 297-298 Any deviation (absence of data or additional data) should be justified and discussed, if required, with the competent authorities before the submission of the application.	This section has to be read in combination with lines 144-145. MAHs are advised to liaise in advance of the submission of the annual update. At this occasion, deviations to the standards requirements should be discussed. *"Any deviation (absence of data or additional data) should be justified in the appropriate summary/overview and should be discussed with the competent authorities before the submission of the application."*
Line 301, 311, 365 and 370		Comment: eCTD format being now mandatory for centrally authorised products, the tables of contents do not need to be mentioned as required. Proposed change: Delete the lines 301, 311, 365 and 370	Comment rejected. Paper application could still be acceptable in specific circumstances.
Line 312		Comment: Addition of '(update or addendum to "previous" CTD	Comment accepted. Wording revised accordingly.

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		Introduction)' is proposed for consistency and clarity Proposed change: 2.2 CTD Introduction (update or addendum to "previous" CTD Introduction)	
Line 313		Comment: for consistency with the European Commission Guidelines in variations (2013/c 223/01) Proposed change: 2.3 Quality Overall Summary (update or addendum to "previous" Quality Overall Summary)	Comment accepted. Wording revised accordingly.
Line 320-322		Comment #1: In the Quality Guideline (see 3.1.1.2.1.5 Characterisation) an additional section is requested for the Annual Update Package (3.2.S.3). This is missing in the Draft 'Guideline on influenza vaccines – submission and procedural requirements' Guideline. Note: the information on the occurrence of protein aggregation, particle size distribution etc. is already presented in 3.2.S.3 in the submission file. Comment #2: Requirements in the fast-track guideline should be aligned with the quality module guideline in respect to the	Section 3.2.S.3 has been aligned with Quality Module. Comment accepted. Wording revised accordingly.

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		requirement for the submission of the characterization data during Annual Update. Comment/Proposed change: Vaccines Europe proposes that lines 321 & 322 (passage level, characterisation of Haemagglutinin and Neuraminidase) are formatted as 2 sub-bullet points to line 320 (seed lot: history).	
Line 344 - 346		Comment: The request for Certificate of Analysis of clinical batches are in contradiction with Line 379: *In principle, there is no need to provide annual clinical data…. Proposed change: 3.2.P.2.2.1 Pharmaceutical development: formulation development (actual formula (new season's strains). Rest of the sentence: … and Certificate of Analysis of batch(es) used in clinical trial(s) when available (either in quality or in clinical submission) to be deleted.	Reworded for clarification *"if clinical trial(s) has been requested to support the 'annual update', certificate of analysis of batch(es) used in the studies ~~(either in quality or clinical submission)~~"*
Line 360		Comment: A single one step procedure (see Comment #1 for lines 133-136) Proposed change: 5.1.2. Submission of additional data, if requested	
Line 361-362		Comment: It should be clearly stated here that additional submission of data is needed only if requested.	Comment accepted. Reworded section:

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		Proposed change: When additional data are requested, the relevant sections of the CTD variation application should be submitted depending on the type of additional data submitted.	*"5.1.2 Second step ~~submission - additional data requested~~ Submission of additional data (if requested)"* *When additional data are requested, the relevant sections of the CTD variation application should be submitted depending on the type of additional data submitted."*
Line 371		Comment: The below changed is proposed for consistency and clarity Proposed change: 2.2 CTD Introduction (update or addendum to "previous" CTD Introduction), if appropriate	Comment accepted. Wording revised accordingly.
Line 372		Comment: The below changed is proposed for consistency and clarity Proposed change: 2.3 Quality Overall Summary (revised to first addendum update or addendum to "previous" Quality Overall Summary), if appropriate	Comment accepted. Wording revised accordingly.
Line 374 – 375		Comment #1: Vaccines Europe proposes to specify that CTD sections 2.5 (Clinical Overview) and 2.7 (Clinical Summary) are not required in principle by adding an asterisk to refer to the note given in lines 379 – 384 at the end of the guideline. Also, the below addition is proposed for consistency and clarity	Comment rejected. It is already highlighted in 5.1.2 and lines 130-132 that additional data may not be required. Reworded sentences: *"2.5 Clinical Overview (update or addendum to the*

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		Proposed change: 2.5 Clinical Overview* (update or addendum to the previous Clinical Overview), if appropriate (Normally not appropriate) 2.7 Clinical Summary* (update or addendum to the previous Clinical Summary), if appropriate Comment: for consistency and clarity (same remark)	*previous Clinical Overview), if appropriate* *2.7 Clinical Summary (update or addendum to the previous Clinical Summary), if appropriate"*
Line 377-378		Comment: No non-clinical data should be requested during the annual update variation. This is in line with the draft clinical and non-clinical EMA influenza guideline, which mentions clearly that non-clinical studies are not required for applications to change vaccine composition for seasonal influenza vaccines. Proposed change: Module 3, 4, 5 Relevant sections of Module 3 and 5 of the CTD variation application should be submitted if additional data on quality, ~~non-clinical~~ and/or clinical data were requested.	Comment rejected. Whilst in principle non-clinical data is not expected to support the seasonal strain update, it cannot be excluded that in particular situations additional data such as non-clinical data may be required. Please see above comment on the type of additional data to be provided.
Lines 380-381		It should be specified that product –specific effectiveness studies and enhanced safety surveillance data are to be submitted as commitments to seasonal annual strain variation (meaning strain update post-approval commitments)	Comment rejected - to be clarified in the non-clinical/clinical module.