21 July 2011
EMA/CHMP/BWP/367594/2011
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Annex I. variation application(s) content for live attenuated influenza vaccines ' (EMA/CHMP/BWP/577998/2010)

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

Stakeholder no.	Name of organisation or individual
1	MedImmune

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1. General comments - overview

Stakeholder number	General comment (if any)	Outcome (if applicable)

1	The main guidance allows for a two-tiered review process, with submission of clinical data occurring at Day 57 of the process. MedImmune proposes a similar two-tiered review process for LAIV as follows:
	o Tier 1:
	  o All CMC data with the exception of MVS genetic stability, drug product thermal stability
	  o Labelling
	o Tier 2:
	  o Nonclinical data
	  o MVS genetic stability
	  o Drug product thermal stability data
		This approach is acceptable for the quality package. Taking into account that it will take some time to generate the data of genetic and thermal stability.
		
		No comments can be made on nonclinical/clinical requirements as, thus far, no conclusion has been reached by VWP/CHMP on the requirement for clinical data.

2. Specific comments on text

Line numbers of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 36	1	Comment: Word missing Proposed change (if any): Add “on” between ‘published’ and ‘the’ so phrase reads “...as published on the Agency website.”	The correction has been included.
Line 47	1	Comment: Wording Proposed change (if any): Change ‘adequate’ to ‘appropriate’.	The proposal is not endorsed. It is difficult to change as it is the wording used in the guideline for inactivated influenza.
Line 51	1	Comment: All testing and information currently listed under the heading “3.2.S.2 Manufacture” should be under a more granular section heading. Proposed change (if any): Add section for ‘3.2.S.2.2 Description of Manufacturing Process and Process Controls’ immediately after current heading for ‘3.2.S.2 Manufacture.’ Lines 64-65 should appear under this sub-heading.	The proposal is not endorsed. It is difficult to change as it is the template used in the guideline for inactivated influenza.
Lines 52-63	1	Comment: Preparation of MVS is described under ‘3.2.S.2.3 Control of Materials-MVS’ in the dossier. Proposed change (if any): Move items from Lines 52-63 to ‘3.2.S.2.3 Control of Materials.’ The current item ‘Monovalent bulks: manufacturing process	It is accepted to move lines 52-65 under 3.2.S.2.3 Control of Materials, except for lines 64-65, which will be put in a new subsection “3.2.S.2.5 Process Validation and /or Evaluation” as it concerns information on process amendments required for introducing

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		strain specific changes' should then be under '3.2.S.2.2 Description of Manufacturing Process and Process Controls.'	the new strain.
Lines 52-65	1	Comment: Parent/progeny relation between list items is not clear because of how the list is formatted. Proposed change (if any): Indent items that are subordinate to previous items.	See previous point.
Line 62	1	Comment: Validation protocol for genotype assay will be included each year. Proposed change (if any): Add "and validation protocol for genotype assay".	The change is accepted as it is an important test.
Line 66	1	Comment: Separate section exists for Control of Materials: MVS Proposed change (if any): Add "MVS" after Control of Materials and move items from Lines 52-63 to be under this heading.	See point on chapter 3.2.S.2.3.
Line 70	1	Comment: Potency assay is not re-validated each time there is a new strain. However, all the reagents are qualified to make sure that they are suitable for use with the new strain. Proposed change (if any): Change 'validation of potency test	The comment is endorsed. It is agreed that a yearly full validation for the potency assay will not be required. Proposal:

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		for new strains' to 'qualification of strain-specific reagents'.	Validation of analytical procedures (validation of potency test for new strains (e.g. by qualification of strain-specific reagents).
Line 71	1	Comment: Thermal stability results will be conducted on the final Drug Product, not the Drug Substance. Proposed change (if any): Remove 'including thermal stability' from this section.	The proposition is acceptable. It is more relevant to perform the thermal stability test on the final (trivalent) lot as it will be Representative of the "real product". But this implies that the results will be available later in the evaluation process.
Line 73	1	Comment: Thermal stability results will be reported in the Stability section. Proposed change (if any): Add 'thermal stability' to the information to be provided in this section.	The Thermal stability results should be part of the drug product batch analysis results. See new Section 3.2.P.5.4. Batch Analyses.
Line 77	1	Comment: Clinical study will not be required as part of the annual update process in the EU. Proposed change (if any): Remove references to clinical trials, clinical submission, and CoAs for batches used in clinical trials.	The comment is not endorsed as thus far no conclusion has been reached by the VWP/CHMP on the requirement for clinical trial data.
Line 87	1	Comment: Unclear what is meant by 'final lot stability.' Is this referring to the final drug product, or the final lot produced for the season?	The comment is endorsed and the text has been amended to add: of the final drug product.

Line numbers of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Clarify wording.	
Line 88	1	Comment: Thermal stability will be performed on final Drug Product. Proposed change (if any): Add 'thermal stability results' to the Drug Product stability section.	The comment is endorsed.
Line 92-95	1	Comment: Further clarification is recommended to define what is a 'novel strain' and a 'non-novel strain'. Proposed change (if any): Add additional criteria for 'novel' and non-novel strain' as follows: • Non-novel strains: o Seasonal strains that arise because of small changes to the HA protein of circulating viruses (i.e., antigenic drift) are not "novel" strains. • Novel Strains: o Influenza virus strains that contain a significant amount of genetic sequences from non-human species such as the H5, H7 and H9 subtypes that have not previously been present in human vaccines. o Subtypes of HA that have previously been components of the commercial human influenza vaccines but are not currently in the vaccine	The comment is partially endorsed, the following wording has been introduced: Neurovirulence testing of annual updates (i.e. antigenically drifted strains) is normally not required. Neurovirulence testing will be required if a new HA subtype of influenza A virus (i.e. non-H1, non-H3 subtype) or a novel influenza B virus type differing from the currently circulating genetic lineages is included in the vaccine or in case specific safety concerns arise.

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		formulation (e.g., the H2 subtype which was part of the commercial vaccine formulation in the past, but is not currently in the vaccine formulation). o Strains containing new subtypes of HA that have not previously been in the commercial influenza vaccine formulation. This includes new subtypes that may have been tested in human clinical trials but have not been components of the commercial vaccine formulation.	