15 July 2011
EMA/CHMP/BWP/453628/2011
Committee for Human Medicinal Products (CHMP)

Overview of comments received on 'Guideline on quality aspects on the isolation of candidate influenza vaccine viruses in cell culture' (EMA/CHMP/BWP/368186/2011)

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	College ter Beoordeling van Geneesmiddelen/ The Medicines Evaluation Board (CBG/MEB), The Netherlands
3	Novartis Vaccines and Diagnostics

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	**<u>Lack of clarity of the scope of the Guideline and its application to vaccine production</u>** Since the main objective of the guideline is around virus isolation, it is unclear why this is addressed to companies. It should be reminded that influenza virus strains used in vaccines follow the recommendations published by WHO; and in the current vaccines, the isolation of these strains is done under the responsibility of WHO-certified laboratories. Vaccine manufacturers receive viruses/reassortants from WHO-accredited labs. At the end of the guideline (end of section 4.2, page 4/5, lines 118-119), the text says, "it is the responsibility of the manufacturer to ensure that their vaccine seed is suitable for production of a human influenza vaccine". **This is misleading and EVM considers the guideline is unclear regarding its scope.** However, if the Guideline covers vaccine production, EVM proposes the following general and specific comments for EMA consideration**:** **<u>Data requirements for cell bank made available to WHO by vaccine manufacturer should be covered by this guideline</u>** We recommend to consider whether this guideline should also address the data requirements to be fulfilled if a vaccine manufacturer would make their cell bank available to WHO for the facilitation of the isolation and production of cell isolated viruses.	These points have been taken onboard in a revised paragraph of the Introduction; see lines 55-64. With regard to the last comment concerning if a vaccine manufacturer provides the cells used for isolation, the data requirements are the same regardless of the source of the cells.

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2	The added value of the proposed Guideline on Quality Aspects on the Isolation of Candidate Influenza Vaccine Viruses in Cell Culture to the current established quality standards applied for influenza vaccines (inactivated or live, produced on fertilised hens' eggs or cell culture) is unclear. It is should be clarified how the proposed recommendations will enhance the quality profile (in terms of safety) of influenza vaccines.	The revised paragraph of the Introduction (mentioned above) addresses this point; see lines 55-64.
3	In stating the rationale for adding qualified cells to eggs in the process for "reference" virus derivation, advantages other than the preservation of HA, NA structure should be added, viz: The increased sensitivity of MDCK cells in isolating viruses of all subtypes but especially H3N2 viruses from clinical specimens. This clear advantage would expand the choice of strains available for consideration and could help avoid compromises in the choice of strains that are recommended for seasonal vaccine composition. A second advantage of cells over eggs pertains to pandemic strains, where working with restricted wild type strains under high BSL containment strains is possible with cells (and was done with the H1N1 pandemic strain) while work in eggs may not be feasible, leading potentially to a time advantage in provision of cell-derived viruses.	Comment appreciated but it is not the purpose of this guidance to list all potential advantages.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 34-36	1	« There is currently no evidence that the use of an egg-derived hgr provides a growth advantage in cells compared with the wild type egg-derived recommended strain" **Comment:** There is currently no published evidence. This should be clarified in the text. **Proposed change :** "There is currently no **published** evidence that the use of an egg-derived hgr provides ..."	Accepted. See line 34.
Line 39	1	"Manufacturers of cell-derived influenza vaccine would prefer to use a cell-only passaged virus and not one that has been egg-adapted." **Comment:** The guideline should leave open the possibility to use egg-derived virus if suitable (time benefit, growth…) **Proposed change:** "Manufacturers of cell-derived influenza vaccine ~~would~~ **may** prefer to use a cell-only passaged virus ~~and not~~ **instead of** one that has been egg-adapted." **Question:**	Accepted. The BWP does not foresee any implications for egg-derived influenza vaccines based upon a cell-derived isolate. A sentence to that effect has been added to the end of the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		What would be the implication for the testing and the data requirements for egg derived influenza vaccines when using cell based isolates for routine production? See also line 62-65	
Line 40	1	"This is because research indicates that when a human influenza virus is adapted to grow in eggs, it undergoes phenotypic changes that might include changes to its antigenicity/immunogenicity." **Comment:** Reference is made to "research indicates [….]", but the actual reference is not given. **Proposed change:** Include reference to the research mentioned.	Accepted. Reference inserted; see line 42.
Line 44-45	1	"...is structurally identical to the virus found in clinical material in contrast to..." **Comment:** The term 'clinical material' is misleading since it could also mean clinical lot. **Proposed change :** "...is structurally identical to the virus found in clinical ~~material~~ **specimen** in contrast to..."	Accepted. See line 44-45.
Line 46	1	"Thus a cell-isolated virus may be more clinically relevant for vaccine than an egg isolate"	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: Sentence ("Thus a cell isolated virus...") should be revised. **Proposed change:** "Thus a cell-isolated virus ~~may~~ **might** be more clinically relevant for vaccine than an egg isolate **although to-date this has not been scientifically fully demonstrated**."	See lines 46-47.
Line 63 – 65	1	"An influenza virus isolated on cell culture could be used to derive a seed virus for either a cell culture or an egg vaccine production process for the manufacture of inactivated or live attenuated influenza vaccines." **Comment/Question:** If it is the intention to make cell-isolated viruses available for both egg and cell derived influenza vaccine, the implications for further testing and for the data requirements of egg-derived vaccines should be addressed. See also comment to line 39	The BWP does not foresee any implications for egg-derived influenza vaccines based upon a cell-derived isolate. A sentence to that effect has been added to the end of the guideline.
Line 66 - 72	1	"Classically, an egg isolate is derived directly from a clinical specimen. Introduction of an intermediate step consisting of a passage in cell culture (essentially an amplification step) prior to egg inoculation enhances the probability of isolating (or recovering) an appropriate 'egg' variant. Consequently, the use of a cell-isolate to derive an	Accepted. See lines 72-76.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		egg-isolate is likely to result in a greater efficiency of obtaining an initial egg-isolate. Thus, the scope of this document is to provide guidance for the isolation on cell culture of any potential influenza vaccine virus intended for cell culture or egg-based influenza vaccine manufacture." **Comment:** In our opinion, the wording of Section 2 is unclear and confusing. **Proposed change:** "**<u>An influenza virus isolated on cell culture could be used to derive a seed virus for either a cell culture or an egg vaccine production process for the manufacture of inactivated or live attenuated influenza vaccines.</u>** ~~Classically, an egg isolate is derived directly from a clinical specimen. Introduction of an intermediate step consisting of a passage in cell culture (essentially an amplification step) prior to egg inoculation enhances the probability of isolating (or recovering) an appropriate 'egg' variant.~~ ~~Consequently, the use of a cell-isolate to derive an egg-isolate is likely to result in a greater efficiency of obtaining an initial egg-isolate.~~ Thus, the scope of this document is to provide guidance for the isolation on cell culture of any potential influenza vaccine virus intended for cell culture or egg-based influenza vaccine manufacture."	

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Line 66-72	2	**Comment:** The guideline concerns the use of cell culture for the isolation of candidate vaccine viruses, regardless whether the final vaccine production system will be cell culture or egg based. The second paragraph under the scope is rather confusing and can be read as if also for cell cultured production systems an egg-propagation step is required. Revision of the text is suggested.	Accepted. See new text as proposed in previous comment; see lines 72-76.
Line 70-72	1	"Thus, the scope of this document is to provide guidance for the isolation on cell culture of any potential influenza vaccine virus intended for cell culture or egg-based influenza vaccine manufacture." **Comment:** It should be reminded however that influenza virus strains used in vaccines follow the recommendations published by WHO; and the current vaccines the isolation of these strains is done under the responsibility of WHO-certified laboratories.	Partly accepted. Regarding WHO recommendations, this is taken onboard (see lines 76-77); however, no need is seen for including the second part of the comment.
Line 86 - 88	1	"There should be good quality control of the cells to be used for the isolation of an influenza virus destined to be a candidate vaccine virus. " **Comment:** There is a lack of definition of "good quality control". So, the guideline should elaborate further on the quality aspects that need to be in place for the cell	See lines 92-93. Partly accepted. The WHO laboratories are not expected to work to GMP; adequate control can be applied to give an acceptable level of assurance of the quality of a candidate vaccine virus without applying GMP. The sentence in question has been deleted

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		bank to be used by WHO – Collaborating Centres or other producers of virus isolates **Proposed change:** Cells to be used for the isolates should be produced and maintained according to GMP.	and quality aspects addressed in section 4.3.
Line 88	1	"There is good knowledge of certain cell substrates used in influenza virus research and development, such as MDCK, Vero and primary cells of chick origin. Regardless of the cell type used, where a cell line is used cells should be derived from a cell banking system." **Comment:** The sentence *("..., such as MDCK, Vero and primary cells of chick origin.")* needs to be completed to open the door to avian- derived cell line such as the EB66 cell line **Proposed change:** *"..., such as MDCK, Vero, ~~and~~ primary cells of chick origin* ***and*** **established avian cell lines such as EB66**"	Not accepted. This is a "such as" and so it is neither all encompassing nor restrictive.
Line 97	1	**Comment:** The sentence *("..., such as MDCK, Vero and primary cells of chick origin.")* needs to be completed to open the door to avian- derived cell line such as the EB66	Not accepted. This is a "such as" and so it is neither all encompassing nor restrictive.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		cell line **Proposed change:** *"..., such as MDCK, Vero, ~~and~~ primary cells of chick origin* ***and*** **established avian cell lines such as EB66**"	
Line 98 - 100	1	"Cells from an approved cell bank system used for human vaccine manufacture are likely to comply with general chapter 5.2.3 and would be acceptable for virus isolation. Similarly, cell substrates that comply with ICH Q5D would be acceptable for use in virus isolation." **Comments:** It is stated that cells that comply with EP 5.2.3 would be acceptable for virus isolation and similarly that cell substrates that comply with ICH Q5D are also acceptable for use in virus isolation. It should be remembered ICH Q5D and EP 5.2.3 are certainly not identical with regard to the testing requirements of each new lot/batch of Working Cell Bank. Moreover EP 5.2.3 is mandatory for cell banks for production of human vaccines. The possibility of ICH Q5D being acceptable "similarly" is confusing and should be deleted. **Proposed change:** "Cells from an approved cell bank system used for human vaccine manufacture ~~are likely to~~ that comply	Accepted. See lines 101-102

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		with general chapter 5.2.3 ~~and~~ would be acceptable for virus isolation. ~~Similarly, cell substrates that comply with ICH Q5D would be acceptable for use in virus isolation."~~	
Line 105	3	**Comments:** Master and working Vero cell banks for rotavirus vaccine have been shown to contain porcine circoviruses. It would seem appropriate to mention this specific concern and the more general issue of adventitious agents detected by alternate detection methods be addressed here.	Not accepted. Porcine circovirus has been highlighted recently due to the discovery of its presence in a specific human vaccine. There is no reason for it to be singled out in this guideline. Also, it is not the purpose of this guideline to address the general issue of virus testing, alternative or otherwise.
Line 112	1	"Only one virus should be handled in an open system at any one time." **Comments:** Proposed rewording for clarification/accuracy. **Proposed change:** "Only one virus **type** should be handled in an open system at any one time."	Partly accepted. This has been explained in more detail; see lines 115-120.
Line 112	3	**Comments:** Only one virus should be handled in an open system at any open time needs clarification. If only one virus at one time in an open system can be processed a huge impact on available number of virus isolates and timeline of provision is anticipated.	Partly accepted. This has been explained in more detail; see lines 115-120.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Only one virus **<u>subtype with a various number of isolates of the same clade in only one cell line</u>** should be handled **<u>at same time</u>** in an open system ~~at any one time~~.	
Line 114	1	"The propagation of cells and viruses should be performed under a quality system." **Comments:** It is unrealistic to expect full-GMP quality system operations before the establishment of the Master Seed. The sentence should clarify that the propagation of cells and viruses should be under a quality system once the master seed has been established and validated. **Proposed change:** The propagation of cells and viruses should be performed under a quality system, **<u>once the Master Seed has been established</u>**.	Partly accepted. Agree with the first sentence of the comment. To avoid confusion the relevant sentence in the draft guideline has been deleted; see lines 123. No comment has been added regarding once the Master Seed has been established; this is covered by the statement on lines 66-69 regarding the Guideline on Cell Culture Inactivated Influenza Vaccines.
Line 114	3	**Comments:** It is not clear how it can be avoided that isolates derived from the qualified cell line be mixed up with isolates derived from other substrates. **Proposed change:**	Accepted. Comment added; see lines 118-120.

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		Segregated (dedicated), lockable storage containers for the qualified cell line and the derived virus isolates	
Line 115	3	**Comments:** Performance of the used equipment **Proposed change:** Qualification of equipment and maintenance of the qualification status	Not accepted. Equipment performance is identified on lines 125.
Line 118 – 119	1	"It is the responsibility of the manufacturer to ensure that their vaccine seed is suitable for the production of a human influenza vaccine." **Comments:** Proposed rewording for clarification/accuracy. **Proposed change:** 'It is the responsibility of the manufacturer *of the cell isolate virus* to ensure that the ~~vaccine seed~~ **virus** is suitable for the production of a human influenza vaccine.'	Not accepted. The statement is correct and stands. A small addition to the text has been made to clarify; see lines 126-129.