18 October 2018
EMA/CHMP/BWP/668918/2018
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on quality aspects included in the product information for vaccines for human use' (EMA/CHMP/BWP/133540/2017)

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

Stakeholder no.	Name of organisation or individual
1	Vaccines Europe
2	Emergent Biosolutions

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	In some sections of the SmPC it states to use "Al^{3+} per dose" and then in subsequent examples it states "Al^{3+} in total". There should be consistency and therefore suggest "Al^{3+} per dose" should be used throughout.	Not accepted. It was specifically added for some vaccines to avoid misunderstandings by patients.
2	Only in section 6.5 of the SmPC, is any reference made to a product being supplied in a multidose container and the number of doses contained. Whilst it should be clear in the posology and administration (Section 4.2) is the fact that the product is multidose and this is 'hidden' in section 6.5 likely to lead to dosing errors? Should there be a statement earlier in the SmPC about multidose vial?	Wording added on pharmaceutical form in multidose containers.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
46-47	2	Comment: Question: It is stated that “in general promotional statements are not allowed”. In a recent approval the Company were asked to include the following after the INN in brackets “(purified cell-free filtrate)”. As a Company we don’t believe this to be promotional but would like confirmation from the EMA.	If it was requested and approved by a NRA as common name it is not considered a promotional statement by this NRA. Without further knowledge about the specificities of the vaccine concerned no general statement can be given. Depending on the product it might be considered promotional if reviewed by other regulatory agencies.
62	1	Comment: The text is unclear as it seems to suggest that types or names of serotypes cannot be mentioned, i.e. only the number. The text also seems to suggest that this only applies to serotypes, and not to antigens. A vaccine may contain several antigens from one specific (sero)type. Proposed change: the invented name may include the number *and/or names* of serotypes present.	Accepted. As mentioned in point 4.3.1 of the NRG guideline different types of antigens might also result in the necessity to add a qualifier to the invented name. (e.g. Mencevax ACWY, NeisVac-C)
62; 96; 111	1	Comment: For multivalent vaccines, not all types that are included are necessarily serologically linked. Proposal to have “sero” between brackets. Proposed change: Line 62: For vaccines composed of several ***(sero)***types the invented names may include the number of ***(sero)***types present.	Accepted with some amendments for clarification.

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		Line 96: As regards multivalent vaccines, no wording on the ***(sero)***types should be included in the common name. Line 111: For multivalent vaccines containing various ***(sero)***types of a pathogen, all ***(sero)***types need to be specified.	
89	1	Comment: The terminology “rDNA” can be confusing because it does not allow to discriminate between a DNA-containing vaccine, or vector based or a full virus, from a simple recombinant protein-based vaccine. It describes the technology used to produce it rather than the product itself. It may also create confusion for patients who may misunderstand and be suspicious of a product that would contain DNA. It is recommend to use the term “recombinant” or “recombinant protein” specifically for proteins and to include the definition of “recombinant”	The wording on common names was amended to allow more flexibility and deviations from Ph. Eur. conventions, such as the use of the term ‘recombinant’ instead of ‘rDNA’.
99-105	1	Comment: The guideline states that the SmPC should specify “the residues of clinical relevance, if applicable”. We presume that “residues of clinical relevance” should be understood as allergens or residues with toxicological concerns. However it is not completely clear what is meant by the term “residue”. In particular, it is unclear which criteria should be used to determine whether a material used upstream should	Not accepted. Wording is in compliance with SmPC Guideline. It is not within the scope of this guidance to address methodological considerations to define residuals, suffice to say it is incumbent on the applicant to justify the nature and clinical relevance of all residuals. For some, it is understood that indeed the threshold of toxicological concern would be relevant although this is not always known and for allergenic

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		be considered as a residue in the drug product and should then be mentioned in the SmPC if it is of clinical relevance. It would make sense from a scientific perspective to work on the basis of a comparison between estimated worst case quantity (or known quantity if material tested) per vaccine dose versus threshold of toxicological concern/permitted daily exposure/safety limits as recommended in the below European Vaccines Manufacturers reflection paper: http://www.vaccineseurope.eu/wp-content/uploads/2012/12/EVM-Safety-Assessment-of-Residuals-and-Contaminants-in-Vaccines-update-Final-Version-FIN.pdf	substances e.g. eggs, there are no thresholds established.
111	1	Comment: The guideline states that "For multivalent vaccines containing various serotypes of a pathogen, all serotypes need to be specified". We believe that in the case of a mix of recombinant antigens, it would be useful that all antigens be also specified. Proposed change: For multivalent vaccines ~~***containing various serotypes of a pathogen,***~~ all serotypes ***or antigens*** need to be specified.	Accepted with amended wording.
156-157	1	Comment: It is recommended to include a reference the EMA "*Guideline on excipients in the label and package leaflet of medicinal products for human use*" (refer to the latest version, March 2018) to define	Amendment of the wording on excipients to be more precise when to include information on excipients in section 2 of the SmPC.

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		"excipients with known effect". Proposed change: Excipients ~~known to have a recognised action or effect~~ with known effect as per "Guideline on excipients in the label and package leaflet of medicinal products for human use" should be listed quantitatively and qualitatively	
159-160	2	Comment: The section on multidose preparations has been removed from Section 2. This means that there is only now ONE reference to multidose preparation located in Section 6.5. Does the Agency consider that sufficient? Our concern is that this may cause an increase in medication errors/overdosing patients if the whole vial is used rather than the dose prescribed in Section 4.2 of the SmPC. Proposed change: Reinstate previous instruction in this section i.e. <u>Multidose preparations</u> In case of multidose preparation include the following statement: *"This is a multidose container. See Section 6.5 for the number of doses per vial"*	Information on multidose containers is to be given as part of the pharmaceutical form. The GL was updated accordingly. No additional wording needed.
177-179	1	Comment: The SmPC is the basis of information for healthcare professionals on how to use the medicinal	The statement is not unique to vaccines but rather, applicable to all biological medicinal products. Therefore, for consistency

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		product safely and effectively, and therefore such a statement which reflects general medical practice should not be included. In particular, section 4.4 (Special warnings and precautions for use) is intended to alert healthcare providers about a specific risk when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk. The guideline provides a list of criteria that need to be met for inclusion of a warning. The proposed text above under the "Traceability" subheading instructing the HCP to record the name and batch number does not meet any of the criteria for a warning or precaution, because no specific risk is described. It is therefore suggested to remove the statement on traceability from the SmPC. However, if the objective is to track the drug name and the batch number in case of adverse reaction reporting, a statement on traceability with a clear explanation on the objective of recording of name and batch number could be added in section 4.8, e.g. "*In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded* ***and included with reporting of suspected adverse reactions.***" Alternatively, if the goal of the statement is a general tracking of biological products even if not related to	reasons, the text and position of the statement (in section 4.4 of the SmPC) is unchanged.

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		the adverse reactions reporting, the statement could be added in section 6.6. Proposed change: ~~***In section 4.4 the following statement on traceability should be included: Traceability***~~ ~~***In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.***~~	
177-179	2	Comment: We welcome the addition of the proposed wording on traceability, but would it be better located in Section 6.6 Instructions for disposal <and other handling>? Rationale for this is that during a recent review procedure we were advised for a multidose preparation to include the following text in Section 6.6 (*Note: we previously had placed this wording in Section 4.4 and were asked to move to 6.6*): "Mark the vial with date and time of opening" It therefore would seem appropriate to have the traceability statement linked with the instruction shown above.	Information on multidose containers is to be given as part of the pharmaceutical form. The GL was updated accordingly. No additional wording needed.
Footnote page 6	1	Comment: Reference "6" in footnote on page 6 should be updated to refer to the 2018 recent version of the guideline on excipients in the label and package leaflet	Accepted.

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		of medicinal products for human use.	
214-216	1	Comment: The purpose of this paragraph is unclear. It is clear from the SmPC Guidance that the SmPC is the basis of information for the end user i.e. healthcare professionals. Proposed change: ~~***The statement on storage and/or transport conditions included in section 6.4 of the SmPC is intended to inform the end user only. Compliance to Good Distribution Practice should be respected in all circumstances.***~~	Not accepted. Vaccines are subject to parallel distribution/importation and it is important to clarify that the statements in the SmPC are intended for end users/health care professionals or patients only.
219-222	1	Comment: We consider that the statement 'when stored at non-standard temperatures' is not clear. We propose to replace by 'after temporary exposure to temperature conditions outside the recommended storage conditions'. In addition, the rationale behind the 72 hours is not clear. The time a vaccine product is stable at non-standard temperatures is product dependent, it is therefore proposed to delete this part of the sentence. It is also proposed to add a statement to the proposed example to strengthen the message that the stability data are not recommendations for storage. Finally, this recommendation is not reflected under section 6.4 of the SmPC guideline. Section 6.3 of the	Proposal accepted.

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		SmPC guideline contains a paragraph on temporary storage. We recommend that an update of the SmPC guideline will be performed as a matter of alignment. Proposed change: "In case appropriate stability data are available which confirm the quality of the vaccine~~,~~ ~~when stored at non-standard temperatures,~~ after temporary exposure to temperature conditions outside the recommended storage conditions, this information might be added in section 6.4. ~~***However the storage at non-standard temperatures should be limited to a maximum period of 72 hours.***~~ ***The statement should specify the temperature range and maximum duration of temporary storage.*** The statement on storage at non-standard temperatures should be expressed as given in the example below: "Stability data indicate that the vaccine components are stable for x hours when stored at temperatures from y°C to z°C. At the end of this period <Invented Name> should be used immediately or discarded. ***These data are intended to guide healthcare professionals in case of temporary temperature excursion only.***"	
229	1	Comment: The following comments are provided on the instructions below in section 6.5 the draft guideline: *In the case of multidose presentations, the number of*	Not accepted. Indeed during the 2009 influenza pandemic, exemptions were granted as reflected in the document "Lessons Learned from

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		doses per container should be stated. In Section 5.7 of the document "Lessons Learned from the review of the labelling of centrally authorised pandemic products" (25 January 2016, EMA/467700/2014, Human Medicines Evaluation Division), agreement is noted to only display the total volume of the vial vs. the total number of doses. This was agreed in the context of administration of half doses for the paediatric population during an influenza pandemic. Therefore, it may be helpful to include some verbiage in the guideline which refers to the fact that under certain circumstances (e.g., influenza pandemics) exemptions may be permitted, per "Recommendations for the implementation of the exemptions to the labelling and package leaflet obligations in the centralised procedure." (30 November 2016, EMA 617541/2016 rev.3*), Human Medicines Evaluation).	the review of the labelling of centrally authorised pandemic products" (25 January 2016, EMA/467700/2014, Human Medicines Evaluation Division), however, this situation is the exception rather than the rule and need not be reflected in this guidance. Companies are aware of provisions for requesting exemptions from labelling provisions.
233	1	Comment: We propose that instructions to check the appearance of the vaccine components before reconstitution (if applicable) should also be added.	Accepted.
247-248	2	Comment: It states “For multidose presentations, the number of doses in the container(s) should be stated. Information about the cellular systems used as production substrates may be omitted from the carton labelling”. Should the latter statement be for all	Accepted.

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		presentations and not just multidose preparations? Proposed change: Suggest a carriage return is added. *"For multidose presentations, the number of doses in the container(s) should be stated.* *Information about the cellular systems used as production substrates may be omitted from the carton labelling."*	
249	1	Comment: In order be in line with the recent updated guideline on excipients in the label and package leaflet of medicinal product for human use, we propose that line 249 specifies that only excipients with known effect should be listed. In addition, there is limited space on the carton, and listing all excipients is not realistic. Proposed change: The list of excipients ***with known effect*** should appear on the carton labelling and be expressed as in section 6.1 of the SmPC.	Not accepted. If the medicinal product is a parenteral, a topical or an eye preparation or if used for inhalation, all excipients must be stated.
260-261	2	Comment: It states: "If used, the pharmaceutical form, patient-friendly term should be added in brackets in section 3 of the SmPC". Should this also not be included in the Package Leaflet (PL) after all this is what the patient sees, rather than the SmPC. Proposed change: "If used, the pharmaceutical form,	Not accepted. It is already stated in the GL that 'As required by Directive 2001/83/EC, the package leaflet should be drawn up in accordance with the SmPC, and be written in clear and understandable terms for the user.'

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		patient-friendly term should be added in brackets in section 3 of the SmPC **and Section 1 of the PL**"	
261	1	Comment: The coma between pharmaceutical "form" and "patient-friendly" should be removed. Proposed change: If used, the pharmaceutical form~~,~~ patient-friendly term should …	Accepted.
290	1	Comment: Typographical error "Smock" should be "SmPC". Proposed change: ~~***Smock***~~ ***SmPC*** of vaccines for human use.	Accepted.
290	2	Comment: What is meant by Smock of vaccines for human use?	Typographical error.
294; 427	1	Comment: A change in the common name for dengue vaccine can be confusing: • Dengvaxia is made of ARN viruses • Dengvaxia are viruses produced using modified plasmids, so DNA, but there is no DNA in the vaccine. Having rDNA in the common name may be understood as it is a DNA vaccine, which is not the case. • rDNA should make no sense for physicians Moreover, the use of recombinant DNA technology	Partially accepted. According to the amendment of the paragraph on the common name in the GL it is acceptable to use the term 'recombinant' instead of rDNA, however the term attenuated should be included in section 2 as given in the examples of the Annex of the GL. There are various examples of approved vaccines, which contain live attenuated virus strains and for which the term live only is used for the common name (e.g. MMR/V, YF vaccines)

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		appears clearly in composition section. When indicating “live”, it is better to precise that the viruses are attenuated. The common name is also used in the leaflet for non HCP use and “Live, attenuated” is probably much more patient friendly than “rDNA, Live”. Proposed change: Lines 294 and 427: Dengue tetravalent vaccine (~~***rDNA,***~~ live, ***attenuated***).	
326	2	Comment: The plus (+) sign should also be superscript Proposed change: Al^{3+}	Accepted.
336	2	Comment: The number 3 and the plus (+) sign should also be superscript. Proposed change: Al^{3+}	Accepted.
370	1	Comment: In this example which refers to a vaccine registered in EU under the Tradename Cervarix, the common name is not correct. Proposed change: Human Papillomavirus vaccine ***[Types 16, 18]*** (~~***rDNA***~~ ***recombinant***, adjuvanted, adsorbed).	Accepted.
382	1	Comment: In this example which refers to a vaccine registered in EU under the Tradename Gardasil 9, the common name is not correct. Proposed change: Human Papillomavirus ***9-valent***	Accepted.

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		Vaccine (~~***rDNA***~~ ***recombinant***, adsorbed).	
418	1	Comment: In this example which refers to a vaccine registered in EU under the Tradename Shingrix, the common name is not correct. Proposed change: Herpes zoster vaccine (~~***rDNA***~~ ***recombinant***, adjuvanted).	Accepted.
427-437	2	Comment: For all other examples numerical footnotes have been used. In this example numerous asterisks (*) have been used. Proposed change: Ensure all footnotes are numerical	No formal requirement to have foot notes listed numerically or with asterisks.
437, 447, 456	2	Comment: In some examples CCID is spelled out with each letter capitalised i.e. Cell Culture Infectious Disease and in other examples all is presented as lower case. Align for consistency. Also suggest throughout that the 50 is formatted as subscript. Proposed change: $CCID_{50}$: 50% Cell Culture Infectious Dose.	Accepted.
442-443	1	Comment: For some vaccines the content is determined otherwise than CCID50, it is therefore proposed to also refer to Plaque Forming Units. Proposed change: … not less than x CCID50 ***or PFU (Plaque Forming Units).***	Accepted.