European Medicines Agency
Post-Authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE CONDUCT OF PHARMACOVIGILANCE FOR VACCINES FOR PRE- AND POST-EXPOSURE PROPHYLAXIS AGAINST INFECTIOUS DISEASES EMEA/CHMP/PHVWP/503449/2007

Organisations that commented on the draft Guideline as released for consultation:

	Name of Organisation or individual	Country
1	European Vaccine Manufacturers (EVM)	EU
2	Merck, Sharp & Dohme Ltd. (MSD)	UK
3	Schering-Plough (SP)	NL
4	Statens Serum Institut (SSI) Department: Regulatory & Medical Affairs	DK
5	Verband Forschender Arzneimittelhersteller e.V. (VFA) - German Association of Research-Based Pharmaceutical Companies	DE
6	Wyeth Research (Wyeth)	FR

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1. GENERAL COMMENTS

Organi-sation	General Comment	Outcome of EMEA review
EVM	• EVM welcomes this guideline, which provides a good oversight of the specific aspects of vaccine pharmacovigilance and appreciates the acknowledgment in the guideline about the value of immunisation. • Scientific evidence for a risk should be a prerequisite, together with feasibility of the measures requested, before making these mandatory. In this context, EVM considers that Marketing Authorisation Holders should not be obliged to make firm commitments (e.g. PASS) in RMPs to address theoretical (or even improbable) risks. • All the aspects or potential issues covered in this guideline are not applicable to all vaccines. EVM believes that there should be a clear introductory statement that not all the measures in the guideline are applicable in every situation. As such, established, widely used vaccines with a well-known safety profile should be assessed differently than newly introduced vaccines in terms of RMP and pharmacovigilance plan, as well as PASS commitments.	Supportive comment. The general scope of RMPs is defined in Volume 9A and applies to vaccines. The scope comprises important identified as well as potential risks and important missing information. What is considered important for an individual product, is subject to its assessment. Agreed. It will be clarified that while as a standard assessment should always be comprehensive and of high quality, the RMP or PASS requests should be specific to the product with view to all available evidence as well as important missing information. Novel approaches on which vaccines may be based will have to be reflected in the RMP. It will be added that feasibility studies may be necessary before finalising a study protocol.
MSD	This guidance gathers together process7 es largely already in place, and as such is a useful compilation – noting that it still remains an ideal to have all such guidance incorporated into Volumes 9A and 10 as applicable.	Supportive comment. The Guideline is planned to be incorporated in Volume 9A during a future revision of Volume 9A.
SP	The document is well written to cover 'normal' vaccines for 'normal' diseases, but the document should mention that for a pandemic situation, certain parts do not apply / are less important.	Agreed. Reference to Volume 9A, Chapter I.5.12 on public health emergencies will be included.
SP	The document does not recommend to report illness in a subject who was not vaccinated, due to shedding of a vaccinated person (expeditedly).	Agreed. Explicit statement will be added.
SSI	Adverse events following Immunisation (AEFIs): Statens Serum Institut recommends that this term is not used in the concerned Guideline. The term 'Adverse Event' is a world-wide recognised terms used for all types of products. There is no reason	The Guideline uses the terms "adverse event" and "adverse reaction" as defined in EU legislation applicable to all medicinal products.

Organi-sation	General Comment	Outcome of EMEA review
	for using a specific term for vaccines. In fact this could lead to confusion, e.g. that other guidelines does not apply for vaccines.	It is considered important, in section 7.1, to explain the relationship of these terms with the AEFI concept, as this is a key concept in vaccine safety surveillance conducted in the framework of WHO programmes.
SSI	Pharmacovigilance/Risk Management: WHO has defined the term pharmacovigilance as: • *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems."* This definition has also been used ICH E2E. Additionally, Risk Management has been defined by ParagonRx (and others) as: • *This discipline [risk management] entails signal detection, risk identification and assessment, intervention program design and testing, program implementation, and evaluation and continuous program improvement.* As these definitions are comparable, but not identical, and both terms are used in the guideline, a definition of the terms is desirable to avoid misinterpretations.	The definitions provided in Volume 9A apply to this Guideline and are in line with the respective ICH Guidelines.
SSI	Reactogenicity: Traditionally, the term reactogenicity have been used to describe local and systemic adverse reactions associated with vaccines, not for non-vaccine biologicals. Given that the nature of the adverse effects often is the same, it can be a source of confusion if the term is only applied for vaccines. The terms local and systemic adverse reactions are preferable.	Agreed. Terminology will be revised.
VFA	Thank you for providing the draft "Guideline on the Conduct of Pharmacovigilance for Vaccines for Pre- and Post-Exposure Prophylaxis Against Infectious Diseases". The German Association of Research-Based Pharmaceutical Companies (VFA) does not have any comments to submit.	Supportive comment.
-	-	Note: Reference to new guidance developed in the framework of the VAESCO project initiated by the ECDC will be included. Also a reference to Ch. 5.12 of Volume 9A re public health emergencies will be provided.

2. SPECIFIC COMMENTS ON TEXT

Section + Para	Organi-sation	Comment and Rationale; Proposed Changes	Outcome of EMEA review
4. Roles and Respon. Para 1, last sent	**EVM**	**Comments:** Stressing the responsibility (for public health) of the media in unbiased communication is important. Nevertheless, it is the role of Competent Authorities (including public health authorities) to provide such communication to Media (See section 9.3). **Proposed change:** Last sentence should be reworded as follows: ~~"Media and~~ Competent Authorities have ~~has~~an important role in unbiased communication in particular in situations where there is a gap between the scientific analysis of experts and public perception of perceived risks which is especially relevant to vaccines. Competent authorities should provide media with the relevant information".	Agreed. Will be reworded.
5.1.1 Type of vaccine Para 1, 1st sent	**EVM**	**Comments:** There is a redundancy in the first sentence. **Proposed change:** "~~The safety profile of~~ Live virus or bacterial attenuated vaccines and inactivated vaccines (including vaccines based on bacterial proteins, polysaccharides or protein-conjugated polysaccharides and recombinant protein vaccines) may have different safety profiles."	Agreed.
5.1.1 Type of vaccine Para 1, 2nd sent	**EVM**	**Comments:** **"**Safety concerns associated with different types of vaccines identified prior to marketing authorisation should be investigated in the pre-authorisation phase and addressed in the Risk Management Plan (RMP)." There's no definition of "safety concern" and the language seems to conflict with current language in Volume 9A which refers to "identified significant risks" and 'potential significant risks." Should be consistent here or, if intended to expand requirement, should define "safety concern." **Proposed change:** It would be helpful to refer here to the definition of "safety concerns " provided in section 6.1.1.	The definition of safety concern provided in Volume 9A applies. According to this definition, a safety concern is an important identified risk, an important potential risks or important missing information.

Section + Para	Organi-sation	Comment and Rationale; Proposed Changes	Outcome of EMEA review
		EVM proposes to add: "Safety concerns for a vaccine include those due to inherent toxicities of the antigen and adjuvant, toxicities of impurities and contaminants and toxicities due to interactions of the vaccine components present in the vaccine formulation"	Agreed. Explanation will be added.
5.1.1 Type of vaccine Para 1, last sent	**EVM**	**Comments:** RMP is mentioned for the pre-authorisation phase, therefore it should also be mentioned for the post-authorisation phase **Proposed change:** "For concerns identified during the post-authorisation phase, appropriate safety investigations and RMP update may be necessary."	Agreed.
5.1.1 Type of vaccine Last para	**EVM**	**Comments:** This paragraph seems to belong to section 5.2	Not agreed.
5.1.2 Adj., Stab., Preser., Resid. Para 1, 3rd sent	**EVM**	**Comments:** "The clinical impact of the adjuvant in respect to impairing the immune response toward a Th2 response…" The Th1/Th2 characterisation may be an oversimplification of the complex immune response a vaccine induced. A more general statement may be more appropriate. It is not clear what "clinical impact" means in that context and needs clarification. EVM suggests to remove this sentence since the phrase 'The immunological mode of action of any novel adjuvants should be addressed in the pharmacovigilance specifications of the Risk Management Plan" covers this point already in a more general and appropriate way. **Proposed change:** Delete the following sentence: "~~The clinical impact of the adjuvant in respect to impairing the immune response toward a Th2 (helper T-cell type 2) response (as known for aluminium-based adjuvants) should be investigated in the post-authorisation phase~~"	Agreed.
5.1.2 Adj.,	**EVM**	**Comments:** **"**It's important to analyse whether the antigen itself or any ingredient has caused the	Agreed.

Section + Para	Organi-sation	Comment and Rationale; Proposed Changes	Outcome of EMEA review
Stab., Preser., Resid. Para 5		adverse reaction**".** EVM wonders whether this is feasible and, what analyses will be done to fulfil this requirement for spontaneous reports. **Proposed change:** "<u>If feasible</u>, it's important to analyse whether the antigen itself or any ingredient has caused the adverse reaction**".**	
5.1.3 Comb. vacc. 3rd sent	**EVM**	**Comments:** In case of combined vaccines, precursor vaccines are not always available. **Proposed change:** EVM suggests to reword the sentence as follows: "…between the combined vaccine and the precursor vaccine(s), <u>if available</u>, whereas smaller differences of local or…"	Agreed with modification as follows: "…between the combined vaccine and the precursor (combined or individual) vaccine(s), if available, whereas … "
5.1.3 Comb. vacc. Last sent	**EVM**	**Comments:** There's a reference to potential risk minimisation strategies including preventative antipyretic treatment in same children. Preventive antipyretic treatment can have benefit in reducing the risk of febrile reactions, but may have potential impact on efficacy for some antigens. **Proposed change:** "If appropriate, risk minimising strategies might be explored ~~(e.g. preventive anti-pyretic treatment in small children)~~."	Agreed. Prophylactic antipyretics may impact on the immune response.
5.1.4 Novel vacc. 1st sent	**EVM**	**Comments:** Grammatical error in first sentence **Proposed change:** "~~Where~~new approaches and novel concepts (e.g. temperature selected mutants), new technologies (e.g. vaccines using novel delivery systems), novel adjuvants or alternative routes of administration (e.g. nasal administration) have recently been developed or are currently in the clinical testing phase and may give rise to new safety concerns."	Agreed.
5.1.4 Novel vacc.	**EVM**	**Comments:** **"**Particular consideration should be given to what methods may be employed to detect long-term, delayed onset and, in case of vaccines for infants, developmental adverse	Agreed with modification as follows: "To establish evidence of safety, particular

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Last sent		reactions**”** Current wording seems to imply that delayed onset and even developmental adverse reactions of vaccines for infants should be studied. The expectation to monitor long-term, delayed onset events and developmental adverse reactions is unfounded. There is no evidence that vaccines have any influence whatsoever on developmental disorders. Distinguishing between the effect of vaccination and the many other potential influences on development is nearly impossible. To include such requirement is beyond reasonable. **Proposed change:** EVM proposes either delete the last sentence of the section : ~~“Particular consideration should be given to what methods may be employed to detect long-term, delayed onset and, in case of vaccines for infants, developmental adverse reactions”~~ or add at the end of the sentence the following words: “Particular consideration should be given to what methods may be employed to detect long-term, delayed onset and, in case of vaccines for infants, developmental adverse reactions in case there is an indication of such an effect”	consideration should be given to what methods may be employed to detect long-term and delayed onset adverse reactions.”
5.1.5 Batch-Related ness Para 1	**EVM**	**Comments:** The current reading of this section could lead to the conclusion that variability between batches is in itself a risk. **Proposed change:** The text should be amended to include the notion that some variability between batches is a normal but well controlled development in vaccine production. Variability between batches is a fact of biological materials and should not be directly translated into a risk. (See 8.2)	See below.
5.1.5 Batch-Related ness Para 1, 1st sent	**EVM**	**Comments:** “…within certain limits of the composition of the final product which may have an impact on safety of the vaccine”. EVM members believe that there is not impact on the safety of vaccines**.** **Proposed change:**	Agreed.

Section + Para	Organi-sation	Comment and Rationale; Proposed Changes	Outcome of EMEA review
		EVM suggests to delete the following wording: "…within certain limits of the composition of the final product ~~which may have impact on safety of the vaccine~~".	
5.1.5 Batch-Relatedness Para 2, 1st sent	**EVM**	**Comments:** "If there is reasonable suspicion of an association between the occurrence of adverse reactions and a particular batch of a vaccine, Competent Authorities for marketing authorisation and the competent authorities for batch release should be informed immediately by the Marketing Authorisation Holder."A full assessment of the possible reason for batch-relatedness of adverse reactions needs to be provided." EVM considers this paragraph leads to several questions: - how will reasonable suspicion be defined? - would a full assessment be expected at the point of informing the authorities or would this come later? This is not clear from the text. If a full assessment is needed this may risk delaying informing the authorities. **Proposed change:** EVM proposes the following wording: If there is a reasonable suspicion <u>that a particular batch of a vaccine</u> ~~of a batch in an association between~~ <u>is associated with</u> the occurrence of <u>an unusual pattern</u> of adverse reactions ~~and a particular rbatch of a vaccine~~, Competent Authorities for marketing authorisation and the competent authorities for batch release should be informed immediately by the Marketing Authorisation Holder	Reference to guidance on handling of suspected quality defects will be added.
5.2.1 Special Age Groups	**EVM**	**Comments:** Age can be categorised in many ways. Some clarification would be helpful. **Proposed change:** Needs clarification	Agreed. Reference to ICH E11 will be included.
5.2.1 Special Age	**EVM**	**Comments:** The sentence**: "**Targeted surveillance of adverse reaction in different age groups is	Agreed.

Section + Para	Organi-sation	Comment and Rationale; Proposed Changes	Outcome of EMEA review
Groups 3rd sent		warranted**”** This is not always justified and therefore too prescriptive. **Proposed change:** EVM suggests the following: “Targeted surveillance of adverse reaction in different age groups may be ~~is~~ warranted”	
5.2.3 Immunocompromised	**EVM**	**Comments:** EVM considers that pointing out HIV-infected persons, as Immunocompromised Individuals does not add much value. **Proposed change:** EVM proposes to change the title to: 5.2.3 Immunocompromised Individuals ~~and HIV-Infected Persons~~ EVM proposes to clarify the paragraph as follows: “Immunocompromised individuals may not only be very sensitive to infectious disease, but may also be very sensitive to the occurrence of serious adverse reactions following vaccination .”	Agreed to delete reference to HIV in the title. Reference will however be introduced in the text because HIV is the focus of one of the WHO programmes, and it might be a common search term. Agreed with modification as follows: “Immunocompromised individuals may not only be very sensitive to infectious disease, but may also be very sensitive to the occurrence of serious adverse reactions following vaccination, including impaired immunoresponse to vaccination. Therefore, the risk-benefit balance in this patient group needs separate consideration in the assessment.”
6.1.3 Potent. Risks Req. further Invest. Para 1, last sent	**EVM**	**Comments:** “The impact of adjuvants, stabilisers, preservatives or residuals …” No distinction is made between new products and those for which the safety has already been established. The text should be more specific on what will be discussed in the RMP. **Proposed change:** EVM suggests to be reworded as follows: “The impact of new adjuvants, stabilisers, preservatives or residuals of the manufacturing process on the safety profile of the vaccine should be discussed in the RMP”	Agreed.
7.1	**EVM**	**Comments:**	The Guideline uses the terms “adverse event”

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AEFIs		There are many Adverse Events that are reported as possibly related to vaccination, generally at low frequencies, that are not possible to qualify as 1a or 1b, because the causal relationship, i.e. the biological underlying mechanism, is very difficult to establish, or is unlikely. An AEFI with a plausible causal relationship to vaccination becomes an adverse reaction, therefore most of the AEFIs will likely be difficult to classify as 1a or 1b. A clear definition of AEFI vs. Adverse events should be provided.(impact on labelling rules). EVM wonders if there is an intention to change reporting requirement for AEFI in the legislation. If this is the case, in-depth discussions should be initiated with relevant parties. **Proposed change:** Needs clarification on the impact of this proposed classification, specifically with regard to reporting and labelling.	and "adverse reaction" as defined in EU legislation applicable to all medicinal products. It is considered important, in section 7.1, to explain the relationship of these terms with the AEFI concept, as this is a key concept in vaccine safety surveillance conducted in the framework of WHO programmes. There is no impact of the AEFI definition on EU reporting requirements or other procedures.
7.1.1. Suspected Adv. Reactions	**EVM**	**Comments:** Even if re-challenge is not always relevant for vaccine adverse events, such information should always be collected whenever possible – (e.g. convulsions) **Proposed change:** To be amended to take into account the comment proposed	Agreed.
7.1.1. Suspected Adv. Reactions Para 2	**EVM**	**Comments:** "For assessment of individual case reports of suspected adverse reactions, it is essential that complete and accurate records documenting administration of all vaccines, together with information on the date of vaccination, product administered, manufacturer, batch number, site and route of administration, detailed description and course of the adverse event/reaction as well as therapeutic intervention are provided." The list of information mentioned can not be considered as an exhaustive list as some elements are missing (e.g. medical history of patient) **Proposed change:** EVM suggests adding the word "notably" to the text: "For assessment of individual case reports of suspected adverse reactions, it is essential that complete and accurate records documenting administration of all vaccines, together with notably information on the date of vaccination, product administered, manufacturer,	Agreed.

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		batch number, site and route of administration, detailed description and course of the adverse event/reaction as well as therapeutic intervention are provided."	
7.1.1. Suspected Adv. Reactions Para 3, bullet 3	**EVM**	**Comments:** It is EVM's understanding that the CIOMS Working Group on Vaccine Pharmacovigilance is currently addressing the topic of suspected adverse reactions, and is planning a White Paper on the subject. EVM requests that the final guideline will be consistent with the CIOMS.	Relevant references will be included in the Guideline as available and applicable.
7.1.2 Vaccine failures	**EVM**	**Comments:** EVM considers that it should be clarify whether cases identified during vaccine effectiveness studies will need to be reported on expedited manner or cluster at the end of the study. **Proposed change:** Needs clarification	Agreed. The following will be clarified: In general, reporting of vaccine failures from effectiveness studies at individual level is not required. Reporting procedures should be described in the study protocol. The final study report should be submitted to the NCAs/EMEA. In certain situations, the MAH may clarify the reporting requirements with the NCA/EMEA prior to the start of study.
7.1.2 Vaccine failures 5th sent	**EVM**	**Comments:** It is stated that **"**…validated analytical tests for confirmation of the infectious agent should be used". In spontaneous reports, this is not under control of the manufacturer (or the agency) and the delay between reporting by the Health Care Professionals to the Marketing Authorisation Holders makes this practically impossible in most cases. **Proposed change:** EVM suggests to reword the sentence as follows: "…validated analytical tests for confirmation of the infectious agent should be used <u>to the extent possible</u>".	Agreed.
7.1.3 Vaccination	**EVM**	**Comments:** Vaccination error is not defined. There are many possible deviations, both from the	Agreed.

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errors Para 1, 1st sent		prescribing information and from the (usually national) recommendations. Are vaccination errors only defined by inappropriate handling, wrong route of administration…? The definition and possible consequences of vaccination error should be introduced in this chapter **Proposed change:** EVM proposes the following: "Inappropriate handling may lead to infection, bacterial contamination, blood-borne infection and abscess formation, loss of efficacy."	
7.2 PSURs Para 1, last sent	**EVM**	**Comments:** "If relevant, the reactogenicity of a vaccine should be analysed for different doses of the vaccine schedule and also across different vaccination schedules." Reactogenicity of a vaccine should be analysed in PSURs for different doses and also across different vaccine schedules. This poses several challenges that may seriously limit the relevance of such analyses. First of all, there are no denominators for exposure by dose. There is also a probable bias towards higher reporting of first dose, particularly in infants. Finally, there are many different schedules possible. EVM wonders which schedules shall be considered. **Proposed change:** Limitations should be acknowledged and some guidance is needed on the schedules to be analysed.	Not agreed, but clarification will be provided. Subanalyses of spontaneous reports with regard to possible differences in reactogenicity linked to different vaccination schedules is considered important and not to be confused with clinical investigations.
7.2. PSURs Last para	**EVM**	**Comments:** "If concomitant vaccination with another vaccines is specifically mentioned in the Summary of product Characteristics (SPC), safety aspects identified with co-administration vaccines should be analysed separately and summarised in the PSUR" **Proposed change:** The sentence should be reworded as follows: "If concomitant vaccination with another vaccines is specifically mentioned in the Summary of product Characteristics (SPC), when there is a safety ~~aspect~~ concern identified with co-administration vaccines should be analysed separately and summarised	Clarification will be included as follows: "If concomitant vaccination with another vaccines is specifically mentioned in the Summary of Product Characteristics (SPC), co-administration of vaccines should be analysed separately and summarised in the PSUR if there is a safety concern. The data have also to be analysed for new concerns regarding concomitant vaccination, independently of whether concomitant use is mentioned in the

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		in the PSUR	SPC or not."
7.3 PASS	**EVM**	**Comments:** Very detailed chapter when compared to others. In addition, most of the proposed methodologies linked to computerised databases are not controlled by, and not always accessible to the Marketing Authorisation Holder. Most of the other sections of the document seem to give guidelines to Marketing Authorisation Holders, while this section is more ambiguous.	The Guideline may also be of interest to investigators.
7.3 PASS Para 2, bullet 2	**EVM**	**Comments:** PASS studies should not be requested to address "perceived risks ad hoc" for which there is no reasonable rationale. **Proposed change:** "Those aiming to evaluate new safety issues ~~including perceived risks ad hoc~~"	Safety issues including perceived risks ad hoc will be replaced by safety concerns.
7.3 PASS Para 3, 3rd sent	**EVM**	**Proposed change:** "Retrospective (i.e. historical) cohort studies may be conducted, where the group in whom the adverse events/reactions is studied".	Agreed.
7.3 PASS Para 4, 1st sent	**EVM**	**Proposed change:** "In order to interpret the rates of the (various**)** ~~disease~~ event(s) that will occur over time in the vaccinated cohort, an unvaccinated control group is also required"	Agreed.
7.3 PASS Para 6	**EVM**	**Proposed change:** "Odds ratios may be adjusted for potential confounders by multiple logistic regressions."	Agreed to delete multivariate.
7.3 PASS Para 8	**EVM**	**Comments:** Typo error **Proposed change:** "…in the past as it might to avoid bias in a case-control design"	Agreed.
7.3	**EVM**	**Comments:**	Agreed. Reference to the WHO-CIOMS

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PASS Para 11, last sent		"Severity categories such as mild, moderate and sever should be avoided". Not clear what is being referred to here **Proposed change:** This sentence requires clarification.	Guideline on vaccine pharmacovigilance will be included as soon as available.
8.1 Signal detection Para 3	**EVM**	**Comments:** The need to stratify by seriousness is questionable. Stratification should occur on variables not assumed to be of interest themselves (e.g. age and geographic region). Identifying a concentration of events in the group of serious events is a potential signal by itself. Limiting the comparison to serious events may mask an unexpected excess of serious events compared to non-serious events. In addition this requirement may also limit the background numbers. **Proposed change:** To delete the "and seriousness" at the end of the sentence: "In a first step, it may therefore be appropriate to examine results of statistical methods using both comparator….with a stratification made at least be by age ~~and seriousness~~." **Comments:** EVM considers that some sections are too prescriptive, as the use of these tools is very dependent on the specificities of the vaccine and the database used. The two following sentences are used as examples: **"**If Consumer/Patient reports of suspected adverse reactions are included in the database, signal detection should also be stratified by source (Healthcare Professionals, Consumers/Patients)." **"**Results should be inspected in each stratum as pooled result of a stratified analysis may miss signals." **Proposed change:** EVM suggests to remove the word "should" by "could": "If Consumer/Patient reports of suspected adverse reactions are included in the database, signal detection ~~should~~ could also be stratified by source (Healthcare Professionals, Consumers/Patients)." **"**Results ~~should~~ could be inspected in each stratum as pooled result of a stratified analysis	Agreed.

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		may miss signals." **Comments:** It is EVM's understanding that the CIOMS VIII Group will be publishing their guidance for signal detection, and that this will include an annex concerning vaccine signal detection. EVM assumes that this section will be revised in accordance with this guidance. **Proposed change:** EVM suggests updating the guideline according to CIOMS'work.	Relevant references will be included in the Guideline as available and applicable.
8.2 Data analysis	**EVM**	**Comments:** Title should be Data Management. It is acknowledged that variations in batches can potentially lead to safety issues. Nevertheless, in normal circumstances the "safety profile" as such is not different from one batch to another. **Proposed change:** "8.2 ~~Data Analysis~~ Data Management"	Agreed.
8.2 Data analysis Para 2, 1st sent	**EVM**	**Comments:** "Key data to be collected and analysed (in addition to the data on the patient and immunisation history), are data about the vaccine and the diluent…." **Proposed change:** EVM proposes to add the following wording: "As part of an investigation, additional data should be ~~Key data to be~~ collected and analysed (in addition to the data on the patient and immunisation history), are data about the vaccine and the diluent…."	Agreed.
8.3 Risk evaluation Para 1, 3rd sent	**EVM**	**Comments:** "Evidence of causality is based on biological plausibility …" Evidence of causality is based on more than only plausibility and evidence excess of events. It may be relevant to make reference to the WER article on causality assessment for vaccines by the GAVSC (Causality assessment of adverse events following immunization, WER No. 12, 2001, 76, 85–92) **Proposed change:**	Agreed.

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		EVM suggests the following rewording: "Evidence of causality is among others**,** based on biological plausibility …"	
8.4 Risk-Benefit Assessment	**EVM**	**Comments:** Title should be Benefit/risk Assessment Guideline should be given on when and how Benefit Risk Assessment should be done **Proposed change:** ~~Risk-Benefit Assessment~~ Benefit/risk Assessment	Article 1(28 a) of Directive 2001/83/EC refers to risk-benefit balance.
9.1 Precautionary Measures 1st and 3rd sent	**EVM**	**Comments:** EVM considers that this section should be reworded to better link it to scientific evidence. **Proposed change:** EVM suggests to reword the first sentence as follows: "… there are ~~reasonable grounds~~ strong indications ~~for concerns~~ that there is a ~~potentially dangerous effects~~ potential risks ~~may be inconsistent with the chosen level of protection~~, which may affect the benefit/risk balance**."** EVM suggests to reword the third sentence as follows: "Because the potential for any risk is considered less acceptable in the case of preventive vaccines than in the context of disease treatment, while taking the overall benefit/risk into consideration, decision makers may respond…."	Agreed to replace potentially dangerous effects by potential risks. The overall risk-benefit balance needs always to be taken into account when assessing a risk for a medicinal product.
9.3 Risk communication Second para, third sent	**EVM**	**Comments:** It is understood that such communication should be a collaborative undertaking. Nevertheless the responsibility of Competent Authorities to provide timely and understandable information on safety aspects of vaccines could be made more explicit. Although balance about what is known and not know is needed, it should be mentioned that any communication needs a clear final recommendation from the Competent Authorities. **Proposed change:** EVM suggests adding the following sentence after: "Communication of safety information is essential to respond to public concern.	Reference to the respective VEASCO Guideline will be added as soon as available.

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		Such a communication should include a clear position on whether the information delivered has any impact on the use of the product"	
9.1	**MSD**	**Comments:** This indicates the CHMP/VWP believe it is appropriate to take precautionary measures even if no causal association is found or when scientific evidence is not yet strong. **Proposed change:** The intent is understood, however we note that overuse of such measures could in itself negatively impact trust in vaccine programs and vaccination coverage due to excessive or unwarranted media attention.	Noted.
5.1.4; p6	**SP**	**Comments:** Grammar: Either the first word of the section ('Where') should be deleted, or the second sentence (starting with "targeted monitoring") should be made part of the first sentence. **Proposed change:** ~~Where n~~New approaches and novel concepts (e.g. temperature selected mutants), new technologies (e.g. vaccines using novel delivery systems), novel adjuvants or alternative routes of administration (e.g. nasal administration) have recently been developed or are currently in the clinical testing phase and may give rise to new safety concerns. Target monitoring…..	Agreed.
6.1.6; p9; line 2	**SP**	**Comments:** Typo: split 'andreversion' **Proposed change:** 'and reversion of virulence'	Agreed.
7.1, p10	**SP**	**Comments:** AEFIs are mentioned (1, 1a, 1b, 2, 3). Procedure-related events do not appear to be included. In two respects: 4a: local AEs due to the vaccination (e.g. redness, pain at injection site) and 4b: events that are due to the device component of the vaccine (needle broken, sharp edge on nasal device, etc). **Proposed change:**	Procedure-related events fall under vaccination – related.

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		Please clarify how procedure-related events should be handled or add.	
7.1.1, p10	**SP**	**Comments:** There is a 4th category of adverse reactions possible, which is not covered by the ADRs mentioned in the 3 bullets: please add: ADRs that are a result of the vaccination procedure (e.g. stiffness of arm, etc).	See above.
7.3, p14, line 14	**SP**	**Comments:** It is specifically mentioned that severity categories should be avoided. It is not clear why this is the case. Please clarify.	The sentence will be deleted and reference to the WHO-CIOMS Guideline on vaccine pharmacovigilance will be included.
Exe sum, line 4	**Wyeth**	**Comments:** Safety surveillance must be specific to each vaccine, and not all vaccines can be shown to be effective when administered "after exposure to [the] infectious agent". **Proposed change:** The sentence should be re-worded as follows: … provide additional guidance on the safety surveillance of each vaccine ~~vaccines~~ used for the prevention ~~against infectious diseases~~ of an infectious disease, administered either before or after exposure to the infectious agent.	The executive summary will be deleted when final guideline is incorporated in Volume 9A.
1. Intro, line 3	**Wyeth**	**Comments:** Although poliovirus vaccine campaigns have effectively eliminated poliomyelitis from most regions of the globe, this disease – unlike smallpox – has not been eradicated (yet). **Proposed change:** The sentence should be re-worded as follows: Prominent examples are the global eradication of smallpox ~~small pox~~ and ~~polio~~ the elimination of poliomyelitis in most parts of the world	Agreed.
5.1.1 Type of Vaccine lines 1-3	**Wyeth**	**Comments:** "Live attenuated viral or bacterial vaccines" would seem to be a clearer way to express the thought contained within the current wording. With respect to inactivated vaccines, the three major categories are: protein, polysaccharide, and protein-polysaccharide conjugate, rather than differentiating bacterial protein (from viral protein) or recombinant protein	Agreed.

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		(from protein). **Proposed change:** The sentence should be re-worded as follows: ~~The safety profile of live virus or bacterial attenuated vaccines~~ Live attenuated viral or bacterial vaccines and inactivated vaccines (including vaccines based on ~~bacterial~~ proteins, polysaccharides or protein-polysaccharide conjugate ~~and recombinant protein~~ vaccines) may have different safety profiles.	
5.1.1 Type of Vaccine Para 1, lines 6-7	**Wyeth**	**Comments:** A clarification of the term "similar vaccines" is necessary: There is currently no accepted definition of vaccines classes, and no guidance on what types of adverse events or other safety issues might be similar across vaccines. The current wording is too vague concerning this issue to allow the MAH to comply. This statement is extremely broad: how similar would a vaccine need to be to trigger such a study/RMP change? Would this be based on disease target, vaccine type, carrier protein, or other criteria?	Agreed. It will be clarified that it will be a case-by-case decision, based on disease, disease target population, vaccine type, carrier protein or other criteria, as scientifically appropriate.
5.1.1 Type of Vaccine Para 4, lines 1-3	**Wyeth**	**Comments:** "In rare occasions, some live attenuated vaccines may cause serious syndromes closely resembling wild-type disease, probably not associated with the vaccine but with individual host factors increasing susceptibility." – rather than this cryptic sentence, it would be preferable to describe precisely the syndrome(s) being alluded to.	The example of yellow fever and vicerotropic disease will be included.
5.1.2 Immunogenic Adjuvants lines 4-6	**Wyeth**	**Comments:** "The clinical impact of the adjuvant in respect to impairing the immune response toward a Th2 (helper T-cell type 2)-response (as known for aluminium-based adjuvants) should be investigated in the post-authorisation phase." – This is a potentially prejudicial phrase, suggesting that a Th2 immune response may or may not represent an impairment. **Proposed change:** The sentence should be re-worded as follows: The clinical impact of the adjuvant ~~in respect to impairing the immune response toward a~~	Agreed.

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		~~Th2 (helper T-cell type 2) response (as known for aluminium based adjuvants) should~~ to modify the immune response, for instance, by the T helper (Th) cell response (towards Th1 or Th2), could be investigated in the post-authorisation phase.	
5.1.3 Comb. Vacc. lines 10-11	**Wyeth**	**Comments:** "If appropriate, risk minimising strategies might be explored (e.g. preventive anti-pyretic treatment in small children)." – Recommendations on the prophylactic administration of antipyretics during childhood vaccinations vary across the EU, and it may be considered inappropriate for the CHMP to impose a standard of medical practice across the EU. By contrast, clear instructions to medical personnel and parents, to monitor body temperature, or consider anti-pyretics in the case of a fever greater than a certain threshold, might be appropriate	See above.
5.1.4 Novel Vacc. lines 1-4	**Wyeth**	**Comments:** "Where new approaches and novel concepts (e.g. temperature selected mutants), new technologies (e.g. vaccines using novel delivery systems), novel adjuvants or alternative routes of administration (e.g. nasal administration) have recently been developed or are currently in the clinical testing phase and may give rise to new safety concerns." – if "novel delivery systems" means viral or bacterial vectors, please state this, so as to avoid any confusion with the subsequent "routes of administration".	Agreed. It will be clarified that novel delivery systems include viral and bacterial vectors as well as patches.
5.1.5 Batch-relatedness Para 2, line 1	**Wyeth**	**Comments:** "If there is reasonable suspicion of an association between the occurrence of adverse reactions and a particular batch of a vaccines, …" - A clarification of the term "reasonable suspicion" is necessary. The term reasonable suspicion is too broad: an MAH would not be able to easily determine which types of potential connections should be reported, and how they should be investigated. Further guidance regarding what might constitute such a suspicion would be helpful.	The explanatory notes in Volume9A, Glossary, Adverse reaction apply.
5.1.6 Vaccination Schedule	**Wyeth**	**Comments:** "The vaccine administration route is known to be another important factor influencing safety of a vaccine. Potential implications need to be considered, in particular for alternative routes of administration (e.g. intranasal, oral, intradermal). The impact of	Such testing may be necessary depending on the case. No change to guideline.

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Para 2, lines 1-3		adjuvants needs to be explored." – the final sentence on adjuvants suggests that safety issues might be related to a novel route of administration and an adjuvant. Is the CHMP suggesting that an adjuvant-free formulation should be tested in parallel?	
5.2.2 Pregnancy Para 1, lines 10-14	**Wyeth**	**Comments:** "Adequate duration of follow-up of the offspring should be guaranteed. Detailed information on vaccine exposure (including number of doses and gestational age at the time of exposure) before and/or during pregnancy is warranted." – We would appreciate more precise guideline on the follow-up and the exposure: how long is an "adequate" follow-up? How long before pregnancy is a vaccination considered to be an "exposure"?	Agreed. Further guidance will be included in the guideline with reference to the Guideline on Exposure to Medicinal Products During Pregnancy. It will be clarified that the adequate time of follow-up is the expected time period until manifestation of potential harm.
5.2.3 Immunocompromised line 3	**Wyeth**	**Comments:** There is no evidence that immunocompromised individuals would have more serious adverse events than other from all vaccines. We would suggest to add "when vaccinated with live vaccines" **Proposed change:** The sentence should be re-worded as follows: Immunocompromised individuals may not only be very sensitive to serious disease after exposure ~~with the natural infectious agents~~ <u>to the infectious agent targeted by the vaccine</u>, but may also be very sensitive to the occurrence of serious adverse reactions <u>when vaccinated with live vaccines.</u>	Agreed.
6.1.5 Epidemiology	**Wyeth**	**Comments:** This section does not fit in the "safety specification" section. Wyeth would suggest moving it in the section 6.2 on pharmacovigilance plan.	The structure of the RMP is provided in Chapter I.3 of Volume 9A.
6.2 Pharmacovigilance Plan	**Wyeth**	**Comments:** "At the time of marketing authorisation, data on long-term duration of protection, the potential for waning immunity and the need for a booster dose are usually not available. Plans for collecting these data should be presented as part of the RMP." – Beginning in the Introduction, this other aspect of vaccine safety (the possibility that a	The aspect raised is intrinsic to the matter of vaccination. A clarification will be included as follows: "At the time of marketing authorisation, data on

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Para 3		less than complete protection might be provided by a vaccination program) needs to be included.	long-term duration of protection, the potential for waning immunity and the need for a (additional) booster dose are usually not available. Plans for collecting these data should be presented as part of the RMP."
7.1 AEFIs	**Wyeth**	**Comments:** It is Wyeth's understanding that the CIOMS Working Group on Vaccine Pharmacogigilance is currently addressing the definition of AEFIs. The CIOMS WG is currently revising this extensively. Wyeth assumes that this section will be revised accordingly.	Correct assumption.
7.1.1 Suspected adverse reactions	**Wyeth**	**Comments:** It is Wyeth's understanding that the CIOMS Working Group on Vaccine Pharmacogigilance is currently addressing the topic of suspected adverse reactions, and is planning a White Paper on subject. The CIOMS WG is currently revising this extensively. Final guidelines should be consistent the CIOMS work. Wyeth assumes that this section will be revised accordingly.	See above.
7.1.2 Vaccine Failures	**Wyeth**	**Proposed change:** The sentence should be re-worded as follows: ~~Most vaccines are not 100% effective~~ No vaccine can be expected to be 100% effective**.**	Not agreed. Some vaccines have demonstrated a 100% seroprotection in clinical trials.
7.1.3 Vaccination Errors Para 1, line 1	**Wyeth**	**Comments:** "the proposed wording adds descriptive phrases to clarify to different types of adverse events caused by inappropriate handing, e.g., infection of the vaccine recipient (because of bacterial contamination of the vaccine), infection of a immunized subject (because of cross-contamination via blood), and local reactogenicity (because of the injection technique or bacterial contamination of the vaccine) **Proposed change:** The sentence should be re-worded as follows: Inappropriate handling might lead to ~~infection, bacterial contamination, blood-borne infection and abscess formation~~ adverse events such as infection due to bacterial contamination of the vaccine, transmission of blood-borne infections, or abscess formation	Agreed.

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		at the site of injection.	
7.2 PSURs Para 3, lines 6-7	**Wyeth**	**Comments:** Many vaccine components are used in numerous vaccine products; further, many have been used for decades, and have a well know safety profile. Analysis of well established stabilizers and preservatives would be difficult, as they are contained in many different vaccines, as well as other pharmaceutical products. Clarification is necessary regarding which components need to be analyzed and summarized in the PSUR. **Proposed change:** The sentence should be re-worded as follows: Literature data should not solely focus on safety information available for the anigen(s), but should also summarise published information relevant for other novel components such as novel stabilisers, novel preservatives and novel adjuvants.	Not agreed. New information becomes available for established ingredients needs to be assessed.
7.2 PSURs Para 4	**Wyeth**	**Comments:** This statement is too broad: We would welcome clarification on what is meant by mention in the SPC: which sections, and in which context should be included (e.g. only when there is a possible drug interaction). Further, the analysis suggested (separate analysis of each vaccine and summary in the PSUR), is unlikely to be of practical use given the nature of spontaneous reporting. **Proposed change:** The sentence should be re-worded as follows: "If concomitant vaccination with another vaccines is specifically mentioned in the Summary of product Characteristics (SPC), ~~safety aspects identified with co-administered vaccines~~ when there is a safety aspect concern identified with co-administration vaccines should be analysed separately and summarised in the PSUR"	See above.
7.3 PASS	**Wyeth**	**Comments:** While this overview of potential methods is appreciated, clarification of specific recommendations would be welcome.	Agreed. A reference to the respective VAESCO guideline will be added as soon as available.

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8.1	**Wyeth**	**Comments:** Care should be taken to ensure that these methods are seen as experimental in nature, and that these comments are suggestions only. Terms such as "should" ("signal detection should be stratified by source"), or "warranted" ("stratification between study reports and spontaneous reports is warranted") should be avoided. Signal detection, esp. concerning vaccines, is an evolving area of study, and no consensus on methods has been reach. Specific methods involved stratification and other techniques should not be proscribed in this guidance. It is Wyeth's understanding that the CIOMS VIII Working Group is planning on publishing their guidance in 2009; this will include an annex on signal detection and vaccines. Wyeth assumes that this section will be revised in accordance with this guidance.	Agreed. The experimental nature will be taken into account in the final guideline. See above.
8.4 Risk-Benefit Assessment	**Wyeth**	**Comments:** The paragraph indicates some of the multiple factors normally utilized in the risk-benefit assessment. We suggest elaborating on these factors in order to clarify the role and the amount of contribution that each one of these factors provides. Additionally, elaborate on some of the methodologies on how to utilize these factors to achieve the risk-benefit balance and how that might change with the success of the vaccination programmes.	Agreed. Reference to Volume 9A, Chapter I.8 will be included.
9.1 Precautionary Measures	**Wyeth**	**Comments:** "A decision to take measures without waiting until all the necessary scientific knowledge is available, may be particularly relevant for vaccines in special circumstances, e.g. vaccines for healthy children." – "special circumstances" is usually taken to mean an epidemic, an emergency, or an important unmet medical need, which may or may not apply to all "vaccines for healthy children".	Agreed. Wording to be clarified in final guideline.
9.1	**Wyeth**	**Comments:** While Wyeth understands the intention of the precautionary principle. However, in the situation where all necessary scientific knowledge is not available, special attention to both benefits as well as the risk of vaccination must be paid. The statement should be amended to include that decision makers should take into account both benefits as well as	Agreed. This is the key element of the applied precautionary principle.

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		risks.	