4 December 2013
EMA/756032/2013

Comments received from public consultation on good pharmacovigilance practices (GVP)

GVP - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases ' (EMA/488220/2012)

The draft of this module was released for public consultation between 12 April and 12 June 2013. The module has been revised, taking the comments received into account.

Those who participated in the public consultation were asked to submit comments using a specific template.

The comments received are published, identifying the sender's organisation (but not name). Where a sender has submitted comments as an individual, the sender's name is published.

The European Medicines Agency thanks all those who participated in the public consultation for their contributions.

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<Date of submission>

Submission of comments on 'GVP - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases ' (EMA/488220/2012)

Comments from:

Name of organisation or individual
Bavarian Nordic GmbH

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
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1. General comments

General comment
This vaccine-specific GVP-module is highly appreciated. It clarifies, in addition to the previously published GVP modules, the vaccine-specific pharmacovigilance tasks and obligations, and still is completely in line with the previous modules.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 351-352	Comment: The current wording suggests that, as part of routine pharmacovigilance, the follow-up of adverse reaction cases includes data on batch release specifications, expiry date(s) and laboratory test results about the batch. These details however are not usually needed for cases of product-inherent adverse reactions (vaccine product-related reaction), but only in the presence of a suspected quality issue (vaccine quality defect-related reaction). Proposed change (if any): In order to clarify that these additional batch-related data are only needed in presence of a suspected quality issue, the following wording might be appropriate (first bullet point starting in line 351): 'the vaccine and the diluent (if applicable), including manufacturer(s) and batch number(s). In case of a suspected vaccine quality-defect related reaction in addition also batch release specifications, expiry date(s) and laboratory test results about the batch'
Line 353-354	Comment: The current wording suggests that, as part of routine pharmacovigilance, the follow-up of adverse reaction cases includes distribution and administration-related data, such as storage and handling conditions for vaccines in the healthcare institution where vaccination took place. These details however are not usually needed for cases of product-inherent adverse reactions (vaccine product-related reaction), but only in the presence of a suspected quality issue (vaccine quality defect-related reaction). Proposed change (if any): In order to clarify that these additional distribution and administration-related data are only needed in presence of a suspected quality issue, the following wording might be appropriate (second bullet point starting in line 353): In case of a suspected vaccine quality-defect related reaction, also distribution and administration-related data, such as storage and handling conditions for vaccines in the healthcare institution where vaccination took place.

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10th May 2013

Submission of comments on 'GVP - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases ' (EMA/488220/2012)

Comments from:

Name of organisation or individual
Nick Andrews

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When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment
	A very useful and well written Guidance document

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 517	Comment: Reference 12 looks wrong – do you mean 11 Proposed change (if any):
Line 135	Comment: I think you need to define effectiveness somewhere (perhaps in Annex I) as many people confuse impact and effectiveness. I assume by effectiveness you mean an estimate of the direct effect of the vaccine as measured in an observational study (not a clinical trial which is impact). Proposed change (if any): Define effectiveness

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<12.06.13>

Submission of comments on 'GVP - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases ' (EMA/488220/2012)

Comments from:

Name of organisation or individual
Vaccines Europe

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1. General comments

General comment
Vaccines Europe acknowledges the effort to address vaccine specificities in a separate guidance. The proposed guidance includes key important elements previously highlighted by Vaccines Europe. Nevertheless Vaccines Europe would like to propose some modifications and improvement: • This guidance should provide some advice about how vaccines manufacturers should deal with patient years units in exposure tables • It is not clear from the guidance how to best manage the conflicting comments about 1) vaccine specificities regarding excipients, adjuvants, manufacturing issues within and across companies with 2) the pooling of manufacturer unknown information with branded product information to perform safety assessments, including in the PBRER. As these biologics are really more complex than standard medicine formulations (i.e., pills, syrups) for the reasons noted in the GVP for vaccines draft, re-consideration needs to be given to this general lumping of data in aggregate safety analyses (i.e. non-integrated sub-analyses). Finally it is important to highlight that this module should be aligned with GVP Module V on Risk Management Plans.

2. Specific comments on text 'GVP - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases '

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 98	**Comment:** Anxiety-related conditions post-immunisation is one of the four Adverse Event Following Immunisation (AEFI) categories defined initially but it is not further addressed in the document
Lines 108-130	**Comment:** Aspects on the seasonal administration of some vaccines should also be added to the list. **Proposed change:** Add the following bullet point to the list of aspects to be considered when conducting vaccine pharmacovigilance: • "Some vaccines are also administered seasonally, at a time when infectious diseases and associated complications have increased incidence in the general population. This increase in background noise may make causality assessment more challenging."
Lines 108-130	**Comment:** The higher degrees of patient advocacy and non-scientifically driven data that becomes part of the general community conversation on vaccines is suggested, but not explicitly noted in this section. This is a critical aspect to vaccine surveillance (and perhaps rare diseases medicinal products) as it drives other sections such as Risk management and Safety Communication. **Proposed change:** Add the following bullet point to the list of aspects to be considered when conducting vaccines pharmacovigilace: • "The higher degrees of patient advocacy and non-scientifically driven data may become part of the community conversation on vaccines having a critical impact in vaccine surveillance impacting risk management and safety communication."
Line 114	**Comment:** Vaccines can also be administered to adults in an age when some diseases could emerge; therefore we propose to add this point in the sentence **Proposed change:** "….vaccination may be given in adults at an age in which certain chronic conditions have a higher incidence /prevalence or in children at the age…"
Lines 122-125	**Comment:** Herd immunity and vaccine coverage level also play an important role for vaccine benefit-risk balance **Proposed change:** "… the proportion of infected persons with a clinical disease and the severity of this disease, vaccine coverage and herd immunity;"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 126-128	**Comment:** The concerns raised by the public that impact the vaccination programme is an aspect that impacts all stakeholders, this aspect should be addressed in a collaborative approach. Furthermore, concerns are raised both by the public and the media. **Proposed change:** "concerns raised by the public and the media may have a negative impact on the vaccination programme and should be adequately addressed in a collaborative effort of all stakeholders;"
Lines 128-130	**Comment:** Effective communication is difficult here also because there are, to a larger extent than generally seen with medicines, multiple audiences to which these important messages must be communicated. In this aspect, third-party scientific bodies that make recommendations regarding use may play an important role, in conjunction with MAHs and Health Authorities, in communicating to Healthcare providers and/or patients. **Proposed change:** "effective communication about safety of vaccines and vaccination is difficult, given the fact that perceptions of harm may persist despite evidence that a serious adverse event is not related to the vaccination and the complexity of communicating these messages to multiple audiences (e.eg healthcare providers, patients, parents, etc.)"
Lines 135 -140	**Comment:** a distinction should be made between vaccine efficacy (largely immunogenicity) and vaccine effectiveness (performance of vaccine seen in real life). The definitions for vaccine efficacy and vaccine effectiveness have been proposed at the end of this document as comments on the annex "PI: Vaccines for prophylaxis against infectious diseases – Definitions for inclusion in GVP Annex I Rev2"
Lines 157-176	**Comment:** In addition to challenges listed in this section around logistical collection and processing of large volume adverse events reports is the need to assess reporting biases arising from rapid use in new populations and the availability of safety indicators in a timely fashion (real-time) to be able to take evidence-base decisions as the vaccination campaign moves along (more relevant in large-scale vaccination campaigns). **Proposed changes:** Add following bullet points: • "need to assess reporting biases arising from rapid use in new populations, atypical health care delivery systems, or in otherwise unusual circumstances that make any findings difficult to validate and/or generalise to the usual use situation/ population; • availability of safety indicators in a timely fashion (real-time) to be able to take evidence-base decisions as the vaccination campaign moves along (more relevant in large-scale vaccination campaigns);"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 170-171	**Comment:** There is a need to provide examples of alternative statistical and epidemiological methods in order to clarify this challenge **Proposed change:** Add the following examples: " ... to allow the appropriate level of safety, e.g. self-controlled case series, case-crossover, and case-time-control, etc.;"
Lines 172-176	**Comment:** It is not always possible to ascertain the total number of vaccinated population. Only an estimate is available based on doses administered. Take into account that for some vaccines it is not possible to determine the proportion of vaccinated versus not by sex or age group when the vaccine is indicated for a large number of cohorts.
Lines 199-200	**Comment:** Depending on available indicators it may be sometimes complex to consider the impact of a vaccine on the epidemiology of the vaccine-preventable disease **Proposed change:** "For vaccines already included into a vaccination programme, the impact of the vaccine on the epidemiology of the vaccine-preventable condition should be considered depending on available indicators"
Line 201	**Comment:** should animal study, in vivo, and in vitro data be presented in this section?
Lines 214-219	**Comment:** The potential impact of impurities, residual proteins of host cells are difficult to anticipate. The risk is addressed at manufacturing level and controls are put in place to proactively look at trends, quality aspects and signal detection. Also, this section does not seem to be in alignment with GVP Module V on Risk Management systems. **Proposed change:** Delete in line 214: ~~"Vaccine-related quality aspects should be discussed in this section."~~ Add in line 219: "These potential risks should be considered when the impact of the change of the profile in the manufacturing process can be anticipated."
Line 203	**Comment:** Add "and the vaccine as a whole" **Proposed change:** "This section should present findings of pre-clinical testing related to the antigen, the adjuvant, impurities, contaminants and the vaccine as a whole, and..."
Lines 221-223	**Comment:** Special population may not only point to age, pregnancy and immunocompromised people.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change: The list of population to be considered for discussion should be completed with "Patients with other relevant underlying conditions or comorbidities (e.g. contraindications)"
Lines 272-273	**Comment:** It is unclear how EMA envisages this being incorporated into potential for medication errors, as this is not product specific but related to good clinical vaccination practices and overall local management of mass vaccination (not specifically managed by MAH). **Proposed change:** Please clarify
Lines 274-276	**Comment:** More guidance is needed in this point. As above, this is not product specific outside of potentially anticipated brand name similarities and otherwise reflects good clinical practice in being aware of vaccination history by clinician. **Proposed change:** Please clarify
Lines 278-312	**Comment:** It is unclear if risks associated with potential interaction with medicinal products usually given in the target population should always be considered in the RMP. It seems difficult as the RMP is a global document and the treatments are country specific **Proposed change:** Please clarify
Lines 288-290	**Comment:** This finding has only been observed once (Infanrix Hexa & Pevnar Phase III B) and therefore it should not be listed at potential risk for all vaccines **Proposed change:** Delete bullet point: • ~~potential interactions with medicinal products usually given to the target population or administered as a prophylactic treatment (e.g. antipyretics in order to minimise adverse reactions);~~
Lines 318-319	**Comment:** Not clear what is meant by "the clinical impact of different policies concerning vaccination schedules and target population" please clarify. It would seem this goes beyond a single MAH as a national/regional policy issue, and is this unclear how MAH to discuss this as outside of its purview. **Proposed change:** Please clarify
Line 335	**Proposed change:** Replace "autoimmune disorders" by "comorbidities of relevance in target population"

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 321-325	**Comment:** While it is possible to analyse the number of Adverse Events Following Immunisation (AEFI) reports by age group it is essentially not possible for the companies to get information on number of doses administered by age group (if vaccine is recommended in different age groups, for example from 4 years + without upper age limit). Frome time to time such study may be performed for signal investigation/ hypothesis testing but not on a routine basis. **Proposed change:** Change the following "Whenever possible and relevant ~~the~~ methodology for data collection from both routine and additional pharmacovigilance activities for vaccines ~~should allow data retrieval and~~ analysis may consider analysis by age groups..."
Lines 349-355	**Comment:** As part of the follow up on adverse reactions some activities described cannot be done in routine basis but are performed to further investigate a signal which is rarely identified on based on a single case, or when quality issue is suspected. **Proposed change:** Implement the following changes: "As part of the follow-up of adverse reactions, efforts have to be made to collect data on ~~data should be collected~~ (in addition to data on the patient, the adverse reaction and the vaccination history) ~~about~~ the vaccine and the diluents (if applicable), including manufacturer(s), batch number(s), the vaccination series administered and the route of administration. ~~batch release specifications, expiry date(s) and laboratory test results about the batch if appropriate~~ In case of a suspected quality defect further to a signal, additional information may be requested as regards batch release specifications, expiry date(s) and laboratory test results about the batch if appropriate, distribution and administration-related data, such as storage and handling conditions for vaccines in the healthcare institutions where vaccination took place. ~~The vaccination schedule and the route of administration."~~
Lines 359-360	**Comment:** This is not always possible, i.e. no immunological assay will allow to distinguish between severe dengue disease post-vaccination whether it's caused by vaccine strain or infection with the wild type virus **Proposed change:** Please clarify or delete the sentence: ~~"Validated and standardised assays, including assays to distinguish between wild and vaccine strains, should be implemented prior to marketing authorisation for appropriate case assessment"~~
Line 366	**Comment:** We propose to add wording on pre-existing disease or medical condition for which the vaccine is indicated as risk factor for vaccine failure.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change: "Risk factors for vaccine failure should be analysed (e.g. obesity, age, smoking status, vaccination schedule, concomitant disease and pre-existing disease or medical condition that is part of the disease the vaccine is indicated for).
Lines 326, 379	**Comment:** Unclear distinction described for "Routine" versus "Additional" pharmacovigilance activities. **Proposed change:** Although there are nice examples in each section, clarify the general distinctions between the two classifications ("Routine" vs. "Additional") in the beginning of each section.
Lines 403-409	**Proposed change:** Add in line 407: "Pregnancy registries should be able to differentiate prospective (unbiased) from retrospective reports and calculation of congenital malformation rates should be independently analysed."
Line 416	**Comment:** "Follow-up time" suggests that only the time after vaccination will be reviewed and the time before vaccination needs to be reviewed in order to distinguish between prevalent and incident cases. **Proposed change:** Replace "follow-up time" with "case ascertainment"
Line 420	**Comment:** "Relevant risk factors" would be an example of a confounder of having the risk factor for disease was also associated with vaccination. Other confounders may also need to be considered. **Proposed change:** "relevant risk factors or other confounders"
Line 450	**Comment:** It is unclear whether the MAH should describe in every RMP the full list of criteria. More specification is needed to avoid overloading RMPs with theoretical suggestions. In fact, batch recall depends on a variety of factors ranging from the nature of the vaccines to quality problems and a worldwide procedure listing criteria for batch recall does not exist. **Proposed change:** Delete the sentence: ~~"Pre-defined criteria for batch recall or quarantine should be included in this RMP section (see P.I.B.5)."~~
Line 451	**Comment:** Should we rather use PBRER than PSUR? The previous RMP module (module V) had not defined this part and the B/R assessment. They used to be part of PBRER.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 454	**Comment:** Minor changes of manufacturing process are not supposed to have an impact on safety. In general changes in manufacturing process are supposed to improve vaccine safety but not result in safety risks. **Proposed change:** Remove "minor" from the sentence: "... special consideration should be given in PSURs for vaccines to any potential impact on safety of major ~~as well as minor~~ changes in the manufacturing process."
Lines 456-458	**Comment:** "Safety aspects in subpopulations (such as pregnant women) should be analysed...". This is not relevant to be addressed in spontaneous reporting as there is too much bias, in particular for pregnant women due to under reporting and to the fact that most pregnancy cases received are retrospective.
Lines 477-479	**Proposed change:** Add after line 479: "Consideration in the planning of the PASS studies should include the fact that some very rare conditions, which occurrence in general population is <1 in 10,000 or 1 in 100,000 or even less, may never been seen in PASS regardless of the size."
Lines 483-487	**Comment:** It should be acknowledged that secondary data in large databases may not be available in some countries (e.g. Eastern Europe)
Lines 495-497	**Comment:** The inability to classify cases using Brighton Collaboration criteria should not discourage investigators from using an alternative case definition that is more compatible with the data available. **Proposed change:** "When feasible, ~~A prerequisite is~~ the use of globally accepted…."
Line 501	**Comment:** The control period does not necessarily include the entire remaining observation period in a SCCS study. Windows can also be defined for this period (before and/or after vaccination) **Proposed change:** Similar to the risk period where "e.g." is used, add "e.g." to "(the remaining observation period)"
Lines 508-510	**Comment:** Another important limitation of SCCS is that it does not control for time-varying confounders. **Proposed change:** Add in line 509: "Like cohort or case-control studies the SCCS method remains however susceptible to bias if vaccination is timed to minimise the risk of an adverse event or it does not control for time-varying confounders."

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Lines 519-525	**Comment:** The largest potential limitation of ecological studies is not mentioned (ecologic fallacy where associations found at the aggregate level do not reflect the true association at the individual level). An added strength of this study design is that individual vaccination status does not need to be obtained so results can often be reported more quickly than when many other study designs are used. **Proposed change:** Introduce the following changes: This comparison at the population level limits the possibility to control for confounding variables. Furthermore, associations found at the aggregate level do not reflect the true association at the individual level. [...] Ecological studies may however be useful to generate hypothesis and have the added strength that as individual vaccination status do not need to be obtained, results can often be reported more quickly than with other study designs."
Lines 539-540	**Comment:** A signal is defined as "either adverse or beneficial." However, an example of signal evaluation for benefits is not described anywhere in the remainder of the document. **Proposed change:** Give an example of the above.
Lines 577, 603	**Comment:** Disproportionality analysis methods (PRR, EBGM) are not described with the same level of detail as O/E methods. **Proposed change:** Add a few more details about PRR and Bayesian approaches.
Line 583	**Comment:** We cannot say that vaccines are all that different when it comes to quantitative signal detection, such as the calculation and interpretation of SDRs as drugs. The data always has to be interpreted in a way that recognises the background population and inherent risks, reporting biases, limitations of the database used, etc... Many of the points made are true for drugs as well as for vaccines, particularly around the generation of false positives, depending on which thresholds is used. A general program could easily be designed with acceptable sensitivity and specificity, but medical interpretation will always be required to screen for false positives and otherwise triage the data. **Proposed change:** The wording should be more balanced as the examples that are proposed in this wording are not only true for vaccines but also for other drugs.
Line 624	**Comment:** In other GVP modules (e.g. module VII line 477) it is recognised that it is difficult to obtain and validate subject exposure

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	data from marketing experience. Nevertheless, this draft document recommends exposure estimation on a "near real-time basis". **Proposed changed:** Change the text as follows: "[...] and near real-time exposure data if available (to determine..."
Lines 649-653	**Comment:** The sensitivity analysis should be made considering realistic ranges of exposure or disease.
Lines 664-668	**Comment:** It should be specified that sequential methods can be used only in longitudinal database. In general, weekly or monthly use of sequential methods will be helpful. However, for most of the databases that industry subscribes to the updates are quarterly or bi-annual. Typically the data is 4-6 months old when it becomes available to the manufacturer. This would limit the signal detection activity as it's not 'real-time'. **Proposed change:** specify that maxSPRT is used on longitudinal data only when the frequent data source updates are available.
Line 678	**Comment:** Challenge and rechallenge are very relevant to vaccines; therefore we suggest removing "often not applicable to vaccines". **Proposed change:** "Information on dechallenge and rechallenge ~~are often not applicable to vaccines, but where they are, such~~ data should be recorded."
Lines 684-695	**Comment:** The season and outbreaks (including pandemics) can be important considerations for signal evaluation **Proposed change:** Add "season" and "outbreaks" to the bulleted list.
Lines 690	**Comment:** There is no mention of adjuvants here; it seems they should be referred to. **Proposed change:** • "past experience with similar vaccines, adjuvants and types of antigens, in order to identify adverse reactions..."
Line 710	**Comment:** Typo: "of a sufficient of amount" **Proposed change:** Change to "of a sufficient amount"
Line 730	**Comment:** Suggest to add to the list of cases reported region and country since there are variability in reporting of events by country

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	and region in the world. **Proposed change:** Change the text as follows: "time and space clustering of cases, e.g. cases reported by a single hospital, physician or locality, region or country;"
Line 779	**Comment:** Transparency should consider lay language for clear presentation of events. Specialist should be involved in providing the communication to the public. Also, the word "use" is missing and there is a typo (regarding the…of (a) vaccine(s)). **Proposed change:** "to the public regarding the use of (a) vaccine(s)"
Lines 815-816	**Comment:** We recommend including differentiation by age group and sex. **Proposed change:** "For the purpose of quantifying safety concerns, relevant background rates, by age group and sex if available, of signs and symptoms which…."
Line 828	**Comment:** We propose to detail published documents. **Proposed change:** "….reference should be made to published documents (documents that meet scientific rigor) and statements by recognized public health entities."
Line 847	**Comment:** Preposition "to" is missing (Member States or … the marketing authorisation) **Proposed change:** add preposition "to"
Line 855-861	**Comment:** The notion of 'severe' may erroneously suggest that medical confirmation of ADRs is limited to severe ADRs. Also it is preferable to use the term reaction than event, it may generate confusion **Proposed change:** Change to: " …and medically confirm the occurrence of any ~~severe~~ adverse ~~event~~ reaction occurring after vaccination"
Lines 865-867	**Comment:** It is practically impossible to know how many doses of vaccine from a single batch have been administered as some GPs may

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	stockpile the vaccine and with a shelf-life 3 years or so vaccine sold in one year may not be used the same year. In many of the databases batch information is either not recorded or not reliable. **Proposed change:** Change wording as follows: "Marketing authorisation holders should collect and record all available information regarding distribution of vaccine batches in Member States and the numbers of doses of vaccines ~~administered~~ distributed by batch"
Lines 883-884	**Comment:** It has to be taken into account that information on vaccine exposure for a batch stratified by age, gender will not be available. This comment related to the rationale above.
Line 903	**Comment:** We recommend adding that also competent authorities should collaborate among themselves. **Proposed change:** "National competent authorities should collaborate among themselves and with the World Health……"
Line 956	**Comment:** Please clarify the sentence "changes in the manufacturing process of a biotechnologically-derived vaccine", since we consider all vaccines to be biotechnological products.

<Date of submission>

Submission of comments on 'GVP - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases ' (EMA/488220/2012)

Comments from:

Name of organisation or individual
World Health Organization – Essential Medicines and Health Product Department

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
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1. General comments

General comment
This is a very well prepared document, easy to read and comprehensive. It does include the latest concepts for vaccine pharmacovigilance that have been developed through international collaborations. We assume that interactions with WHO will be explained in Module XIV. The new EU GVP document is an opportunity to further develop the content of Module XIV. In addition, it would be good if we could also see the WHO EMA relationship more explicit / better articulated in section P.1.C.7. WHO is available to contribute with suggestions/input to this section. In particular, the following aspects would need to be addressed for vaccines that are intended for use outside the EU: 1. The importance of capturing vaccination errors from EPI: how will these be reported in EPI (see line 929, for EU, where vaccination errors will not be reported through ICSRs, but only through PSURs). In EPI, the concept of PSURs will not apply 2. Section P.I.C.7 mentions that 'for vaccines intended for use outside EU, companies that acquire a marketing authorisation in a third country or are entitled to place the product on the market in a third country on the basis of the opinion should implement the pharmacovigilance activities specified in the procedure'. However the 'procedure' (reference 19 in the doc) does not mention how pharmacovigilance activities for such products will be pursued, or by who, when these products are introduced through EPI. Towards this, there needs to be an explicit reference on roles and responsibilities for pharmacovigilance (including AEFI reporting), collaborations between EPI, the manufacturer and the national pharmacovigilance centre

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 66	Comment: Could you say *the overall objectives and processes of pharmacovigilance are* ***similar*** *for vaccines and other types of medicinal products* rather than ***no different*** Proposed change (if any):
Lines 158-176	Comment: How about the aspect of risk groups (immunocompromised) not having been included in trials before marketing in PIA4. Proposed change (if any): These are dealt with in PIB123 but might deserve being mentioned here.
Lines 547	Comment: Brighton Collaboration case definitions are very restrictive and important information might be lost if a report is not filed because the AEFI does not match closely enough a case definition Proposed change (if any): ICSR should be submitted even if the AEFI does not match the available case definition
562-7	Comment: Background rates are of limited use in a spontaneous reporting system in which no denominator is known and the numerator subject to significant underreporting Proposed change (if any): Comparison with background rates in studies with known exposure and systematic data collection
Lines 673-695	Comment: Two possible additions to this section PIB4.6 Proposed change (if any): Add Cluster investigation vs single case investigation, and What AEFI reports should be investigated
Lines 696-717	Batch recall and quarantine should describe more clearly the indications for recalling a batch

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
922-4	Comment: The collaboration with WHO should include the timely transmission of AEFI reports either by EMA or the National Authorities to the UMC in order to guarantee that this global, central repository of ICSRs is kept up to date and can perform its tasks in a timely and adequate manner

Please add more rows if needed.