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3 Guideline on good pharmacovigilance practices (GVP)

4 Product- or Population-Specific Considerations I: Vaccines for prophylaxis 5 against infectious diseases

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This track-change version identifies the majority of changes introduced to the public consultation version of this document as the Agency's response to the comments received from the public consultation. This track-change version is published for transparency purposes and must not be taken or quoted as the final version.

* For this reason, the timetable above, and in particular the date of coming into effect, apply only the clean version published as final.

For the final version of this module and any future updates, please see the GVP webpage of the Agency's website.

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P.I.A. Introduction

Vaccination is one of the most effective and widely used public health interventions, whose benefits for individuals and the community have been abundantly demonstrated. Prominent examples are the global eradication of smallpox and the elimination of poliomyelitis in most countries. As with any other pharmaceutical product, however, no vaccine is without risks. Robust systems and procedures must be in place to continuously monitor quality, safety and efficacy ~~of the product~~. ~~In this context,~~ V~~v~~accine pharmacovigilance has been defined by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance as the science and activities related to the detection, assessment, understanding and communication of adverse events following immunisation and other vaccine- or immunisation-related issues, and to the prevention of untoward effects of the vaccine or immunisation.[1]

The objective of this Module is to strengthen the conduct of pharmacovigilance for vaccines. It should be noted that the overall objectives and processes of pharmacovigilance are ~~no different~~similar for vaccines and other types of medicinal products and this guidance does not replace the information provided in the other modules of the Good Pharmacovigilance Practices (GVP). This Module focusses on vaccine-specific aspects and unique challenges that should be borne in mind when designing and implementing pharmacovigilance activities for vaccines.

This Module is relevant to vaccines used for pre- and post-exposure prophylaxis of infectious diseases and does not cover therapeutic vaccines (e.g. viral-vector based gene therapy, tumour vaccines, anti-idiotypic vaccines such as monoclonal antibodies used as immunogens). This guidance is addressed primarily to marketing authorisation holders and competent authorities but may also be useful to other stakeholders (e.g. sponsors of clinical studies, healthcare professionals, public health authorities).

P.I.B. provides guidance specific for vaccines in relation to the main pharmacovigilance processes described in the Modules of the GVP. Where applicable, specific recommendations are provided for situations where vaccines are administered in mass vaccination programmes and where a large number of reports of suspected adverse reactions is expected in a short period of time.

P.I.C provides specific guidance related to the operation of the EU network.

The legal references for this guidance are Directive 2001/83/EC, as amended by Directive 2010/84/EU (referenced as DIR), Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010 (referenced as REG), and the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC (referenced as IR).

Other relevant guidance include the CHMP Guideline on Clinical Development of Vaccines[2], guidance on design and specific aspects of clinical trials to be conducted pre and post marketing authorisation, and the CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data.[3]

P.I.A.1. Terminology

It is acknowledged that the term Adverse Event Following Immunisation (AEFI) is used at international level. The term was defined as any untoward medical occurrence which follows immunisation and

[1] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.~~Definition and Application of Terms for Vaccine Pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, CIOMS 2012;available at http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf.~~

[2] EMEA/CHMP/VWP/164653/2005, available on EMA website http://www.emea.europa.eu.

[3] EMEA/CHMP/313666/2005, available on EMA website http://www.emea.europa.eu.

which does not necessarily have a causal relationship with the usage of a vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. AEFIs have been further classified by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance into four categories according to possible causes (apart from a coincidental event): vaccine product-related, vaccine quality defect-related, immunisation error-related and immunisation anxiety-related.[4] ~~–~~The term AEFI is not used in this guidance as the term "adverse event" (~~defined in~~ see Annex I) already designates any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this medicinal product. In addition, EU regulatory requirements concerning pharmacovigilance activities apply to adverse reactions, this term being defined in the legislation (see Annex I).

The terms immunisation (the process of making a person immune ~~to an infection~~) and vaccination (the administration of a vaccine with the aim to produce immune response) have slightly different meanings and are not used interchangeably in this guidance. The term vaccination is generally used unless ~~otherwise~~ justified otherwise by the context.

P.I.A.2. Aspects specific to prophylactic vaccines

When conducting vaccine pharmacovigilance, the following aspects should be considered:

- vaccines are usually administered to otherwise healthy individuals, often very young or vulnerable; they may be administered to a large fraction of the population and vaccination is mandatory in some countries; there is therefore a high level of safety required for vaccines and tolerance to risk is usually low;
- assessment of causality between adverse events and vaccines may be difficult: several vaccines are often administered concomitantly, it is inevitable that, with high vaccine uptake, incident cases of many natural diseases in given population cohorts will occur in temporal association with vaccination~~vaccination may be given in children at the age where some diseases may emerge, ~~, and considerations of dechallenge and rechallenge are not relevant to many vaccines which are administered only once or have long-term immunological effects;
- vaccines are complex biological products which may include multiple antigens, live organisms, adjuvants, preservatives and other excipients, and each of these components may have safety implications; variability and ~~small~~ changes in the manufacturing process, new components and new production and administration technologies may impact on safety, and this may require specific pharmacovigilance systems;
- the benefit-risk balance for vaccines also depends on factors acting at the population level, including the incidence, geographical distribution, seasonal characteristics and risk of transmission of the infectious disease in the target population, the proportion of infected persons with a clinical disease, ~~and~~ the severity of this disease, vaccine coverage and herd immunity;
- concerns raised by the public may have an ~~negative~~ impact on the vaccination programme and should be adequately addressed;
- 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 communicating about vaccine safety to multiple audiences (e.g. healthcare providers, patients and parents) is complex.

[4] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.~~Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, CIOMS 2012.~~

P.I.A.3. Changes of the benefit-risk balance

The benefit-risk balance of many vaccines is dynamic and may change over time, or may appear to change over time, and this may impact on pharmacovigilance activities. Factors associated with these changes include their efficacy~~/~~ and effectiveness in vaccination programmes and their biological variability.

P.I.A.3.1. Efficacy~~/~~ and effectiveness

Unlike most medicinal products which are given to treat an illness, prophylactic vaccines offer the potential to significantly reduce, or even eradicate, communicable diseases. This introduces a real dynamic to the balance of risks and benefits, whereby the former may outweigh the latter over time (e.g. live oral polio vaccine and vaccine-associated paralytic polio). This may decrease tolerance to the risks of vaccines.

P.I.A.3.2. Biological variability

Unlike most medicines which are composed of relatively small molecules, vaccines are often highly complex multi-component products manufactured from biological systems that are inherently variable over time and between manufacturers (and sometimes between different production plants of the same manufacturer). As with other biological products, the safety, quality and efficacy of vaccines are as dependent on the product-specific manufacturing process as on the inherent profile of active antigens and excipients.

Due to this biological variability, the safety profile of vaccines with well-established safety profiles demonstrated by substantial use over many years may change over time. Such changes may be unpredictable and may arise from slight modifications in the manufacturing process or unintended quality deviations. Such changes can also be batch-specific. Furthermore, introduction of new or more sensitive assays may reveal previously unknown impurities or adventitious agents which may warrant a re-evaluation of quality and clinical safety.

This variability underlines the importance of brand-specific, and even batch-specific, pharmacovigilance activities for vaccines, and for traceability and continuous surveillance even for ~~the most~~ 'well-established' vaccines.

P.I.A.4. Aspects related to vaccination programmes

Most vaccines are 'universal', i.e. they are offered routinely to everyone in a given population cohort via a national public health programme. A typical new vaccine may achieve nearly 90% coverage in a given age group over a relatively short time period. Vaccines may also be offered to population cohorts via a targeted 'campaign' to tackle a specific infectious disease outbreak at a given point in time or under special circumstances, such as in a national emergency, military or pandemic situation.

Such vaccination programmes are associated with a variety of challenges for pharmacovigilance. The key ones include:

- a large number of suspected adverse reaction reports in a short time period may require resources for processing, analysing, presenting and communicating data;
- it is inevitable that rare or serious incident illnesses will occur in temporal association with vaccination; new suspected adverse reactions must be very rapidly investigated and distinguished from coincidental illnesses;

- lack of a comparable unvaccinated concurrent cohort requires alternative statistical and epidemiological methods to allow appropriate analysis of safety, e.g. case-only designs (see Appendix 1 of Module VIII and the ENCePP Guide on Methodological Standards in Pharmacoepidemiology[5]);
- mass vaccination in a short time period may be associated with very unique business continuity and infrastructure constraints; under such circumstances, specific consideration should be given to adapting pharmacovigilance plans to meet these challenges and ensure that resource is prioritised and necessary technical requirements are met (see Module I for public health emergency planning);
- the vaccinated population may include immunocompromised individuals, including those infected with human immunodeficiency virus (HIV), whose clinical status may not be known at the time of vaccination and who may be at a higher risk of risk of occurrence of the infectious disease targeted by the vaccine and of impaired immune response to vaccination, in particular when vaccinated with live vaccines.

P.I.B. Structures and processes

P.I.B.1. Risk management system

Most aspects of Module V on risk management systems are as applicable to vaccines as to other medicinal products. P.1.B.1. This section supplements that Module V and presents vaccine-specific aspects of the risk management plan (RMP).

P.I.B.1.1. RMP part I "Product overview"

This section should describe the intended purpose and impact of the vaccine, e.g. whether it is intended to prevent a disease or serious outcomes of the disease. It should provide information relevant to the safety of the vaccine and describe:

- the type of vaccine, e.g. whether it is a live attenuated viral or bacterial vaccine, an inactivated vaccine, a vaccine based on proteins, polysaccharides or protein-conjugated polysaccharides, a genetically engineered vaccine or a novel concept (e.g. temperature selected mutants);
- details of combined vaccines, where two or more vaccine antigens are combined in one pharmaceutical preparation in order to prevent multiple diseases or one disease caused by different serotypes;
- any new technology or novel delivery systems such as viral and bacterial vectors or patches, or alternative route of administration such as nasal administration;
- any immunogenic adjuvants, stabilisers, preservatives, excipients and residual material from the manufacturing process, including the immunological mode of action of any novel adjuvant.

P.I.B.1.2. RMP part II "Safety specification"

P.I.B.1.2.1. RMP module SI "Epidemiology of the indications and target population"

This section should focus on the natural history of the target disease, highlighting any difference between countries as appropriate. It should discuss any relevant examples of the impact of previous

[5] See http://www.encepp.eu/standards_and_guidances/index.shtml

and similar vaccines on the disease. For vaccines already included into a vaccination programme, the impact of the vaccine on the epidemiology of the vaccine-preventable condition should be considered.

P.I.B.1.2.2. RMP module SII "Non-clinical part of the safety specification"

This section should present findings of pre-clinical testing related to the antigen, the adjuvant, impurities ~~and~~, contaminants and the vaccine as a whole, and to interactions of the vaccine components, as well as any impact these findings have on the clinical testing and post-authorisation surveillance.

Cells from human, animal (including insects), bacterial or yeast origin may be used in an early step of the manufacturing process. As a consequence, residual proteins of the host cells may be present in the final product. As these impurities may consist of proteins that have structural homology with human proteins, potential harm caused by these residuals should be discussed, including any need for clinical testing.

Preservatives and stabilisers may not be immunologically inert (e.g. polygeline). Removal of a preservative and/or stabiliser from a well-established vaccine, or change of the source of any vaccine component, may have an impact on the safety profile of the vaccine and may require amendment of the RMP to include non-clinical data on the modified vaccines.

Vaccine-related quality aspects should be discussed in this section if relevant to safety. Manufacturing of medicines in biological systems, such as fermentation of bacteria, growth of virus in cell culture or expression of proteins by recombinant technology, may introduce variability within certain limits of the composition of the final product. In principle, contamination with unwanted infectious agents and other risks linked to any aberrant material cannot be totally excluded. These potential risks should be considered as they may result in adverse reactions.

P.I.B.1.2.3. RMP module SIV "Populations not studied in clinical trials"

Sample size and duration of clinical trials should be discussed in terms of power to detect common and uncommon adverse reactions and to address long-term risks. Limitations of the clinical trials should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population for vaccination.

Populations to be considered for discussion should include:

- Special age groups

  Immunological responses to vaccines depend on the independent and coordinated function of innate and adaptive immune responses which evolve with age. Differences of the immune response in different age categories may not only translate to different efficacy/effectiveness of vaccines, but also to differences in the safety profile. Adverse reactions may occur solely in certain age categories, e.g. hypotonic-hyporesponsive episodes in young children. Furthermore, the frequency of adverse reactions may change in relation to age. Targeted surveillance of adverse reactions in different age groups may be warranted.

- Pregnancy

  Although most live attenuated vaccines are contraindicated in pregnant women due to the known or suspected risk of transplacental infection of the foetus, inadvertent exposure during pregnancy cannot be totally excluded. Risk to the developing foetus from vaccination of the mother with an inactivated vaccine during pregnancy is considered theoretical but should be discussed, including data collected in the post-authorisation phase if available.

- Immunocompromised individuals

  Immunocompromised individuals, including those infected with human immunodeficiency virus (HIV), may have a higher risk of occurrence of the infectious disease targeted by the vaccine and of ~~an~~ impaired immune response to vaccination, in particular when vaccinated with live vaccines. Therefore, the benefit-risk balance in this patient group may need specific consideration.

- Patients with other relevant underlying conditions or comorbidities (e.g. contraindications).

P.I.B.1.2.4. RMP module SVI "Additional EU requirements for the safety specification"

The following aspects should be addressed in this section:

- Potential for transmission of infectious agents

  For live attenuated vaccines, this section should address aspects such as shedding (including shedding from vaccinated individuals to unvaccinated close contacts), transmission of the attenuated agents to close contacts, risk for pregnant women and the foetus, and reversion to virulence.

  As for all biological products, the potential for infections caused by residuals of biological material used in the manufacturing process as well as contaminations introduced by the manufacturing process should be evaluated and addressed.

- Potential for medication errors

  This section should address potential for vaccination errors and mechanisms put in place to adequately follow-up and investigate the root cause of any errors. Causes of vaccination errors to be considered include:

  - inappropriate handling or breakdown in the cold chain, which may lead to adverse reactions such as infection due to bacterial contamination of the vaccine, transmission of blood-borne infection, abscess formation at the site of injection or loss of efficacy/effectiveness; these issues apply particularly to multi-dose container vaccines without preservatives;
  - the method of administration (wrong or suboptimal route, inadequate dose, incorrect diluent), which may be associated with adverse reactions or vaccination failure;
  - non-compliance with recommended vaccination schedule, which may lead to vaccination failure;
  - product packaging and branding, which may lead to administration errors, especially if other types of vaccines are used concurrently in the vaccination programme, in which case similar packaging and branding should be avoided;
  - circumstances of a mass vaccination (e.g. in a pandemic) with use of multi-dose vials or with the need for dilution;
  - situations where several vaccines are marketed in a same country for the same indication, which may lead to patients receiving a vaccination series with different products or too many doses of a vaccine.

P.I.B.1.2.5. RMP module SVII "Identified and potential risks"

This section should provide information on the important identified and important potential risks associated with use of the vaccine pre- and post-authorisation.

The following important potential risks should be considered:

- waning immunity, requiring a continuous evaluation of the need for a booster dose;
- potential risks anticipated from experience with similar vaccines and vaccine ingredients (considering the biological plausibility); what constitutes "similar" will be a case-by-case decision, based on the disease, the disease target population, the vaccine type, the carrier protein or other criteria, as scientifically appropriate;
- potential risks associated with concomitant administration of several vaccines, such as for paediatric vaccines or vaccines used in travel medicine;
- 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);
- syndromes closely resembling wild-type disease, caused on rare occasions by some live attenuated vaccines (e.g. vaccine-induced measles meningitis or encephalitis, yellow fever vaccine and viscerotropic disease); in these cases, host risk factors such as age, gender and immune status should be described and the need for further investigations should be addressed, including clinical, serological and immunochemical analyses, and antigen detection, quantification and sequence analysis; certain strains may also be associated with adverse events usually seen with the wild-type disease;
- adverse events proposed to be reported and assessed with high priority, because, based on experience with the vaccine concerned or similar vaccines in terms of manufacturing process, composition (e.g. adjuvants), immunogenicity and novelty, they represent potential risks that would need immediate investigation or regulatory action, they could lead to a change in the benefit-risk balance of the vaccine, or they would require prompt communication to the public by regulatory or public health authorities; proposal for such adverse events of special interests (AESIs) may be particularly useful in situations of a mass vaccination programme where it is expected that a large number of adverse reactions may be reported and their processing may need to be prioritised.

The information on potential mechanisms for each identified or potential risk should include available data on association of the risk with the antigen itself, any other ingredient of the vaccine, including adjuvants, stabilisers, preservatives or residuals of the manufacturing process, the target population, interactions with other vaccines or medicinal products or the vaccination schedule. If some of these factors are clearly associated with some identified or potential risks, it may be appropriate to present these risks in different categories.

P.I.B.1.2.6. RMP module SVIII "Summary of the safety concerns"

This section should include a summary of the safety concerns (important identified risks, important potential risks and important missing information).

Important missing information to be considered includes long-term duration of protection, waning immunity and need for (a) booster dose(s) (in absence of information justifying their classification as potential risks) and the possible clinical impact of ~~different policies concerning~~ vaccination schedules and target population which differ from those studied pre-authorisation.

P.I.B.1.3. RMP part III "Pharmacovigilance plan"

What constitute routine and additional pharmacovigilance activities is described in Module V.

The methodology for data collection ~~from~~ in both routine and additional pharmacovigilance activities for vaccines should allow data retrieval and analysis by age groups (including premature infants, neonates, infants and the elderly), number of doses, different vaccination schedules and defined risk factors or underlying diseases. ~~Clusters of reported adverse events/reactions should be identified. Full traceability of all manufacturing changes and links to safety data should be ensured.~~

P.I.~~.~~B.1.3.1. RMP section "Routine pharmacovigilance activities"

Where routine pharmacovigilance activities normally used by the marketing authorisation holder for medicinal products have been adapted to vaccines, these amendments should be described in this section, for examples alternative methods to perform signal detection or alternative algorithms to evaluate individual case safety reports.

Where appropriate, this section should ~~also~~ describe routine pharmacovigilance activities ~~carried out~~put in place for the surveillance ~~-~~of the following events and reactions:

- serious but rare adverse reactions (even if the sole aim is to provide reassurance on safety);
- batch-related adverse reactions, including the measures taken to clearly identify the name of the product and the batch numbers involved in suspected adverse reactions (see Module VI~~.B.3.~~) and a description of how traceability of manufacturing changes will allow identify any related adverse reactions;~~;~~
- ~~udingautoimmune disorders;~~
- identified and potential interactions with co-administration of other vaccines, including the increased risk for adverse reactions and clinically relevant immunological interference;
- possible safety concerns reported with combined vaccines such as increased frequency or severity of known adverse reactions (local or systemic), as small differences of local or systemic adverse reactions between the combined vaccine and the precursor (combined or individual) vaccine(s) are usually not detected in pre-authorisation studies;
- any adverse events of special interest (AESIs) identified as an important potential risk in the safety specification; standard case definitions should be provided (e.g. Brighton Collaboration case definitions [6]) and age-stratified data on incidence rates in the population targeted by the vaccination programme should be compiled ~~and presented~~; if such data do not exist, they should be included in the pharmacovigilance plan as data to be collected in the post-authorisation phase (see P.I.B.1.3.2.);
- inappropriate use of vaccines and patterns of error;
- cases of breakthrough infections, which are expected without necessarily indicating a problem with the vaccine, as vaccines and vaccination programmes are not 100% effective; although this issue cannot be fully investigated via spontaneous reporting, reports of vaccine failure can nonetheless generate signals, and risk factors should be analysed (e.g. obesity, age, smoking status,

[6] Available on Brighton Collaboration website http://www.brightoncollaboration.org.

vaccination schedule, concomitant disease); appropriate case definitions and validated analytical tests for confirmation of the infective agents should be used whenever possible and the recommendations of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance should be considered for the definition and classification of cases of vaccination failure;[7]

- adverse reaction reports indicating a possible reversion to virulence, especially for new live attenuated vaccines; validated and standardised assays, including assays to distinguish between wild and vaccine strains, should normally be implemented prior to marketing authorisation for appropriate case assessment.~~,~~

As part of the routine follow-up of adverse reactions, data should be collected (in addition to data on the patient, the adverse reaction and the vaccination history) ~~about~~on:

- the vaccination schedule and the route of administration;
- the vaccine and the diluent (if applicable), including manufacturer(s) and~~,~~ batch number(s);
- in case of a suspected quality defect, batch release specifications, expiry date(s) and laboratory test results about the batch if appropriate, and distribution and administration-related data, such as storage and handling conditions for vaccines in the healthcare institutions where vaccination took place;
- relevant comorbidities in the target population (including autoimmune disorders).
- ~~Any arrangements established to promptly investigate any emerging issues, such as access to electronic health records, registries (e.g. pregnancy registries) or other data sources, should be described in this section.~~~~, 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 institution where vaccination took place;~~
- ~~the vaccination schedule and the route of administration.~~

~~Reversion to virulence after multiplication in the human host might be of particular concern for some live attenuated vaccines. Careful investigation of spontaneous suspected adverse reaction reports indicating a possible reversion to virulence is essential, especially for new live attenuated vaccines. Validated and standardised assays, including assays to distinguish between wild and vaccine strains, should be implemented prior to marketing authorisation for appropriate case assessment.~~

~~As vaccines and vaccination programmes are not 100% effective, cases of breakthrough infections are expected without necessarily indicating a problem with the vaccine. Although these issues cannot be fully investigated via spontaneous reporting, reports of vaccine failure can nonetheless generate signals to be further evaluated by other methods. Such signals may need prompt action and further investigated through post-authorisation studies as appropriate. Risk factors for vaccine failure should be analysed (e.g. obesity, age, smoking status, vaccination schedule, concomitant disease). If there is concern that a higher than expected rate of vaccine failures and break-through infections in certain risk groups exists, appropriate systematic investigations should be carried out. Appropriate case definitions and validated analytical tests for confirmation of the infective agents should be used whenever~~

[7] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.

~~possible. The recommendations of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance should be considered for the definition and classification of cases of vaccination failure.[8]~~

~~As under-reporting of suspected adverse reaction reports is an inherent characteristics of pharmacovigilance, including for vaccines, appropriate national communications to optimise and facilitate reporting may be proposed in specific situations where mass vaccination takes place and prompt identification and evaluation of safety concerns are needed. This communication should involve collaboration between national regulatory and public health authorities to ensure provision of information to patients to describe which vaccine they have used, the batch number and how events can be reported.~~

P.I.B.1.3.2. RMP section "Additional pharmacovigilance activities"

~~This section should describe the tools established to promptly investigate any emerging issues, such as access to electronic health records, or prior arrangements made with managers or users of registries (e.g. pregnancy registries) or other data sources.~~

In addition to the investigation of important identified risks, important potential risks or important potential missing information, additional pharmacovigilance activities may be needed in the following situations:

- to detect strain replacement phenomena (with genotyping of circulating strains as necessary) for vaccines that may protect against only some types of organisms within a species;
- to address the pattern of shedding, transmissibility to contacts and the potential of the strain to survive in the environment;
- to establish evidence of safety for novel vaccines or for vaccines with a novel adjuvant, in order to:
  - assess the risk of induction of rare or delayed onset adverse reactions, local or systemic;
  - detect occurrence of auto-immune diseases and immune-mediated reactions resulting from a synergistic action of the adjuvant and the biologically active antigen;

  ~~particular in relation to long-term and delayed-onset adverse reactions;~~
- ~~to assess~~ the effectiveness of the vaccine, especially where pre-authorisation data are limited~~;~~
- ~~in cases where a novel adjuvant has been incorporated into the vaccine formulation:~~
- ~~to assess the risk of induction of rare or delayed onset adverse reactions, local or systemic;~~
- ~~to detect occurrence of auto-immune diseases and immune-mediated reactions resulting from a synergistic action of the adjuvant and the biologically active antigen.~~
-
- to investigate clusters of reported adverse events/reactions;
- where spontaneous reports raise concerns that a higher than expected rate of vaccine failures and breakthrough infections in certain risk groups exists.

Where additional investigations regarding the impact of different vaccination schedules are needed, it is acknowledged that it might not be feasible to study all recommended priming and booster schedules

~~[8] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, CIOMS 2012.~~

across the EU, but a rationale for further evaluation should be presented (e.g. studying the most accelerated schedule based on 2 or 3 doses~~).~~

~~When initiating an additional pharmacovigilance activity, the marketing authorisation holder should investigate~~) and the availability of systems for collecting data in different countries should be investigated.

A pregnancy register may be needed to address risks of the vaccine in pregnant women, in which case the design of the registry should be provided as part of the RMP. It should allow identification of spontaneous abortions, stillbirths and congenital malformations with an adequate duration of follow-up of the offspring. Detailed information on vaccine exposure (including number of doses and gestational age at the time of exposure) before and/or during pregnancy should be collected. The Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data [9] and the Systematic overview of data sources for drug safety in pregnancy research[10] should be consulted.

Where adverse events of special interest (AESIs) are presented in the safety specification as important potential risks and baseline/background incidence rates of those AESIs in the target population are not available, it may be necessary to design a study to collect this information in order to provide rapid answers to vaccine safety concerns emerging from spontaneous reports of suspected adverse reactions. The types of data sources (e.g. in-patient or out-patient databases) available to estimate background incidence rates will differ across countries and is likely to impact diagnostic validity in terms of sensitivity and specificity. ~~Follow-up time~~The study design should ~~be sufficient for~~ allow~~ing~~ differentiation between prevalent and incident cases. Furthermore, bias could arise from misclassification of disease type or changes in diagnostic criteria and disease management over the study period. Whenever possible, data should be stratified by age, sex, geographical region as well as by other potentially relevant risk factors or confounders. If relevant, seasonal variability should be taken into account.

In exceptional circumstances (for example in a pandemic with mass vaccination), competent authorities and marketing authorisation holders may agree on an additional ~~communication~~ system to rapidly exchange information on emerging safety data whose submission timelines would depend on the extent of vaccine exposure, epidemiological situation and emerging risk. For example, a structured worksheet could present the observed and expected numbers of cases and integrate simple signal detection methods discussed in P.I.B.4., such as observed-to-expected analyses. Where such an additional ~~communication~~ system has been agreed, its inclusion ~~–~~as an additional pharmacovigilance activity in the RMP, along with information on its rationale, format and periodicity, should be discussed between the marketing authorisation holder and the competent authority.

As under-reporting of suspected adverse reaction reports is an inherent characteristics of pharmacovigilance, including for vaccines, appropriate national communications to optimise and facilitate reporting may be proposed in specific situations where mass vaccination takes place and prompt identification and evaluation of safety concerns are needed. This communication should involve collaboration between national regulatory and public health authorities to ensure provision of information to patients to describe which vaccine they have used, the batch number and how events can be reported. ~~–~~

[9] EMEA/CHMP/313666/2005, available on EMA website http://www.em~~e~~a.europa.eu.
[10] Charlton R and de Vries C, for the European Medicines Agency. Available at http://www.encepp.eu/encepp/openAttachment.htm?field=documents.otherDocument%5b0%5d&id=2756.

P.I.B.1.4.RMP part IV "Plans for post-authorisation efficacy studies"

~~Any~~ ~~P~~plans for post-authorisation efficacy studies (PAES) ~~should be included in this section.~~may include t~~T~~he assessment of vaccine efficacy/effectiveness and immunogenicity ~~in the post-authorisation phase may be particularly important~~ in order to get additional information on waning immunity, long-term protection, cross-protective efficacy/effectiveness and the most appropriate use of the vaccine (e.g. the need for booster doses in at least some population groups, such as immunodeficient individuals, to maintain adequate protection over time).

P.I.B.1.5. RMP part V "Risk minimisation measures"

In principle, regulatory tools and risk minimisation activities for vaccines are similar to those used for other medicinal products (see Module XVI). ~~However, the~~The use of additional risk minimisation activities might be challenging given the diverse settings of use of vaccines within and outside (e.g. travel clinics) vaccination programmes.

Appropriate communication to healthcare professionals by marketing authorisation holders and regulatory and public health authorities is a critical component of risk minimisation aiming to avoid errors in vaccine handling and vaccine administration and to reiterate warnings and precautions. Routine risk minimisation measures such as the Summary of Product Characteristics and the Package Leaflet are the most used channels of communication to the healthcare professionals (SmPC) and the patients for vaccines. To further minimise the risks associated with the vaccination (e.g. medication errors) and to facilitate the traceability of vaccine's brandname and batch number in the reporting of adverse events, the MAH should also consider labelling and packaging as risk minimisation tools.

~~Pre-defined criteria for batch recall or quarantine should be included in this RMP section (see P.I.B.5.).~~

P.I.B.2. Periodic safety update report

In addition to information which should be provided in the periodic safety update report (PSUR) for all medicinal products (see Module VII), 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. Issues related to batch(es), as well as age-related adverse reactions should be evaluated. ~~Safety aspects in subpopulations (such as pregnant women) should be analysed.~~ If relevant, the potential for local and systemic adverse reactions should be analysed for different doses of the vaccine and also across different vaccination schedules. ~~Sub-analyses of spontaneous reports with regard to possible differences in the adverse reaction profile linked to different vaccination schedules are considered important but do not replace clinical investigations.~~

The following data should also be summarised and analysed in the PSUR:

- reports of vaccine failure, lack of efficacy/effectiveness;
- vaccination errors;
- vaccination anxiety-related reactions such as syncope;
- literature data with information relevant to other similar vaccines and vaccine components such as stabilisers, preservatives and adjuvants.

If concomitant vaccination with another vaccine is specifically mentioned in the SmPC, co-administration of vaccines should be analysed separately and the analysis be summarised in the PSUR if there is a safety concern. The data should also be analysed for new concerns regarding concomitant vaccination, independently of whether concomitant use is mentioned in the SmPC or not.

P.I.B.2.1. Integrated benefit-risk analysis

When a new or changing risk is identified, it is important to re-evaluate the benefit of the medicinal product using all available data and estimate the impact of the new or changing risk on the benefit-risk balance of the vaccine. Benefits may include prevention of the target disease, severity of symptoms, hospitalisation, complications, effect of target disease on offspring (in case of vaccination of pregnant women) and any other clinical outcome relevant for individual patients.

P.I.B.3. Post-authorisation safety studies

Objectives, methods and procedures for post-authorisation safety studies (PASS) as described in Module VIII should be followed.

~~P.I.B.3.1. Aspects of study design~~

Appendix 1 of Module VIII presents a range of methods for post-authorisation safety studies (PASS). Controlled clinical trials and prospective cohort studies are considered to provide the highest level of evidence but may not be possible to conduct in many cases, especially for rare or long-term risks which may only become evident several years or even decades after vaccination. In this case, cohort studies based on secondary data collection could be designed, whereby the group in whom the adverse events/reactions is studied is defined at the time the study is initiated rather than at the time of vaccination.

Traditional study designs such as cohort and case-control studies may however be difficult to implement where they involve populations with high vaccine coverage rates ~~and~~, an appropriate unvaccinated group is lacking or adequate information on covariates at the individual level is lacking. See the ENCePP Guide on Methodological Standards in Pharmacoepidemiology for alternative study designs that can be used in such cases.[11] ~~A frequent source of confounding to be considered in vaccine studies comparing vaccinated and unvaccinated individuals is the underlying health status influencing the probability of being vaccinated. Epidemiological methods involving cases only are useful in such situations. These methods include some ecological methods, case-coverage methods, case-crossover and self-controlled case series methods.[12]~~

Safety parameters in PASS should be appropriate for the specific vaccine. A pre-requisite is the use of globally accepted standards for case definitions (e.g. those published by the Brighton Collaboration[13]) to compare the frequency of adverse reactions across different studies.

~~P.I.B.3.2. Case-only designs~~

~~In the self-controlled case series (SCCS) design,[14] the observation period following each vaccine dose for each case is divided into risk period(s) (e.g. the days immediately following each vaccination) and control period (the remaining observation period). Incidence rates within the risk period after vaccination are compared with incidence rates within the control period, under the null hypothesis that incidence rates would be equivalent if no association with vaccination is present, taking age into account. A SCCS analysis adjusting for age effects has the advantage of an implicit control of any known or unknown confounders which are stable over time. For unique events, this method requires~~

[11] See http://www.encepp.eu/standards_and_guidances/index.shtml

~~[12] Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. Vaccine. 2004;22(15-16):2064-70.~~

[13] Available on Brighton Collaboration website http://www.brightoncollaboration.org.

~~[14] Weldeselassie YG, Whitaker HJ, Farrington CP. Use of the self-controlled case-series method in vaccine safety studies: review and recommendations for best practice. Epidemiol Infect. 2011;139(12):1805-17.~~

~~the additional assumption that the cumulative incidence of events in the population over the observed period is low. Data analyses may be performed early and time efficiently. 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. Moreover, relevant time intervals for the risk and control periods need to be defined and this may become complex with primary vaccination with several doses.~~

~~Case-coverage methods make use of exposure information on cases, supplemented by data on vaccination coverage in the population. This design may be considered as an unmatched case-control study with the entire population serving as control. Therefore, no individual data on non-cases or denominators are required. Three main shortcomings should be considered: reliable coverage data are needed; the population for which vaccination statistics are available may not correspond exactly to that from which cases are drawn, which may lead to biased estimates; and the aggregated coverage data generally do not permit control of confounding by stratified analysis.[12]~~

~~P.I.B.3.3. Other designs~~

~~Ecological studies examine the correlation between the trends in an indicator of vaccine coverage and the trends in incidence of a disease that is a presumed effect of the vaccine. These trends can be examined over time or across geographical regions. In such analysis, it is hypothesised that a strong correlation between the two trends is consistent with a causal relationship, while a weak correlation would indicate a weak relationship. This comparison at the population level limits the possibility to control for confounding variables. Their results should therefore be interpreted with caution. Ecological studies may be however useful to generate hypotheses.~~

Vaccination registries established in many countries may be used in vaccine safety by creating a source population for large cohort studies. Using a vaccination registry as a source population for studies should be made with caution where enrolment may be biased or there is no systematic collection of exposure in the population. Moreover, a large number of vaccinated individuals is required for the active surveillance of rare adverse reactions by follow-up of a cohort recruited at the time of vaccination.

Non-clinical studies and experimental investigations should also be considered to address safety concerns. This may include virological, bacteriological and/or immunological experiments and other methods to elucidate the aetiology of an adverse reaction.

P.I.B.4. Signal management

The signal management process (see Module IX) covers all steps from detecting signals to recommending actions. A signal is information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events~~, either adverse or beneficial,~~ that is judged to be of sufficient likelihood to justify verificatory action [IR Art 19(1)]. In the field of vaccines, a signal may also relate to evidence of reduced efficacy~~/~~ or effectiveness, vaccine failures and quality deviations with potential impact on safety ~~or,~~ efficacy~~/~~ or effectiveness (which may be batch-specific).

P.I.B.4.1. Standard case definitions

Standardised case definitions of adverse events are a key element for signal validation and evaluation as they provide a common terminology and understanding of adverse events/reactions and thus allow

for comparability of data. Definitions published by the Brighton Collaboration[15] should be used where available. If a Brighton Collaboration definition is not available, the definition which is used should be carefully chosen based on scientific criteria and amenable for justification. Adverse reactions should however be reported even if no standard definition exists.

Standardised MedDRA (Medical Dictionary for Regulatory Activities) Queries (SMQs)[16] may be used in the process of signal detection, validation and evaluation. Sensitivity and specificity testing of SMQs for vaccines needs to be done beforehand in order to adequately interpret the results.

P.I.B.4.2. Single report of a serious adverse event

A single report of a serious adverse event occurring in temporal association with the vaccination, especially if the event is unexpected or fatal, could have a detrimental impact on vaccination programmes due to perception of unsubstantiated risks or risk amplification.

A single report of a serious adverse event should be processed as a signal only if there is a possible causal association to the vaccine. This requires adequate information on the clinical course of the event (time to onset, signs and symptoms, results of relevant laboratory and diagnostic tests, evolution, treatment of the event, autopsy report in case of a fatal event and~~,~~ pathophysiological mechanism), medical history, vaccination history, co-medication and details of the vaccine(s) administered (including brandname, batch number, route of administration and dose). Signal validation should also be based on contextual information. Relevant data to be collected for this purpose should include the number of reported cases of a similar event and the probability of occurrence of the event in a non-vaccinated population of the same age category, calculated from clinical trials and observational studies. If adequate data are available on the number of vaccinated individuals of the same age category, the observed and expected numbers of cases should be estimated.

P.I.B.4.3. Signal detection in mass vaccination programmes

In mass vaccination programmes which involve large exposure over a relatively short time period, signal detection should be as real-time as possible, ideally to inform decision-making as the vaccination progresses. It should be ~~, and~~ adapted to the specific circumstances of the vaccination programme. A particular challenge is the association of such vaccination programmes with very high numbers of spontaneously reported adverse reactions over a relatively short time period. Quickly analysing and communicating the significance of such data is critical. The priority is to rapidly identify possible new signals, but also to rapidly assess the likelihood that the number of reports may be consistent with the expected background incidence in the vaccinated cohort, and thereby possibly coincidental.

P.I.B.4.4. Disproportionality analyses

A statistic of disproportionate reporting (SDR) refers to a statistical association between medicinal products and adverse events. There are several statistical methods used to identify SDRs, such as the proportional reporting ratio (PRR) and Bayesian approaches. Of note, a statistical association does not

[15] Available on Brighton Collaboration website http://www.brightoncollaboration.org.
[16] Council for International Organizations of Medical Sciences (CIOMS).
Development and rational use of Standardised MedDRA Queries (SMQs). Geneva: CIOMS; 2004.
Available at ~~on CIOMS website~~ http://www.cioms.ch/.

imply any kind of causal relationship between the administration of the vaccine and the occurrence of the adverse events.[17]

Vaccines may require special consideration when applying such ~~tools~~methods (see P.I.~~.~~A.). Intrinsic differences between vaccines and other medicinal products should be considered, for example frequent reporting of unrelated adverse events in the target population (e.g. Sudden Infant Death Syndrome (SIDS) and infant vaccination, cardiorespiratory events and influenza vaccines). Furthermore, the safety profile of a vaccine may differ substantially within the target population (e.g. higher risks in the youngest age groups). In order to reduce background noise, estimates of disproportionality should be calculated based on a comparison across groups that have a similar age-specific background risk for illness. The choice of the comparator group will depend on the objectives of the analysis and the information available in the database. A comparison with all medicinal products may result in the detection of reactions specifically related to vaccines, but may also identify a high number of false signals (e.g. SIDS in infants) or already known mild and expected reactions (e.g. local reactions). On the other hand, using only vaccine-related reports available in the database may result in signals of age-related reactions (e.g. cardio-vascular disorders if the vaccine of interest is used in the elderly). In a first step, it may therefore be appropriate to examine results of statistical methods using both comparator groups, or to use reports for other vaccines as the comparator group with a stratification made at least by age.

Stratification by geographical region may also be considered and seasonality of vaccine administration may be relevant for some vaccines and needs consideration. When stratification is performed, ~~it may be wise to examine the~~ results of both adjusted and non-adjusted analyses should be examined. Results could be inspected in each stratum as pooled result of a stratified analysis may miss signals.

P.I.B.4.5. Observed to expected analyses

When there is little time to validate signals, it is essential to make best use of suspected adverse reaction reports. Observed vs. expected (O/E) analyses based on good-quality data can optimise the utility of passive surveillance data, allowing determination of the strength of a signal for prioritisation and further evaluation, and can help in communication of these data (particularly when serious, rare reported events are well within an expected range). ~~-~~O/E analyses are particularly useful during mass vaccination programmes where there is little time to review individual cases and prompt decision-making about a safety concern is required. Although such analyses cannot exclude risks or determine causality, they can help put suspected adverse reaction reports into context and should be used as a routine tool for real-time surveillance. They can also be useful in signal validation and, in the absence of robust epidemiological data, in preliminary signal evaluation.

Key requirements of O/E analyses and statistical methods are described in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.[18]

~~O/E analyses are particularly useful during mass vaccination programmes where there is little time to review individual cases, and prompt decision-making about a safety concern is required. Although such analyses cannot exclude risks or determine causality, they can help put suspected adverse reaction reports into context and should be used as a routine tool for real-time surveillance. They can also be useful in signal validation and, in the absence of robust epidemiological data, in preliminary signal evaluation.~~

[17] Guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system, available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011434.pdf.

[18] See http://www.encepp.eu/standards_and_guidances/index.shtml.

It should be kept in mind that certain characteristics of an adverse event increase its probability of being reported, such as when the outcome is unexpected, severe or disabling, when it is poorly understood and when it affects a previously healthy person. Also, the shorter the time that has elapsed between the vaccination procedure and the event, the more likely it is to be perceived as a trigger and subsequently be reported. Conversely, events that are expected, common and mild, or occur late after vaccination, are less likely to be reported.

~~***P.I.B.4.5.1. Key requirements of O/E analyses***~~

~~The key requirements of O/E analyses are the 'observed' number of cases detected in a passive or active surveillance system, appropriately stratified background incidence data (the 'expected') and near real-time exposure data (to determine the observed rate and expected incidence). Optimal use of O/E analyses therefore requires a high level of preparedness. The following aspects should be carefuly considered before the start of and during a vaccination programme:~~

- ~~under reporting and under ascertainment of the observed number of cases should be reduced by stimulating reporting and optimising data capture; diagnostic certainty should be assured by gathering relevant clinical and laboratory test results and using standardised and validated case definitions (e.g. case definitions (see P.I.B.4.1));~~
- ~~background incidence rates of defined adverse events of special interest (AESIs) should be collected or compiled before vaccination starts; this should be complemented by securing easy access to one or several data sources allowing quick estimation of incidence rates of other (unexpected) events;~~
- ~~mechanisms should be put in place to collect, compile and make available stratified (e.g. age, risk group, country/region) and up-to-date vaccine exposure data.~~

~~***P.I.B.4.5.2. Statistical aspects of O/E analyses***~~

~~From information on a vaccinated population and baseline incidences of events, it is possible to estimate the numbers of new cases that will occur purely by chance within various time windows after a vaccination (e.g. cases/100 000 vaccinated persons within 6 weeks). However, these rates of new cases occurring purely by chance cannot directly be translated to anticipated rates of spontaneous reporting.~~

~~When comparing spontaneous reporting rates and baseline incidence rates, secular trends gives information on the validity of such a comparison. If baseline trends indicate a significant increase or decrease, discrepancies between reports and baseline rates should be interpreted in this context. The inclusion of sex ratio adds information which can be used when comparing baseline incidences in periods before and after a vaccination program is introduced. Any changes in the sex ratio indicate that the degree of exposure of certain sex specific risk factors for a given disease has changed.~~

Given uncertainties around the 'observed' number of cases, the levels of diagnostic certainty, the level of vaccine exposure and the background incidence rates, sensitivity analyses should be applied in statistical analyses around assumed levels of under-reporting, numbers of 'confirmed' and 'non-confirmed' cases (using several categories of diagnostic certainty as appropriate), numbers of vaccinated individuals or vaccine doses administered and confidence intervals of incidence rates.

~~Calculations should be appropriately stratified. Analyses should be performed regularly (e.g. weekly), ideally with statistical methods applied for sequential analysis with signal thresholds.~~

~~Specific statistical methods may include:~~

- ~~a 'snapshot' method for ad hoc analyses using an appropriate risk period post-vaccination to calculate the expected number of cases, and comparing it to the observed number of cases to calculate an O/E ratio with a 95% confidence interval; this method can be applied with a simple worksheet displaying for each reaction of interest the expected rate, the observed number of cases and the vaccine exposure, with regular updates; sensitivity analyses can be added; the method is easy to understand and results are easy to communicate, but it may not be fully appropriate for continuous monitoring and signal detection due to issues of multiplicity;~~
- ~~a sequential method (for example, the Maximised Sequential Probability Ratio Test (MaxSPRT) for weekly surveillance19) allowing to perform O/E analyses with adjustment for multiplicity; the O/E ratio can therefore be calculated on a weekly basis using cumulative data; sequential methods are more complex to perform than the 'snapshot' method and are less easy to understand and communicate to a non-statistical audience.~~

~~Combination of sequential and snapshot methods may be helpful: while the 'snapshot' method provides a method that is preferable to use for communication purpose, the sequential method provides a more robust method for continuous surveillance.~~

P.I.B.4.6. Signal evaluation

For the evaluation of validated signals based on individual case reports of suspected adverse reactions, complete and accurate individual records documenting administration of all vaccines should be provided, 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. Information on ~~dechallenge and rechallenge~~rechallenge, where ~~are often not~~ applicable, ~~to vaccines, but where they are, such data~~ should be recorded. The investigation of clusters of reported adverse events or adverse reactions is described in the report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.[20]

Appropriate follow-up of serious suspected adverse reactions is essential, including data on possible alternative causes. It may be helpful to develop pre-defined check lists or formats for those reactions which may be anticipated from experience with similar vaccines in order to consistently ascertain relevant clinical information and support the quality of causality assessment for individual cases (see also Module VI).

The following aspects need to be considered for signal evaluation:

- the incidence of the natural disease in the target population for vaccination and its seasonality, as this population is usually large and heterogeneous and coincident adverse events are likely to occur;
- additives and excipients used for the production, inactivation, preservation, and stabilisation of the vaccine;
- past experience with similar vaccines, adjuvants and types of antigens, in order to identify adverse reactions which are unexpected and for which a causal relationship remains to be elucidated;

~~[19] Brown JS, Kulldorf M, Chan KA et al. Early detection of adverse drug events within population-based health networks: application of sequential testing methods. Pharmacoepidemiology and Drug Safety 2007;16(12): 1275–1284.~~

[20] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.~~See http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf~~

- distinction between suspected adverse reactions to the vaccine and those reflecting the clinical picture of the disease for which vaccination has been given (e.g. rash following measles vaccination);
- public information (public campaign, press) that may favour certain reports in some periods.

P.I.B.5. Batch recall and quarantine

In order to protect public health, it may become necessary to implement urgent measures such as to recall or halt the distribution (quarantine) of (a) batch(es) of a vaccine due to a suspected batch-specific signal or defect.[21] The legal reference for batch recall is the Good manufacturing practice and good distribution practice.[22]

The principle of public health protection may be particularly relevant in certain situations, e.g. vaccines for healthy children, particularly in case of a localised incident. A vaccine batch recall or quarantine is sometimes taken in the absence of the full facts and evidence and before the assessment of the issue is finalised. However, batch recall or quarantine may have a detrimental impact on the vaccination programme itself, even if absence of association between the suspected batch(es) and the severe adverse events is later demonstrated, and may cause more harm than good. As with any mass intervention, vaccination programmes are inevitably associated with serious adverse events in temporal association with vaccine administration but many of these are coincidental. As a batch recall may also lead to issues of vaccine supply and sometimes a shortage of vaccines, the possibility of a chance association and the availability of a sufficient ~~of~~ amount of vaccines or of alternative vaccines for the vaccination programme should also be considered in this context.

In situations where a batch-specific quality or safety issue has not been confirmed, measures other than recall or quarantine may be warranted initially whilst an investigation is on-going, e.g. providing recommendations on patient surveillance and follow-up post-vaccination. This may be considered when recall or quarantine may lead to vaccine supply shortages and alternatives are not widely available.

The following sections present elements that should be taken into account when considering recalling or quarantining batches.

P.I.B.5.1. Data requirements

The following data should be collected as soon as possible and should ideally be available when taking a decision about a batch recall or quarantine:

- detailed description of the case(s) presented in CIOMS format with narrative(s), including any additional information as appropriate (e.g. laboratory results, autopsy reports, literature);
- characteristics of the adverse event, e.g. severity, expectedness (new adverse reaction vs. increased frequency of a known adverse reaction), outcome;
- characteristics of patients presenting the adverse event, e.g. age, concomitant diseases, concomitant vaccination;

[21] Compilation of community procedures on inspection and exchange of information. Procedure for handling rapid alerts rising from quality defects. London 18 May 2009. EMEA/INS/GMP/313510/2006 Rev 1. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004713.pdf

[22] European Medicines Agency. Good manufacturing practice and good distribution practice compliance [webpage]. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000154.jsp&mid=WC0b01ac0580027088.

- crude number of cases and reporting rate or incidence rate of the adverse event in the vaccinated population using, if possible, actual vaccine usage data rather than sales data and~~;~~ observed vs. expected calculations of the event observed;
- time and space clustering of cases, e.g. cases reported by a single hospital, physician or ~~locality~~region;
- geographical distribution (both spatial and numbers of doses used) of the suspected batch(es);
- manufacturing records of the suspected batch(es) (certificates of analysis, information on deviations observed at in-process controls or manufacturing steps, documentation of recent changes to the manufacturing process);
- storage and administration conditions of the suspected batch(es);
- re-analysis of retained samples of the suspected batch(es), focussing, if necessary, on additional parameters to those required for the release of the product.

Time is a critical factor in the evaluation of potential batch-related issues. Marketing authorisation holders should therefore continuously maintain a high level of preparedness to provide the information needed for a quick evaluation of batch-related safety issues. Competent authorities should investigate any other available source of information that may promptly provide information on similar events (including batch-related information), and provide a preliminary assessment of all available data within a short timeframe.

P.I.B.5.2. Action based on clinical events in the absence of a known quality issue

A batch-specific signal based on an observed clinical event is often based on spontaneous reporting. In the absence of a known quality issue, decision making on a precautionary recall or quarantine is difficult, as a causal association with the vaccine can rarely be established at the time when an initial decision is required.

In the absence of a known quality issue and where there is an apparent increase in frequency or severity of known adverse reactions without serious clinical risk, consideration should be given to the geographical distribution of the suspected batch and of the case(s) at the origin of the signal. If it is established that a suspected batch has been used to a significant extent in many regions/countries and a signal is apparent in only one geographical area, this could potentially indicate a false signal. Conversely, an apparent signal in more than one locality may potentially strengthen the signal and support a recall or quarantine.

For single fatal adverse events, particularly where the cause of death is unknown, the reporting rate of the event relative to both the usage of the vaccine batch and the 'expected' age-specific all-cause mortality should be considered before deciding on a recall or quarantine action (see also P.I.B.4.2). The probability of a chance association should be considered. If a fatal event is initially thought to be a consequence of a known adverse reaction (e.g. due to anaphylaxis), it would not necessarily imply a batch-specific issue requiring a recall or a quarantine. On the other hand, where contamination of a batch is suspected based on individual case details or a localised cluster, due to possible cold chain and handling deviations, localised action should be considered before escalation to a national recall or quarantine.

P.I.B.5.3. Action due to identified quality deviations

Identified quality deviations may be associated with no apparent clinical risks, and may not warrant recall or quarantine. However, quality deviations may result in increased reactogenicity and/or increased frequency of expected adverse reactions (such as severity and frequency of febrile reactions, localised reactions and allergic reactions), or reduced potency, which may necessitate recall of a given batch(es). In the case of a confirmed quality deviation, the decision to recall or quarantine can often be relatively straightforward and supported by the likelihood of clinical risk and availability of alternative batches or products.

P.I.B.6. Safety communication

Appropriate communication about the benefit-risk balance and safe use of vaccines to the target population, vaccinated individuals, their parents/carers, healthcare professionals, health policy makers and the general public is essential for ensuring the appropriate use of vaccines as well as for the implementation of the vaccination programme.

Principles and guidance on safety communication, its planning and effectiveness evaluation is provided in Modules XV and XII. In addition, the following principles should be considered for vaccines.~~:~~

Being transparent and providing explicit information in lay language to the public regarding the use of (a) ~~o~~vaccine(s) should be fundamental to the communication approach. Incomplete or unclear messages may lead to confusion of the general public and the decision not to vaccinate or not to be vaccinated on unsubstantiated grounds. Communication should help preventing anxiety-related reactions (see Annex I). Any potential risks for specific population groups should be clearly communicated.

Specific safety communication objectives in relation to vaccines may also aim at avoiding errors in vaccine handling and administration and at reiterating warnings and precautions for use.

Safety communication about a vaccine should also describe the benefits of vaccines, explain the risks for individuals and the population of a decrease in vaccination coverage, and explain its impact on disease control. When drafting communication texts, it should be considered that, as vaccination programmes mature, incidence rates of the targeted diseases decrease substantially, and so does personal experience with the disease in a given population. This may result in an increased attention to concerns related to vaccine safety, and information on the target disease itself may need to be provided. It should be considered that risk perceptions may differ between stakeholders, especially when there is uncertainty about a risk. Public confidence in vaccination programmes may only be maintained by knowledge that systems are in place to ensure complete and rapid assessment and to take precautionary measures if needed. Therefore, safety communication about vaccines may also profit from describing key functions of the pharmacovigilance systems.

Communication about vaccines may also include informing vaccinators/healthcare professionals on the management of vaccine-related anxiety and associated reactions, particularly in individuals with special conditions (e.g. pregnancy, puberty, immunosensitive conditions, general anxiety or other mood disorders, epilepsy).

Communication to the public should be a collaborative task undertaken by the industry, regulators and public health organisations, with input from other stakeholders (see Module XII for collection of data on information needs and public concerns and see Module XI for mechanisms for public participation).

The processes for planning and implementing safety communication at the level of marketing authorisation holders and competent authorities described in Modules XII and XV apply and are interlinked with the risk assessment and communication effectiveness evaluation processes also

described in these Modules. Communication interventions may be part of a risk management plan (RMP) (see Modules V and XVI). During the communication planning and implementing phases, international collaboration (see Module XIV) should be facilitated as necessary. Special planning should be undertaken in case of public health emergencies (see Module I) or pandemics.

Communication planning should include being prepared for frequent public communication needs, such as those regarding excipients, residues, identified or potential risks for individuals with special conditions, coincidental events, temporal versus causal association, a single case of an adverse event rarely identified as a risk, safety monitoring requirements being different to identified risk, or the mock-up concept not being related to an experimental/not tested/not authorised vaccine. For the purpose of quantifying safety concerns, relevant background rates, by age group and sex, of signs and symptoms which are also present in adverse events, whether known to be causally related, suspected to be causally related or likely to be coincidental, should be kept up-to-date, as well as exposure data. Communication planning should also include preparing standard texts. Frequently needed explanations should be ideally tested by representatives of likely target audiences. Concerns raised by the public should also be addressed by proactively communicating results of benefit-risk evaluations.

Competent authorities should ensure appropriate communication with the public and in particular the media. Media monitoring should be especially conducted for vaccines. The media can play an important role in influencing the public perception of vaccine safety, in both a negative and positive way, and information to the media should be given in timely and meaningful manner (see Module XII). In this respect, it is essential to maintain a high level of transparency on how regulatory decisions were reached and on the roles and responsibilities of each stakeholder. In communication materials, reference should be made to published documents.

P.I.C. Operation of the EU network

P.I.C.1. Roles and responsibilities

Stakeholders involved in the process of vaccine pharmacovigilance in the EU include the target population for the vaccine, consumers of vaccines (vaccinated persons and, in the case of paediatric vaccination, their parents/carers), healthcare professionals, marketing authorisation applicants/holders, sponsors of clinical trials, regulatory authorities, public health authorities recommending vaccination programmes, the European Medicines Agency, the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO). Each stakeholder has an important contribution to the vaccine pharmacovigilance process. Efficient collaboration between stakeholders is particularly important in situations of mass vaccination where it is anticipated that a large number of suspected reactions may be reported in a short period of time (e.g. during a pandemic) and it is necessary to quickly assess potential safety issues and take regulatory decisions. In such cases, collaborations should be established prior to the start of the vaccination programme to identify source of data and agree on processes to exchange information.

All obligations laid down in Regulation (EC) No 726/2004 and Directive 2001/83/EC regarding roles and responsibilities apply to vaccines.

P.I.C.1.1. Vaccinated persons and parents/carers

Vaccinated persons and their parents/carers may report a suspected adverse reaction to a healthcare professional or directly to the competent authorities in Member States or to the marketing authorisation holder. Competent authorities in Member States should facilitate reporting, for example through a web platform. They should encourage reporting of complete information on the vaccine and

the vaccination, including the invented name and batch number. This can be facilitated by providing adequate and easily retrievable information at the time of vaccination, for example with a patient card.

P.I.C.1.2. Healthcare professionals

Healthcare professionals should follow national guidelines regarding the collection, recording and reporting of suspected adverse reactions to vaccines. ~~, and medically confirm the occurrence of any severe adverse event occurring after vaccination and reported by a vaccinated person or a patient/carer.~~ In vaccination programmes where ~~the~~ a physician diagnosing the adverse reaction was not involved in the administration of the vaccine, this physician should document the product name, batch number and other information relevant for the evaluation of the severe adverse event either from information provided to the vaccinated person or the patient/carer, or by contacting the medical centre or person that provided the vaccine. Any suspected adverse reaction should be reported to the competent authorities in Member States according to national recommendations.

P.I.C.1.3. Marketing authorisation holders

Marketing authorisation holders may establish a specific pharmacovigilance system for vaccines (see Module I~~.C.1.~~).

Marketing authorisation holders should collect and record all available information regarding the distribution of vaccine batches in Member States. Marketing authorisation holders should make an effort to collect information on ~~and~~ the numbers of doses of vaccines administered/distributed by batch. They should also take appropriate measures in order to collect and collate all reports of suspected adverse reactions associated with vaccines originating from unsolicited or solicited sources. The definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the brandname of the product and the batch number. Where necessary, attempts should be made to contact the patient or healthcare professional reporting the adverse reaction (see GVP Module VI~~.B~~ and Appendix 1 on the identification of biological medicinal products). Marketing authorisation holders should communicate as an emerging safety issue (see Module VI~~.C.2.2.6~~) any safety concern related to the vaccine that may impact on its benefit-risk profile.

Marketing authorisation holders should continuously maintain a high level of preparedness to quickly document and investigate safety issues and batch-related issues, as precautionary measures may need to be taken by competent authorities in absence of adequate information (see P.I.B.1.3.2).

P.I.C.1.4. Competent authorities in Member States

National regulatory and public health authorities should collaborate for recording, collating, exchanging and integrating all information relevant to the safety surveillance of vaccines. This includes information on the distribution of vaccine batches within the Member States and vaccine exposure stratified by batch, age and sex and in the target population (or other characteristics, e.g. pregnant women) where possible. Where a registration system is in place, procedures should allow quick compilation and analyses of data to estimate exposure. Information to be collected and exchanged also include available data on incidence of diseases which may also be adverse events of the vaccine, reports of adverse reactions and their assessment, results arising from specific surveillance programmes, clinical or non-clinical investigations and post-authorisation studies, including safety and efficacy/effectiveness studies, seroepidemiological studies and studies on circulating strains and strain replacement. If the vaccine is anticipated to be used in vaccination programmes, attempts should be made before the start of the vaccination to collect missing data, e.g. background incidence rates of adverse events of special

interest. Relevant data sources for vaccine efficacy/effectiveness and benefit-risk evaluation of the vaccine should be identified and data availability should be explored, including possible use by marketing authorisation holders.

National regulatory authorities should have in place a web-based reporting system of suspected adverse reactions for patients and healthcare professionals, and should encourage these to provide accurate information on invented names and batch numbers. They should establish channels for an adequate communication to the public and play an important role in unbiased communication, in particular in situations where there is a gap between results of scientific ~~analysis~~ analyses made by experts and public concerns. National regulatory authorities should ensure that the public is given important information on pharmacovigilance concerns relating to the use of the vaccines. Media should receive timely and relevant information on the benefit-risk balance of vaccines.

National competent authorities should collaborate with the World Health Organisation in the field of vaccine safety (see Module XIV).

P.I.C.1.5. European Medicines Agency

As for all medicinal products, the European Medicines Agency has the responsibility for coordinating the existing scientific resources for the evaluation, supervision and pharmacovigilance for vaccines. It supports Member States in these activities by operating and maintaining the infrastructure needed for the surveillance of vaccines, such as EudraVigilance (see Module VI), EPITT (see Module XII), the EU PAS register (see Module VIII) and by providing reaction monitoring reports to facilitate the monitoring of EudraVigilance data (see Module IX). The Agency also facilitates the identification of relevant networks and research groups in the EU in the view of conducting post-authorisation studies.[23]

The Agency has the responsibility for EudraVigilance data monitoring, signal detection and signal validation for centrally authorised vaccines and for active substances contained in several vaccines where at least one is centrally authorised (see Module IX~~.C.1~~).

For vaccines authorised in more than one Member State, the Agency is responsible for the coordination between national competent authorities of safety announcements (see P.I.C.5). For centrally authorised vaccines, the Agency publishes on the European medicines web-portal information including a summary of the risk management plan (RMP), protocols and public abstracts of results of the post-authorisation safety studies imposed as an obligation and conclusions of assessments, recommendations, opinions and approvals and decisions taken by its scientific committees.

See Module XIV for the agency's cooperation with the World Health Organization (WHO) on matters of pharmacovigilance and on transmission of information and suspected cases of adverse reactions to WHO.~~The EMA should collaborate with the European Centre for Disease Prevention and Control (ECDC)zz and the World Health Organization in order to monitor the efficacy/effectiveness of vaccines and collect information on their benefit-risk balance.~~

P.I.C.2. Reporting of reactions and emerging safety issues

Reporting of suspected adverse reactions and emerging safety concerns should follow the guidance in Module VI. Communication of signals from EudraVigilance by marketing authorisation holders should follow the guidance of Module IX.

[23] See ENCePP website: http://www.encepp.eu.

Reports of vaccination errors with no associated adverse reaction should not be reported as individual case safety reports. They should be considered in periodic safety update reports as applicable (see Module VII). When those reports and any suspected quality defect or batch-related issues constitute safety concerns which may impact on the benefit-risk balance of the medicinal product or representing a significant hazard to public health, they should be notified immediately in writing to the competent authorities in accordance with the recommendations provided in Module VI.

When a batch-related issue is suspected, activities at the level of Agency and competent authorities in Member States may include, as appropriate:

- early distribution of information on the issue via the rapid alert system (see Module XII) to national competent authorities; this communication may include questions to Member States (e.g. on usage of the batch(es) and similar cases reported to the national competent authorities);
- triggering of the incident management plan established in the EU ~~if considered necessary~~ (see Module XIII);
- interactions with other European agencies, the WHO and non-EU national competent authorities ~~as appropriate~~ (see Module XIV).

Where a quality defect is suspected, marketing authorisation holders should follow the procedures explained on the EMA website[24] as well as the applicable national procedures.

P.I.C.2.1.Reporting of vaccination failures

Cases of vaccination failures should be reported as cases of lack of therapeutic efficacy within 15 days, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccinated individuals, waning immunity or strain replacement. Such a signal may need prompt action and further investigation through post-authorisation studies as appropriate.

P.I.C.3. Risk Management System

A RMP or an update, as applicable may be submitted at any time during a vaccine's life cycle, i.e. during both the pre-and post-authorisation phase (see Module V~~.C~~). In addition, because a change to the manufacturing process of a biological product may potentially have an unpredictable impact on safety, situations where a RMP or RMP update may be required include a significant change in the marketing authorisation, including, on a case to case basis (depending on the nature of the changes), changes in the manufacturing process of ~~a~~ the ~~biotechnologically derived~~ vaccine. Therefore, any potential or theoretical impact on safety, and thereby the possible need to update the RMP, must be considered ~~with any change to the manufacturing process of a vaccine~~in this situation.

P.I.C.4. Signal management

Where a signal is based on a single report of a serious adverse event following vaccination, the signal should be validated by the signal identifier (see Module IX~~.B.3.3~~ and P.I.B.4). The validation should be performed in collaboration with the PRAC Rapporteur or Lead Member State, if appropriate, to facilitate collection of contextual information. Where the report does not meet the criteria for signal validation, it should not be communicated as a confirmed signal to the PRAC by the PRAC Rapporteur or Lead Member State but should be tracked by the signal identifier and special attention should be paid to any follow-up information or other cases of the same adverse event (see Module IX~~.C.1~~). If a non-validated signal has to be shared with the EU regulatory network by a national competent authority for

[24] Available on EMA website http://www.ema.europa.eu under http://www.ema.europa.eu/Inspections/Defects.html.

information or collection of additional data, it may be communicated to the network via a Non Urgent Information.

Vaccines should be subject to additional monitoring if they have been authorised after 1 January 2011 or at the request of the European Commission or the national competent authority where the optional scope for additional monitoring is applicable (see Module X). In such cases, the periodicity for the monitoring of data from EudraVigilance ~~will~~ may be ~~every 2 weeks~~increased to every 2 weeks. ~~for the duration of the additional monitoring.~~ In some circumstances, more frequent monitoring ~~than every 2 weeks~~ may be proposed by national competent authority or the Agency. It should be targeted to a safety concern of interest especially during public health emergencies (e.g. pandemics) and may be applied in the context of custom queries conducted in the EudraVigilance Data Analysis System (see Module IX).

P.I.C.5. Safety communication about vaccines in the EU

Further to the guidance in P.I.B.6., the following should be considered for safety communications about vaccines in the EU. Operational details of communication processes may differ according to different scenarios of vaccine use among Member States and with regard to different vaccines. Also, benefit-risk perceptions may vary between Member States and cultures. Hence, these differences and variations should be accounted for during the EU-wide coordination of safety communication with consistent messages. Communication in the EU should be underpinned by transparency on how regulatory decisions were reached and on the roles and responsibilities of each stakeholder in the EU (see P.I.C.1.). Where special planning should be undertaken in case of public health emergencies or pandemics, the Agency and the national competent authorities should announce requirements and guidance for marketing authorisation holders ~~and competent authorities in Member States~~ on their ~~website and the~~ respective webportals.

P.I.C.6. Transparency of pharmacovigilance for vaccines in the EU

The public summary of the RMP is to be made publicly available by the Agency for centrally authorised vaccines and by national competent authorities for nationally authorised vaccines [REG Art 26(1)(c), DIR Art 106(c)]. It should be written in lay language and considerations should be given to the target audience~~.~~, which ~~that~~ might be different for a vaccine than for a usual medicinal product (e.g. general population *vs.* informed patient groups).

P.I.C.7. Vaccines intended for markets outside the EU

In the context of the cooperation of Member States and the Agency with the World Health Organization (WHO) (see Module XIV), the Agency may give a scientific opinion for the evaluation of vaccines for human use intended exclusively for markets outside the EU [REG Art 58]. ~~-~~Examples for this procedure include vaccines to be possibly used in the WHO Expanded Programme on Immunization, vaccines for protection against a WHO public health priority disease and vaccines that are part of a WHO managed stockpile for emergency response. 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 Agency's opinion should implement the pharmacovigilance activities specified in the procedure.[25]

[25] European Medicines Agency. Article 58 applications: ~~r~~Regulatory and procedural guidance. www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240d1.