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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

# GUIDELINE ON THE CONDUCT OF PHARMACOVIGILANCE FOR VACCINES FOR PRE- AND POST-EXPOSURE PROPHYLAXIS AGAINST INFECTIOUS DISEASES

## DRAFT FOR PUBLIC CONSULTATION

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**EXECUTIVE SUMMARY**

This guideline is addressed to Marketing Authorisation Holders and Competent Authorities. It should be read in conjunction with the other pharmacovigilance guidelines contained in Volume 9A of the Rules Governing Medicinal Products in the EU and provides additional guidance on the safety surveillance of vaccines used for the prevention against infectious diseases before or after exposure to an infectious agent. This guidance takes into account the relevant specific aspects of vaccines, such as the balance between risks for the healthy vaccinee and the benefits for that individual as well as the whole population and side-effects due to the activation of the immune system. In its final version, this guideline will be included in Volume 9A.

## 1. Introduction

Immunisation is one of the most effective and widely used public health interventions. The benefit of vaccination has been demonstrated for authorised vaccines, both at individual as well as community level. Prominent examples are the eradication of small pox and polio in most parts of the world. No vaccine is however 100% safe or effective. As the incidence of vaccine preventable diseases is reduced by increasing coverage with the efficacious vaccine, vaccine-related adverse events, whether causally related or perceived as such, become increasingly prominent.

Vaccines are different from most other medicinal products in ways that influence safety considerations. Vaccines are a preventive measure, usually given to healthy individuals and especially young children at vulnerable age. They have a complex composition and a short duration of exposure with a long-term response. No (immediate) health benefit might be apparent to the individual vaccinee due to the success of vaccines in reducing illness in the community. As a consequence, there is limited acceptance of any potential risks. Any safety concern arising with a vaccine might impact on a significant number of subjects. Therefore, safety concerns need to be promptly evaluated. As vaccines are often used in several birth cohorts or even in the whole population, events inadvertently occur in temporal but not in causal association to vaccination. Perceived safety concerns have been increasingly discussed in the public area. Public confidence in vaccination programmes may only be maintained if it is considered that Competent Authorities will assess the safety of vaccines in a timely and adequate manner and take appropriate action. This includes investigation of rare and unexpected adverse events, increases in the occurrence of known adverse reactions and careful analysis of theoretical concerns.

In the EU, effective pharmacovigilance systems including systems covering the pharmacovigilance of vaccines are implemented in accordance with the legal requirements and the guidance provided in Volume 9A of the Rules Governing Medicinal Products in the EU. This guidance is intended to further strengthen the conduct of pharmacovigilance of vaccines for pre- and post-exposure prophylaxis of infectious diseases and to encourage development of new approaches.

## 2. Scope

This guidance is addressed to Marketing Authorisation Holders and Competent Authorities. It should be read in conjunction with other pharmacovigilance guidance and is not intended to replace any other relevant guidance. This guidance mainly covers post-authorisation aspects specific for vaccines. Special attention is paid to the development of Risk Management Plans prior and after marketing authorisation.

The guidance is directed to Applicants/Marketing Authorisation Holders and Competent Authorities/the European Medicines Agency and also aims at providing guidance to other stakeholders (e.g. sponsors of clinical studies, Healthcare Professionals, public health authorities) who are expected to use the guidance and thereby strengthen the cooperation of all stakeholders.

The guidance outlines the special considerations for pharmacovigilance of vaccines used in all age groups for pre- or post-exposure prophylaxis of infectious diseases. It is not intended to cover

therapeutic vaccines (e.g. viral-vector based gene therapy, tumour vaccines, anti-idiotypic vaccines such as monoclonal antibodies used as immunogens), as these will require different considerations.

## 3. Legal Basis

This guidance should be read in conjunction with Regulation (EC) No 726/2004, Council Directive 2001/83/EC as amended (Title IX), Commission Regulation (EC) 540/95, Volume 9A of the Rules Governing Medicinal Products in the EU and other relevant guidance documents as referred to.

## 4. Roles and Responsibilities of Different Stakeholders

Stakeholders involved in the process of vaccine pharmacovigilance include the vaccinee and, in the case of paediatric vaccination, their parents/carers, Healthcare Professionals, Applicants/Marketing Authorisation Holders, sponsors of clinical trials, Competent Authorities and public health authorities recommending vaccination programmes and the World Health Organization (WHO). Depending on their responsibility, each stakeholder may have an important role in contributing to this process. Media has an important role in unbiased communication in particular in situations where there is a gap between the scientific analysis of experts and public perception of perceived risks which is especially relevant to vaccines.

## 5. Key Factors Contributing to Safety Profiles of Vaccines

### 5.1 Vaccine-Intrinsic Factors

#### 5.1.1 Type of Vaccine

The safety profile of live virus or bacterial attenuated vaccines and inactivated vaccines (including vaccines based on bacterial proteins, polysaccharides or protein-conjugated polysaccharides and recombinant protein vaccines) may have different safety profiles. Safety concerns associated with different types of vaccines identified prior to marketing authorisation should be investigated in the pre-authorisation phase and addressed in the Risk Management Plan (RMP). For concerns identified during the post-authorisation phase, appropriate safety investigations may be necessary. Both also apply to safety concerns which arise from experience with similar vaccines.

Certain attenuated virus vaccine strains may be associated with adverse reactions usually seen with wild type virus. The level of attenuation and the possible impact on safety should be discussed in the Safety Specification of the RMP. If necessary, targeted post-authorisation safety studies (PASS) should be conducted.

Reversion to virulence after multiplication in the human host might be of particular concern for some live attenuated vaccines. Careful investigation of cases indicating a possible reversion to virulence in the post-authorisation phase is essential, especially for new live attenuated vaccines. Validated and standardised assays, including assays to distinguish between wild and vaccine strains, should be developed and implemented prior to marketing authorisation for appropriate case assessment. Post-authorisation studies should also address, if relevant, the pattern of shedding, transmissibility to contacts and the potential of the strain to survive in the environment.

In rare occasions, some live attenuated vaccines may cause serious syndromes closely resembling wild-type disease, probably not associated with the vaccine but with individual host factors increasing susceptibility. Host risk factors such as age, gender and immune status of the vaccinee should be carefully investigated. Clinical, serological and immunochemical analysis as well as virus detection, quantification, sequence analysis and cytokine release, may be helpful to further investigate the immune response elicited in the individual cases. Close collaboration with reference laboratories or specialised laboratories is recommended.

### 5.1.2 Immunogenic Adjuvants, Stabilisers, Preservatives and Residual Material from the Manufacturing Process

Incorporation of a particular adjuvant into vaccine formulations to enhance immunogenicity may be linked with induction of both local and systemic adverse reactions. Use of (novel) adjuvants targeted at stimulating a specific immune response justify particular attention to specific issues such as auto-immune diseases and rare and/or delayed onset adverse reactions. The clinical impact of the adjuvant in respect to impairing the immune response toward a Th2 (helper T-cell type 2)-response (as known for aluminium-based adjuvants) should be investigated in the post-authorisation phase. Synergistic immune-mediated reactions of adjuvants and the biologically active antigen should be considered. Whereas currently used adjuvants are mainly aluminium salts and oil-in-water emulsions, a greater emphasis by vaccine manufacturers is now placed on discovery, development and testing of novel adjuvants for use, with the possibility of the occurrence of new safety concerns. The immunological mode of action of any novel adjuvants should be addressed in the pharmacovigilance specification of the Risk Management Plan. Where deemed necessary, post-authorisation safety studies (PASS) investigating potential rare and delayed onset effects of new adjuvants should be conducted.

Cells from human, animal, insect, 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. These impurities may consist of proteins that have structural homology with human proteins. In addition to extensive pre-clinical and clinical testing, post-authorisation surveillance may be appropriate to demonstrate that these residuals do not cause harm to vaccinees.

Preservatives and stabilisers may not be as immunologically inert as previously thought (e.g. polygeline).

Removal of a preservative and/or stabiliser from a well-established vaccine may also have an impact on the safety profile of the vaccine as seen with a recent tick-bone encephalitis vaccine.

It is important to analyse whether the antigen itself or any ingredient has caused the adverse reaction. If necessary, risk minimisation strategies need to be explored.

### 5.1.3 Combined Vaccines

Combined vaccines consist of two or more vaccine antigens in one pharmaceutical preparation, intended to prevent multiple diseases or to prevent one disease caused by different serotypes. Possible safety concerns such as increased frequency of known adverse reactions (local or systemic) or increase of severity of adverse reactions should be carefully followed up. In the pre-authorisation phase, it is only feasible to detect large differences in the incidence and severity of common adverse reactions between the combined vaccine and the precursor vaccine(s), whereas smaller differences of local or systemic adverse reactions are usually not detected in pre-authorisation studies. Therefore, pharmacovigilance for combined vaccines should focus on a possible increase in the frequency and severity of local and systemic adverse reactions which might translate into tolerability of the vaccine. If appropriate, risk minimising strategies might be explored (e.g. preventive anti-pyretic treatment in small children).

### 5.1.4 Novel Vaccines

Where new approaches and novel concepts (e.g. temperature selected mutants), new technologies (e.g. vaccines using novel delivery systems), novel adjuvants or alternative routes of administration (e.g. nasal administration) have recently been developed or are currently in the clinical testing phase and may give rise to new safety concerns. Targeted monitoring and special studies are required for certain types of rare but serious adverse reactions. These may be anticipated from the particular composition of the novel vaccine or from their relatedness to well-established vaccines. Particular consideration should be given to what methods may be employed to detect long-term, delayed onset and, in case of vaccines for infants, developmental adverse reactions (see Chapter 7.3).

### 5.1.5 Batch-Relatedness of Adverse Reactions

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 which may have impact on safety of the vaccine. In principle, contamination with unwanted infectious agents at many different points, as well as generating aberrant materials cannot be totally excluded. Although a great deal of effort is put into control of raw and starting materials and the manufacturing process as well as testing of each single batch to exclude contamination with infectious agents and other risks linked to any aberrant material, these potential risks which may result in adverse reactions should be considered. As these adverse reactions may be related to certain batches, pharmacovigilance systems in Member States should be capable of recording individual lots.

If there is reasonable suspicion of an association between the occurrence of adverse reactions and a particular batch of a vaccine, Competent Authorities for marketing authorisation and the competent authorities for batch release should be informed immediately by the Marketing Authorisation Holder. A full assessment of the possible reason for batch-relatedness of adverse reactions needs to be provided. Where a quality defect is suspected or confirmed, the procedures laid down in the Compilation of Community Procedures on Inspections and Exchange of Information[1] should be followed.

### 5.1.6 Vaccination Schedule and Route of Administration

Different immunisation schedules may impact on the safety profile of a given product. The pharmacovigilance plans of the Risk Management Plan, study designs and causality assessments should be focused as appropriate, drawing from prior experience (e.g. incidence and severity of limb swelling with subsequent doses of DtaP (Diphtheria, Tetanus and Pertussis-acellular) vaccine).

The vaccine administration route is known to be another important factor influencing safety of a vaccine. Potential implications need to be considered, in particular for alternative routes of administration (e.g. intranasal, oral, intradermal). The impact of adjuvants needs to be explored.

## 5.2 Host Factors

### 5.2.1 Special Age Groups

Immunological responses to vaccines depend on the independent and coordinated function of innate and adaptive immune responses which is different in young children, young adults and elderly persons. Differences of the immune response in different age categories may not only translate to different efficacy of vaccines, but also to differences in the safety profile. Adverse reactions may occur solely in certain age categories, e.g. hypotonic hyporesponsive episode (HHE) in young children. Furthermore, the frequency of adverse reactions may change in relation to age. Targeted surveillance of adverse reactions in different age groups is warranted. Prior to marketing authorisation it may not be possible to study all aspects of age related safety issues for a new vaccine. Therefore, these aspects may be addressed in the Risk Management Plan, if relevant.

### 5.2.2 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 avoided. Risk to the developing foetus from vaccination of the mother with an inactivated virus, bacterial or toxoid vaccine during pregnancy is considered theoretical and should be further investigated on the basis of data collected in the post-authorisation phase. This may range from follow-up of spontaneously reported pregnancies up to additional pharmacovigilance activities such as

[1] Doc.Ref. EMEA/INS/GMP/3351/03 latest version, available on EMEA website http://www.emea.europa.eu.

pregnancy register (in particular if a new adjuvant is used). The detailed design of the preferred approach to collect such data should be provided as part of the Risk Management Plan. The studies should be designed to identify spontaneous abortions, stillbirths and congenital malformations. Adequate duration of follow-up of the offspring should be guaranteed. Detailed information on vaccine exposure (including number of doses and gestational age at the time of exposure) before and/or during pregnancy is warranted. Documentation and investigation should also include other risk factors. Pregnancy registers which are already available may be capable of providing the necessary data.

Careful monitoring and follow- up of reported pregnancies is necessary for all vaccines.

### 5.2.3 Immunocompromised Individuals and HIV-Infected Persons

Immunocompromised individuals may not only be very sensitive to serious disease after exposure with the natural infectious agents, but may also be very sensitive to the occurrence of serious adverse reactions.

## 6. Risk Management Plan

As most aspects of existing RMP guidance is equally applicable to medicines and vaccines, this section should be read in conjunction with Chapter I.3 of Volume 9A of the Rules Governing Medicinal Products in the EU. That section provides guidance on some issues specific for vaccines.

### 6.1 Safety Specification

### 6.1.1 Pre-Clinical Aspects for Further Consideration

Safety concerns for a vaccine include those due to inherent toxicities of the antigen and adjuvant, toxicities of impurities and contaminants and toxicities due to interactions of the vaccine components present in the vaccine formulation.

If findings from pre-clinical testing with a possible impact on safety and/or serious adverse reactions possibly related to the investigated vaccine occur, there may be a need to extend the safety database in the post-authorisation phase in order to ensure that the pre-clinical findings do not translate into a risk in humans (e.g. potential concern of enhanced pathology in small children to subsequent infections after whole viral inactivated aluminium adjuvanted vaccines).

### 6.1.2 Limitation of the Safety Database and Population Not Studied in the Pre-Authorisation Phase

Serious and clinically relevant adverse reactions are mostly rare and thus are unlikely detected prior to marketing as the sample size of clinical trial database is mostly limited to detect common and uncommon adverse events. Long-term follow-up of vaccinees might also be limited and pre-authorisation data will most likely not address concerns of long-term risks. Furthermore, in pre-authorisation clinical trials the study population is highly selected, whereas in the post-authorisation phase immunisation might be targeted at a heterogeneous population with diverse background diseases.

### 6.1.3 Potential Risks Requiring Further Investigation

Experience with similar antigens, types of antigen and/or other adjuvants and other vaccine excipients should be described in the RMP. The impact of adjuvants, stabilisers, preservatives or residuals of the manufacturing process should be discussed in the RMP.

Safety concerns anticipated from experience with similar vaccines and vaccine ingredients should be addressed in the RMP and, if necessary, a commitment to undertake post-authorisation safety studies should be provided. Safety parameters based on biological plausibility of the occurrence of certain

adverse reactions or previous experience with a similar authorised vaccine should be investigated in detail. It should be considered whether more additional information (e.g. cytokine profiles) might be of value.

### 6.1.4 Identified and Potential Interactions

Emphasis should be placed on identified and potential interactions with co-administration of other vaccines. This should include a prospective specification based on issues with likely concomitant use across Member States such as higher reactogenicity of concomitant vaccination and clinically relevant immunological interference. Past experience with similar vaccines and types of antigens should be considered.

If clinical trials or literature data indicate 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) adequate investigations in the post-authorisation phase might be warranted.

### 6.1.5 Epidemiology of the Target Disease and Background Incidence of Adverse Events of Interest

This section of the RMP should focus on the different natural histories of the target disease across Member States as appropriate and highlight any particular considerations required. The section should discuss any relevant examples of impact of previous and similar vaccines on the disease and any potential concerns to monitor. For vaccines that may protect against only some types of organisms within a species, appropriate surveillance should be in place to detect strain replacement phenomena.

Emphasis should be given on assessing the population and age-specific background rates of adverse events of special interest in order to assist evaluation of spontaneous reports of adverse reactions.

### 6.1.6 Potential of Transmission of Infectious Agents

The RMP should address for live attenuated vaccines aspects such as shedding, transmission of the attenuated agents to close contacts, risk for pregnant women and the foetus, andreversion to virulence (see Chapter 5).

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 in the RMP.

## 6.2 Pharmacovigilance Plan

This section of the RMP is covered by Chapter I.3 of Volume 9A in general terms. There are special considerations for both routine and additional pharmacovigilance activities for vaccines such as the need to investigate serious but rare adverse reactions (even if the sole aim is to provide reassurance on safety), batch-related adverse reactions, if appropriate, safety of concomitant vaccination and evaluation of the impact of different immunisation schedules.

Different policies on use of vaccines concerning vaccination schedules and target population might give rise to different safety issues. It is acknowledged that it might not be feasible to study all recommended priming and booster schedules across the EU, however the Marketing Authorisation Holders should discuss the need for further evaluation (e.g. studying the most accelerated schedule) and should provide Pharmacovigilance Plans in the RMPs accordingly. If a specific safety concern associated with the vaccination schedule or the target population can be anticipated from other vaccines, targeted post-authorisation studies should be considered.

At the time of marketing authorisation, data on long-term duration of protection, the potential for waning immunity and the need for a booster dose are usually not available. Plans for collecting these data should be presented as part of the RMP.

Marketing Authorisation Holders should explore availability of systems for collecting data in different countries, particularly when addressing specific safety concerns. Pharmacovigilance methods with regard to data collection and signal detection and evaluation are further explored in Chapters 7 and 8.3.

## 6.3 Risk Minimisation

Risk minimisation measures for vaccines are considered to be the same as for other medicinal products (see Chapter I.3 of Volume 9A).

# 7. Data Collection

## 7.1 Adverse Events Following Immunisation (AEFIs) and Adverse Reactions

Adverse Events Following Immunisation (AEFIs) are clinical observations of adverse nature in vaccinees, and they may be classified as occurring:

1. in suspected causal relationship with the vaccination; or
2. coincidentally after vaccination.

Those AEFIs which are suspected to occur in causal relationship with the vaccination represent suspected adverse reactions and may be further classified as follows:

1. Vaccine-related

1.a due to the intrinsic characteristics of the vaccine as formulated;

1.b due to a quality defect of the vaccine;

2. Vaccination error (e.g. use not as authorised, prescription error, storage error, dispensing error, administration error);

3. Vaccination anxiety (e.g. syncope).

Vaccines are intended to have powerful effects on the immune system. It is understandable therefore that healthcare professionals and the public may perceive adverse events occurring in temporal association with vaccination as causally related, even if no causal link exists. AEFIs might be reported to either regulatory authorities as well as marketing authorisation holders as spontaneous reports. In the EU, legal definitions and reporting requirements are laid down for adverse reactions but not for AEFIs.

### 7.1.1 Suspected Adverse Reactions

Spontaneously reported suspected adverse reactions remain an important source for the detection of safety issues in the post- authorisation phase, in particular with regard to rare, serious adverse reactions with a low background event rate. Spontaneous reporting is also useful to cover safety aspects in the diverse populations. Different types of adverse reactions should be considered:

- those that are perceived as adverse reactions, but may be visible signs of the immune response of the host (interleukine response, e.g. fever);
- those reflecting the clinical picture of the disease for which immunisation has been given (e.g. measles-like rash following vaccination); and
- those that are unexpected and for which a causal relationship remains to be elucidated.

For assessment of individual case reports of suspected adverse reactions, it is essential that complete and accurate records documenting administration of all vaccines, together with information on the date

of vaccination, product administered, manufacturer, batch number, site and route of administration, detailed description and course of the adverse event/reaction as well as therapeutic intervention are provided. Appropriate follow-up of serious suspected adverse reactions is of inherent importance including data on possible alternative causes of the adverse event. It may be helpful to develop pre-defined check lists or formats for those reactions which may be anticipated from experience with similar vaccines for reporting in the post-authorisation phase in order to ascertain consistently relevant clinical information to ensure the quality of the causality assessment of an individual case. Standardised case definitions of adverse events are a key element for scientific assessment of immunisation safety as they provide a common terminology and understanding of adverse events/reactions and thus allow for comparability of data. Case definitions of the Brighton Collaboration[2] should be used, if appropriate.

Several aspects need to be considered when assessing single cases of suspected adverse reactions.

- The population of vaccinees is usually large and heterogeneous and coincident adverse events are likely to occur.
- In addition to the intended active ingredient, the antigen, additives and excipients for production - inactivation, preservation, and stabilisation of vaccines also play an important role in evaluating the causal relationship of a suspected adverse reaction with a given vaccine.
- Categories or algorithms used for causality assessment for medicinal products might not be equally applicable for vaccines. There might be a need to adopt the categories to vaccines. This should be stated in the RMP. The currently ongoing work of the Joint Council for International Organizations of Medical Sciences (CIOMS)/WHO Working Group on Vaccine Pharmacovigilance should be regarded in this respect. De-challenge and re-exposure testing which are important criteria for several causality are mostly not applicable to vaccines.

### 7.1.2 Vaccine Failures

Most vaccines are not 100% effective. Therefore cases of breakthrough infections are expected. A higher-than-expected efficacy of a vaccine, waning efficacy over time or replacement phenomenon cannot be fully investigated via spontaneous reporting. Nevertheless, expedited reporting is recommended in Volume 9A. Risk factors for vaccine failure should be analysed (e.g. obesity, age, smoking status, vaccination schedule, concomitant disease). This may provide signals for reduced immunogenicity of the vaccine under daily life conditions in risk groups. 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. Case definitions for vaccine failure, lack of effect, break-through infection are not universally agreed at present, but it is expected that consistent case definitions will be published in the near future by the Joint CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Vaccination failure should be defined in the RMP.

### 7.1.3 Vaccination Errors

Inappropriate handling may lead to infection, bacterial contamination, blood-borne infection and abscess formation. These issues apply particularly to multi-dose container vaccines without preservatives.

For some vaccines, the method of administration may be associated with adverse reactions and this should be considered when assessing a single case report of a suspected adverse reaction.

Marketing Authorisation Holders should adequately follow-up the root cause of any errors (e.g. cold chain investigation, batch investigation) and address this appropriately through communication. The potential for and risk minimisation actions addressing such errors need to be described in the RMP. It is of inherent importance to measure outcome of the actions taken.

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[2] Available on the website of the Brighton Collaboration: http://www.brightoncollaboration.org.

## 7.2 Periodic Safety Update Reports (PSURs)

In addition to information which should be provided in the Periodic Safety Update Report (PSUR) for all medicinal products (see Chapter I.6 of Volume 9A), 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 reactogenicity of a vaccine should be analysed for different doses of the vaccine schedule and also across different vaccination schedules.

Reports of vaccine failure / lack of efficacy should be assessed in a separate chapter of the PSUR.

Vaccination errors and vaccination anxiety-related reactions such as syncope should also be summarised and analysed in the PSUR. Actions taken to avoid vaccination errors may be described in the PSUR. In accordance with Chapter I.6 of Volume 9A, relevant published data on safety should be presented in the PSUR. Literature data should not solely focus on safety information available for the antigen(s), but should also summarise published information relevant for other vaccine components such as stabilisers, preservatives and adjuvants.

If concomitant vaccination with another vaccine is specifically mentioned in the Summary of Product Characteristics (SPC), safety aspects identified with co-administered vaccines should be analysed separately and summarised in the PSUR.

## 7.3 Post-Authorisation Safety Studies (PASS)

As rare but serious adverse reactions, reactions with delayed onset and reactions in subpopulations are usually not detected prior to marketing authorisation post-authorisation evaluation of safety in studies is critical for vaccines. Safety concerns arising during the post authorisation may relate to:

- the increased incidence of a natural disease;
- vaccine specific adverse reactions;
- a higher rate of expected adverse reactions compared to comparators or precursor vaccines.

Certain aspects of post-authorisation safety studies (PASS) may be of particular interest:

- those aiming to confirm that the safety profile is acceptable under real life conditions (large numbers of patients studied with the aim of expanding the safety database, pro-active safety testing);
- those aiming to evaluate new safety issues including perceived risks ad hoc;
- those intended to evaluate known or expected safety concerns (e.g. those detected in the pre-authorisation phase and those anticipated from other similar vaccines);
- those aimed at providing laboratory confirmation of a causal link; and
- those aimed at investigating the aetiology of the adverse event/reaction.

For assessment of safety signals, controlled clinical trials and prospective cohort studies are considered to provide the highest level of evidence. Active surveillance of rare adverse reactions by follow-up of a cohort recruited at the time of vaccination requires follow-up of a large number of vaccinees. Retrospective (i.e. historical) cohort studies may be conducted, since the group in whom the adverse events/reactions is studied is not defined at the time of vaccination but is defined retrospectively, according to the population-based data set available at the time the study is conducted.

In order to interpret the rates of the (various) disease(s) that will occur over time in the vaccinated cohort, an unvaccinated control group is also required, consisting of individuals born during the same period, recruited at the same age and followed up since recruitment through the same methods. However, this may not be feasible because of a large sample size needed. Furthermore, once a vaccination is recommended for use, it may not be possible to identify appropriate concurrent controls. In such cases, historical controls may be an option.

An alternative to clinical trials and cohort studies for the active surveillance of adverse events/reactions is the use of databases with computerised data sets of clinical diagnosis and information on immunisation records of a large number of individuals. Integrated databases such as the General Practice Research Database (GPRD) or IMS Health database may be appropriate for epidemiological studies. By use of databases, studies may be conduced following different designs. Studying large populations may provide the opportunity to even study rare adverse events. A recently established method in this respect is the use of record linkage of computerised data sets (disease/diagnosis and immunisation records) from different databases using a unique patient identifier. Clinical diagnosis/disease data may be diverted from computerised hospital discharge data, computerised general practice records data or other clinical databases (insurance company database). Such linked data sets have been used for formally testing hypothesis raised by uncontrolled observations. When such linked data sets are trawled for statistically significant associations for which no a priori hypothesis was used, and if enough associations are sought, some will be considered statistically significant just by chance. Therefore, database studies should be interpreted with particular caution. Caution should also be exercised if such database studies are used for generating hypotheses.

Computerised databases may also be used for conducting case-control studies. Vaccination histories of cases and controls may be compared in order to study the effect of vaccination on the risk of an adverse event/reaction and to study the effects of co-variables. This method allows for detection and assessment of risk factors and identification of vulnerable subgroups. It is ideal for rare events/reactions and for such reactions preferable to cohort studies. However, the limitations of such a study design needs to be acknowledged. This is in particular important for vaccines as many serious adverse events are so rare that it is even difficult to study them in a case control design (e.g. anaphylactic reactions). Using the case-control approach in rare events, relative risk may reliably be estimated by odds ratios. Odds ratios may be adjusted for potential confounders by multivariate logistic regression. It is important to select controls appropriately, since selection bias in controls may potentially compromise representativeness and introduce a systematic error in effect estimates.

Particularly in studies on vaccination, one has to expect potential confounding by health awareness, for example if subgroups are more or less likely to be immunised. In studies unable to adjust for such effects, odds ratios for immunisation effects may systematically over- or under-estimate any true association.

To estimate an association between vaccination and adverse events, the self-controlled case-series (SCCS) design proposed by Farrington et al (Am J Epidemiol. 1996; 143:1165-1173) has been used in the past as it might to avoid basis in a case-control design when the coverage rate of immunisation is high in universal vaccination programmes (lack of appropriate un-immunised control group). According to this study design, only vaccinated cases are included in the analysis. For each case, the observation period following each vaccine dose is divided into risk period(s) (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, taking age, in particular, into account, under the null hypothesis, that incidence rates would be equivalent if no association with vaccination is present. An SCCS analysis has the advantage of an implicit control of any potential confounders, even when unknown, which are stable over time and may also control for age effects. For unique events, this method requires 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. Compared to cohort or case-control studies, an SCCS analysis tends to be faster and may be more feasible when examining rare events, as only information on cases is required. Besides these strengths, the SCCS method has some limitations. Like cohort or case-control studies, the SCCS method remains susceptible to some bias if vaccination is timed to minimise the risk of an adverse event. In principle, the case series method is capable of estimating relative risks. Another problem is that a relevant time interval needs to be defined. Primary immunisation with several doses might result in problems of ascertainment of cases.

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 that 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. However, they compare data at the population level and not at the individual level and are unable to control for confounding variables and differentiate between true association and coincidence. Their results should therefore be interpreted with caution. Ecological studies may be useful to generate hypotheses.

In many Member States, vaccination programmes are organised in a way that provide the opportunity to establish vaccination registries also addressing vaccine safety (source population for large cohort studies). Vaccination registries may be usefully augmented by disease registries.

Safety parameters in PASS should be appropriate for the specific study vaccine. A pre-requisite is the use of globally accepted standards for case definitions (e.g. those published by the Brighton Collaboration[3]) to compare the frequency of adverse reactions across different studies. The possibility of meta-analysis of different studies for identification of rare adverse reactions should be discussed. Severity categories such as mild, moderate, and severe should be avoided.

Despite availability of the above mentioned tools, the difficulty of investigating possible long term risks which may only become evident several years or even decades after vaccination is acknowledged.

Experimental investigations should be considered in addition to address safety concerns including virological, bacteriological and/or immunological experiments and methods to elucidate the aetiology of an adverse reaction.

The guidance on PASS in Chapter I.7 of Volume 9A should be followed.

## 8. Data Evaluation

### 8.1 Signal Detection

Signals of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions may arise from any source including preclinical and clinical data (e.g. spontaneous reports from Healthcare Professionals or Consumers; epidemiological studies; clinical trials), published scientific and lay literature. .

In databases containing spontaneous reports where incidence rates cannot be computed, the method of choice may be a measure of disproportionality, detecting a signal of disproportionate reporting (SDR). SDRs refer to a statistical association between medicinal products and adverse events. There are several statistical methods used to detected SDRs, such as the proportional reporting ratio (PRR)) or Bayesian approaches.

Vaccines may require special consideration when applying such tools. 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 childhood vaccination, myocardial infarction and flu vaccines). Furthermore, the safety profile of a vaccine may differ substantially among the target population (e.g. higher reactogenicity in younger vaccinees). In order to reduce background noise, estimates of disproportionality should be calculated based on a comparison across groups that have a similar likelihood of experiencing similar adverse events. The choice of the comparator group will depend of 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

[3] Available on the website of the Brighton Collaboration: http://www.brightoncollaboration.org.

the other hand, using all vaccine-related reports available in the database may result in signals of age-related reactions (e.g. cardiac 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 and seriousness. Given the large differences in reporting rates between regions and countries, stratification by geographical region may also be considered. Stratification by co-morbidity or co-medication is desirable, but may be difficult to achieve. If Consumer/Patient reports of suspected adverse reactions are included in the database, signal detection should also be stratified by source (Healthcare Professionals, Consumers/Patients). Stratification between study reports and spontaneous reports is warranted. When stratification is performed, it may be wise to examine the results of both adjusted and non-adjusted analyses. Results should be inspected in each stratum as pooled result of a stratified analysis may miss signals.

Due to often universal vaccination policies, it is inevitable that coincidental events causing concerns will be reported in close temporal association with immunisation. There is therefore a need to assess the population and age-specific background rates of events of interest in order to assist evaluation of passive data. A simple method of investigating a signal is to compare the number of cases observed in temporal relationship to a suspected exposure during a period of time (O) to the number of natural incidences of the disease estimated to occur in the same period of time (E), assuming no relationship to the suspected exposure. Observed means usually reported via spontaneous reporting. O/E analyses are the first level of evaluation of safety signals. A classical approach is to calculate the O/E ratio and determine if this ratio is significantly different from one. Certain limitations of this analysis should be considered (e.g. underreporting, healthy vaccinee effect). A robust calculation of the exposed population and the incidence of the natural disease are warranted. Usually, the classical O/E analysis does not account for variability of parameters that were used to estimate the expected number of cases, such as variability of the incidence of the event, the age distribution of the event and the age distribution of vaccination. As a consequence the approach is considered to be rather conservative. Less conservative but more complex approaches have been developed recently. These approaches focus on E rather than on O/E and accounts for an age effect on E. In this analysis E is not a fixed number and O/E must be interpreted as a point estimate with variability around them.

Standardised MedDRA (Medical Dictionary for Regulatory Activities) Queries (SMQs)[4] may be used in the process of signal detection and evaluation. Sensitivity and specificity testing of SMQs for vaccines needs to be done beforehand in order to adequately interpret the results.

Signal evaluation is of inherent importance. Case definitions as e.g. published by the Brighton Collaboration[5] may be used for signal validation. However, this needs to be justified on a case by case basis.

When evaluating signals, the following potential biases should be taken into account (in addition to age and seriousness):

- vaccination policy (target group of subjects to be immunised);
- the incidence of natural disease in the target population;
- public information (public campaign, press) that may favour certain reports in some periods;
- seasonality.

Of note, a statistical association does not imply any kind of causal relationship between the administration of the vaccine and the occurrence of the adverse events.

[4] Council for International Organizations of Medical Sciences (CIOMS). Development and rational use of Standardised MedDRA Queries (SMQs). Geneva: CIOMS; 2004. Available on CIOMS website http://www.cioms.ch/.

[5] Available on the website of the Brighton Collaboration: http://www.brightoncollaboration.org.

## 8.2 Data Analysis

It is of inherent importance that data are managed in a form that allows data retrieval and analysis by age groups (e.g. premature infants, neonates, infants and the elderly), number of doses, different vaccination schedules, defined risk factors or underlying diseases and adverse event/reaction types. Clusters of reported adverse events/reactions should be identified. The safety profile of a vaccine may vary across different batches, therefore retrieval by batch number is also necessary. The same holds true for changes which are introduced into the manufacturing process. Full traceability of all manufacturing changes and links to safety data should be ensured.

Key data to be collected and analysed (in addition to the data on the patient and the immunisation history), are data about the vaccine and the diluent (if applicable) administered to the patient. Manufacturer(s), batch number(s), batch release specifications, expiry date(s), distribution data, storage conditions, and laboratory test results about the vaccine/batch, if appropriate. Distribution and administration -related data should also be collected and analysed, such as storage and handling conditions for vaccines in the healthcare institution where immunisation took place. This information may help identify products inappropriately used or patterns of error.

## 8.3 Risk Evaluation

The objectives of pharmacovigilance for vaccines are to identify rare or new adverse events, identify those that are causally related to the vaccine /vaccination and estimate their rate of occurrence. In addition, any change in the frequency or severity of a known safety concern requires prompt evaluation. Evidence of causality is based on biological plausibility supported by laboratory evidence and/or statistically significant excess of events in the post-vaccination period. Passive reporting systems have methodological limitations, particular for ascertaining reliable adverse event/reaction rates and investigating causal relationship. Therefore, additional pharmacovigilance activities are required.

Errors in manufacturing, handling and administration should also be evaluated. Action to avoid such errors should be explored.

## 8.4 Risk-Benefit Assessment

The risk-benefit balance for vaccines depends largely on the incidence of the infectious disease in the target population, the proportion of infected persons with clinical disease, the severity of clinical disease as well as the risk of transmission, identification of high risk groups and geographical and seasonal characteristics of the infectious disease. For vaccines already included into the extended vaccination programme, the impact of the vaccine on the epidemiology of the vaccine-preventable condition should be considered as well as the impact on individual protection. Due to the success of vaccination programmes in their later stages, whether there is herd immunity as well as individual protection, the risk-benefit balance might change. Differences in morbidity and mortality of an infectious disease in different countries have to be considered.

# 9. Risk Minimisation and Regulatory Action

In principle, regulatory tools and risk minimisation activities for vaccines are similar to those of conventional medicinal products.

## 9.1 Precautionary Measures

There may be circumstances where scientific evidence is insufficient, inconclusive or uncertain and where there are reasonable grounds for concerns that the potentially dangerous effects may be inconsistent with the chosen level of protection. A decision to take measures without waiting until all the necessary scientific knowledge is available, may be particularly relevant for vaccines in special circumstances, e.g. vaccines for healthy children. Because the potential for any risk is considered less acceptable in the case of preventive vaccines than in the context of disease treatment, decision makers

may respond to concerns which may be linked to vaccination despite uncertainties of scientific knowledge by taking precautionary measures.

## 9.2 Product Information

The guidance documents on the Summary of Product Characteristics (SPC) and the Package Leaflet (PL)[6] should be adhered to when evaluating proposed SPC/PL wordings. Please also refer to the Annex on SPC Requirements (CHMP/VWP/382703/2006) of the Guideline on the Clinical Evaluation of New Vaccines (CHMP/VWP/164653/2005)[7] for guidance on format and content concerning SPCs for vaccines.

## 9.3 Risk Communication

As immunisation programmes in countries mature, incidence rates of the targeted diseases are substantially decreased by high vaccine coverage rate. The level of trust in immunisation is usually high at the beginning of an immunisation programme when the disease is frequent and Patients and Healthcare Professionals have personal experience with the disease. As immunisation programmes successfully reduce the incidence of vaccine-preventable diseases, an increasing proportion of vaccinees and Healthcare Professionals are removed from personal experience with the disease and consequently rely for on historical and other more distant descriptions. This situation markedly influences risk perception and in return real or perceived adverse effects of immunisation receive relatively more attention.

Risk perception may differ between stakeholders (Patients, Healthcare Professionals, scientists, vaccination programme officers, regulators), especially when there is uncertainty about a risk. Public confidence in vaccination programmes may only be maintained by the public knowledge that systems are in place to ensure a complete and rapid safety assessment and to take measures even on precautionary basis. Communication of safety information is essential to respond to public concerns. Delivery of rapid, transparent, accurate and well-balanced information on the scientific evidence base is warranted. Communication to the public should be a collaborative undertaking between industry, regulators and public health organisations with input from all stakeholders. A key element is to clearly explain what is known about the safety and efficacy of a vaccine when it is first used in the population and what processes are in place for gathering additional safety data.

Communication may differ in different scenarios of vaccine use among Member States and with regard to different vaccines. It is essential to maintain a high level of transparency and to define the roles and responsibilities of each stakeholder in each phase.

## 9.4 Audit and Outcome Assessment

There is a need to ensure effective follow-up of the pharmacovigilance process and measurement of the outcomes of any actions taken. Actions taken, measures and methods as well as time-lines should be clearly described in the RMP.

[6] Available in Volume 3 of the Rules Governing Medicinal Products in the EU on the EMEA website.

[7] Available on the EMEA website.