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NOTE FOR GUIDANCE ON THE CLINICAL EVALUATION OF VACCINES

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1. INTRODUCTION AND SCOPE

This guideline on the Clinical Evaluation of Vaccines replaces the previous Note for Guidance on Clinical Evaluation of New Vaccines (CPMP/EWP/463/97) that was adopted in May 1999.

Extent of the revisions

This revision to the 1999 Note for Guidance includes the following changes and additions:

1. The guideline has been reformatted extensively, with changes made to the order, titles and contents of different sections.
2. A separate section expands on the requirements for the characterisation of the immune response. Detailed guidance is provided on the extent of the immunogenicity data that should be provided regardless of whether protective efficacy studies can not or need not be performed.
3. Guidance on the design and conduct of studies of protective efficacy, including considerations of when these might be feasible and necessary, now appears in a separate section.
4. A new section covers a range of special considerations that may arise during vaccine development. These include, among others, the evaluation of potentially clinically important immune interference, concomitant use of vaccines, interchangeability of vaccines within schedules and circumstances in which very limited data might be acceptable for vaccine approval (e.g. vaccines against rarely encountered diseases).
5. The section on safety now focuses mainly on pre-authorisation data since separate guidance is under development regarding pharmacovigilance. This section is currently a provisional draft.
6. A new section provides recommendations on the presentation and content of SPCs for vaccines that are additional to those in the CHMP's general guidance on this matter.

It is recommended that any proposals for major deviation(s) from this guidance should be discussed with EU Competent Authorities before implementation. All such deviations should be explained and discussed in the Clinical Overview. In addition, it is not possible to provide specific and/or concise guidance in this document to cover every conceivable situation that may arise. Therefore, applicants may find it particularly useful to discuss certain matters with EU Competent Authorities. These might include special issues for the development of vaccines against infective agents that are rarely encountered and/or might be used in biological warfare and vaccines against protozoal pathogens.

Scope

This guidance covers the clinical evaluation of vaccines for pre- and post-exposure prophylaxis against infectious diseases and is primarily intended to assist applicants and competent authorities to design, and evaluate data from, appropriate clinical development programmes. It addresses studies to be performed during the clinical development of new vaccines (e.g. those that contain at least one novel antigen, a novel antigen conjugate and/or a new combination of antigens). The guidance may also be applicable to the further development of licensed vaccines. For example, the generation of clinical data to support changes to indications, use in additional age groups, alternative dose schedules, recommendations for booster doses and the concomitant use of vaccines.

The guidance is relevant to vaccines that may contain one or more immunogenic antigens and is generally applicable whatever the type of antigen(s) included. For example, vaccines that contain:

- Organisms that have been inactivated by chemical or physical means
- Live organisms that are naturally avirulent in man or that have been treated or genetically modified to attenuate their virulence
- Substances extracted from pathogens or secreted by them. These include antigens used in their native state, detoxified by chemical or physical treatments, rendered non-toxic by genetic

modification or aggregated, polymerised or conjugated to a carrier to increase their immunogenicity.
- Substances produced by recombinant DNA technology

The guidance may also be applicable to:
- Live vector vaccines expressing foreign antigens (e.g. pox virus vector expressing non pox virus antigens)
- DNA vaccines expressing foreign antigens

However, guidance is not provided on matters specific to these types of vaccines, such as the choice and characterisation of vectors. Applicants should consult the available specific guidance relevant to these types of vaccines.

The following issues are not addressed in this guideline:
- Pre-clinical studies, except with regard to those that might be relevant to characterisation of the immune response to the antigenic components of vaccines.
- Pharmacokinetic studies. These are generally not required for vaccines because the kinetic properties of antigens do not provide useful information for determining dose recommendations. However, such studies might be applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients.
- Clinical development of therapeutic vaccines, viral-vector based gene therapy products, anti-tumour vaccines and anti-idiotype vaccines (including monoclonal antibodies used as immunogens)

This guideline should be read in conjunction with Directive 2004/27/EC, as well as all other pertinent current and future CHMP and ICH guidelines and WHO regulations. For example:

- CHMP guidance documents specific to certain vaccine-related issues, such as various types of influenza vaccines, smallpox vaccines, adjuvants.

- ICH guidelines, especially: E1, E2A, E2B/M2, E2C, E2CA, E2D, E2E, E 3 – E6, E8-E11

- The WHO Guideline on clinical evaluation of vaccines: regulatory expectations.

2. IMMUNOGENICITY

2.1. Introduction

This section provides guidance regarding the essential data on immunogenicity that should be assembled during the clinical development programme to support a marketing authorisation regardless of whether or not studies of protective efficacy will be feasible or necessary (see section 3). Further guidance on some specific types of immunogenicity studies that might be performed is given in section 4.

2.2. General methodological considerations

Immunogenicity data are usually generated in all phases of a clinical development programme.

If an appropriate animal disease model is available, primary pharmacodynamic studies to evaluate immunogenicity (and protection) of a new vaccine should be undertaken to indicate the doses, schedules and route(s) of administration to be evaluated in clinical studies (see CPMP/SWP/465/95).

Early clinical studies should provide sufficient information on the safety and immunogenicity of the antigenic components in a candidate vaccine in the target population to identify the optimal dose and primary immunisation schedule to be evaluated in subsequent confirmatory studies of safety and immunogenicity and, where feasible and necessary, protective efficacy. If studies of protective efficacy are performed, the immunological response should be characterised in a subset of the vaccinated population and the data should be used to attempt to identify an immunological correlate with protection if none is already established (see sections 2.3.3 and 3.)

2.3. Characterisation of the immune response

2.3.1 Minimum requirements for immunological testing

Biological specimens (e.g. serum, cellular fractions, mucus) should be collected from all participants at appropriate and pre-defined intervals throughout each study for the assessment of the immune response. The rationale for the timing of samples should be provided in the protocol and should take into account any data available on the kinetic of the immune response.

Protocols should specify and give details of the methodologies to be used to evaluate immune responses to vaccination. These should be consistent across studies, externally validated (including the use of international standards such as those of WHO if available) and demonstrated to be reproducible. If changes to methodologies are unavoidable during the clinical development programme, adequate cross-validation data should be provided.

Information should be provided on the quality and quantity of the immune response (humoral and cell-mediated) according to the known or presumed properties of each antigen in the candidate vaccine. Whenever feasible, immune responses to vaccination should be compared to those seen as a result of natural infection.

For antigens for which a widely accepted immunological correlate of protection already exists (e.g. diphtheria and tetanus toxoids and hepatitis B surface antigen), evaluation of the immune response to these antigens in a candidate vaccine may be limited to the usual parameters used to assess immunogenicity (and, thus, predict protective efficacy). For well known antigens for which no immunological correlate of protection exists (e.g. pertussis toxin), evaluation of the immune response should at least employ a comparison with results obtained with other vaccines containing the same or similar antigens.

For novel antigens, characterisation of the humoral immune response should include:

- Determination of the amount, class, sub-class and function (e.g. neutralising, bactericidal or opsonising ability) of specific antibody that is elicited by each antigen.
- Exploration of the relationship between functional (e.g. measured in neutralisation assays) and non-functional antibody assays (e.g. measured in enzyme-linked immuno-assays)
- Description of the kinetic of the immune response such as the lag-time for onset, antibody persistence, seroconversion rate (which should be adequately defined) and induction of immune memory.
- Depending on the delivery route, monitoring of certain components of the immune response might be indicated, such as antigen specific secretory IgA responses after mucosal administration.
- Assessment of the quality of the antibody response, which may include parameters such as specificity and/or epitope recognition and avidity. Changes in these parameters over time and/or with subsequent doses should be evaluated.
- Evaluation of the potential for formation of cross-reactive antibodies or immune complexes.
- Exploration of immunological factors that might affect the humoral immune response, such as pre-existing antibodies (including maternal antibodies).

An assessment of the cell-mediated immunity (CMI) component of the immune response to each novel antigen is considered to be important and, for some types of antigen, would be essential. It is recommended that studies should monitor quantity and quality of T-cell responses (for example antigen specific T-cell frequencies with methods of verifiable validity, Th1, Th2, T regulator cells, memory T cells and relevant cytokines). The range of tests performed, with an explanation of the rationale for each investigation, should be justified in the application dossier.

2.3.2 Immunogenicity in various types of possible recipients for the vaccine

Potential effects on the vaccine immune response of various host factors (e.g. age, prematurity, maternal antibody, nutritional status, genetics, coexisting disease, immunosuppression, and prior exposure to an infectious agent) should be considered. Extrapolation of data from one population to another requires scientific justification that may not be possible without provision of specific data. For some types of vaccine it may be acceptable that some of these issues are explored after initial authorisation. However, if the vaccine has potential to be useful in specific populations (e.g. the immunosuppressed) studies should be performed as early as possible in the clinical development programme.

Maternal immunisation during pregnancy to reduce infant morbidity and mortality might be a useful strategy to be explored for some types of vaccines against certain infectious diseases. Establishing a successful vaccine programme for pregnant women is a complicated task and companies that are considering such studies should seek scientific advice from EU Competent Authorities at an early stage.

2.3.3 Immunological correlates of protection

At present, widely accepted immunological correlates of protection exist for certain antigens only and consist of defined humoral antibody responses above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.

When there is no established immunological correlate for protection, every effort should be made to describe the correlation between the immune response to an antigen and the protective efficacy of the vaccine. Ultimately, it is desirable that one or more immunological correlate(s) of protection should be defined for short and long-term protection. In most cases it is anticipated that the immunological correlate will be based on measurement of functional antibody but a defined level of non-functional antibody (e.g. measured by enzyme-linked immunoassay) may be acceptable if the relationship with functional antibody is well described.

Ideally, confirmation of an immunological correlate for protection (at least in the short-term) should be based on exploration of immune responses in at least a subset of vaccinees during clinical studies of protective efficacy. The protocols for protective efficacy studies should also pre-define when and how, in case of vaccine failure, the immunological evaluation of the patient and typing of the infecting micro-organism is performed (see section 3).

However, efficacy studies will not always be feasible. For some antigens, a possible alternative may be to use estimates of effectiveness from prospective studies conducted during vaccination campaigns after authorisation in order to establish at least putative correlates for short and/or long-term protection (see section 3.5).

Established animal challenge models for infection could be used to support a putative immunological correlate for protection in man. Human challenge studies may also provide valuable information. However, such studies are appropriate only for selected diseases that have no serious complications or long-term sequelae and for which successful treatment is available. Applicants are advised to seek

specific advice from EU Competent Authorities on the need for and design of such studies if they are contemplated. If applicable, data on the use of passive immunisation may also assist in identifying threshold antibody levels for protection.

Although it would be expected, and in some cases has been demonstrated, that specific types of antigens elicit cellular immune responses, these have not been unequivocally correlated with protection against infection or disease progression. When it is expected that CMI constitutes an important or even essential component of the overall immune response to an antigen, clinical studies to evaluate some type of cell-mediated immune correlates are encouraged.

2.3.4 Clinically important differences in immune responses

In the pre-authorisation period comparative immunogenicity studies are commonly performed to explore immune responses:

- to antigen(s) in a candidate vaccine *vs* similar antigen(s) in licensed comparator(s)
- to antigens in a candidate vaccine when administered to different populations (e.g. age groups, ethnic groups, previous immunisation histories) or at different doses or schedules
- to antigens when given separately *vs* administration as components of a candidate combined vaccine
- to antigens in a candidate vaccine when given alone or concomitantly with other vaccine(s)
- to antigens in different formulations (including different antigen or adjuvant doses) or lots of a candidate vaccine

In the post-authorisation period, such studies may be used to support extensions of indications, modifications of dose schedules, changes to vaccine formulation and other modifications of the initial marketing authorisation.

In most of the examples above, the primary aim of the study will be to demonstrate non-inferiority between treatment groups with respect to immune responses to each antigen of interest. However, in some cases (e.g. comparisons of formulations with and without an adjuvant) the aim will be to demonstrate superiority of the immune response to at least one antigen in the formulation. In both cases, criteria need to be established and laid out in the study protocol for the judgement of non-inferiority or superiority of immune responses to each antigen of interest.

The usual difficulty encountered in such studies is the selection of the most important primary criterion and the definition of what might constitute a clinically meaningful difference in immune responses to an antigen (whether the aim is to demonstrate non-inferiority or superiority) between vaccine groups. If there are established immunological correlates of protection relevant to one or more antigens in a vaccine, the primary focus should usually be on comparisons between seroprotection rates. If there is no established immunological correlate for protection with respect to an antigen, failure to achieve a certain seroconversion rate may be more important than differences between GMCs/GMTs.

Based on the criteria that are proposed with regard to clinically meaningful differences, the sample size should provide sufficient power to rule out and/or demonstrate such differences in one or more of seroconversion rates, seroprotection rates and geometric mean antibody concentrations/titres (GMCs/GMTs). In this regard, applicants should consult available guidance on the choice of non-inferiority margin (CHMP/EWP/2158/2005) and on similar biological products containing biotechnology-derived proteins as active substance (EMEA/42832/2005). As appropriate, applicants should also take note of available CHMP and ICH guidance regarding statistical issues surrounding multiplicity and the demonstration of non-inferiority and superiority within a single study.

2.3.5 Analysis and presentation of immunological data

The immunological data obtained from each study should be presented in detail and using a standard approach in each study report. As a minimum:

- The percentage of "responders" should be presented. When there is an established immunological correlate of protection, "responders" should be defined as those vaccinees that develop an immune response above a defined threshold level. Otherwise, "responders" might be defined as those reaching a certain minimum increment in antibody concentration/titre post-vaccination.
- "Non-responders" should be carefully characterised in order to attempt to provide specific recommendations (e.g. re-vaccination) for these individuals.
- GMCs/GMTs (with 95% confidence intervals) and pre-/post-vaccination ratios should be calculated
- Reverse cumulative distribution curves should be provided
- When available, data on antigen specific T-cell responses including CD4+ T-cells and CD8+ cytotoxic T-lymphocytes (CTLs) and relevant cytokines should be presented.

It is important that protocols should select and justify the choice of the primary and secondary endpoints. All anticipated analyses should be described, including purely descriptive analyses. Any post-hoc analyses that might be performed require adequate justification.

Depending on the aim of the study, a *per protocol* (evaluable) population (e.g. defined as subjects completing vaccination with complete serological data and no major protocol violations) or a well-defined intent to treat population (e.g. as above but including those with protocol violations) may be chosen for the primary analysis. However, applicants should always provide analyses for both populations and any others (such as modified ITT) that may be defined in the protocol. Depending on the nature of the study population, it may be very important to plan for analyses in subsets according to factors such as age, ethnicity and pre-existing antibody status.

2.4. Essential immunogenicity studies

2.4.1 Dose finding studies

Dose finding studies, which are of major importance for novel antigens, may also incorporate exploration of schedules. Studies should be designed and powered to minimise the risk that suboptimal doses/dose regimens are chosen for further evaluation. Although pilot studies sometimes have to be performed in healthy adults, dose-response data should be obtained as early as possible in the clinical development programme in the target population (e.g. selected age group or groups).

The lowest amount of antigen that elicits a protective immune response (if known) should be explored and is important for the determination of an appropriate shelf-life of the vaccine. If it is not known what might constitute an adequate immune response, it becomes very important to evaluate antigen levels above which there is no appreciable increment in response.

2.4.2 Determination of the primary vaccine schedule

In most cases, more than one dose of an antigen will be needed to achieve continued protection against infection and so sufficient data must be generated from immunogenicity and efficacy studies to support the recommendations for the primary schedule, including evidence of adequate priming. The ability of a primary series to elicit immune memory may be demonstrated in challenge (e.g. giving an unconjugated antigen to subjects primed with a conjugate vaccine) and/or boosting studies and may also be supported by in-vitro detection of antibody production by B lymphocytes.

The planning of studies to identify appropriate schedules needs to take into consideration the nature of antigens, the target population (e.g. infants, travellers, elderly), the kinetic profile of the vaccine-induced antibody response and any applicable official recommendations for schedules. If the vaccine is intended for use in patients with impaired immune function (e.g. premature infants, the immunosuppressed and haemodialysis patients) it may be necessary to explore schedules specific to these groups. Geographical variations in the epidemiology of the infection(s) to be prevented and in the prevalence of different strains/serotypes may also require modifications of the immunisation schedule.

Within the European Union (EU) the various primary infant immunisation schedules in use for vaccines that protect against diphtheria, tetanus and pertussis (and other diseases) generally fall into those in which three doses are given within the first six months of life or in which two doses are given during the first six months and a third dose is given at around 11-12 months of age. While it is not necessary to study every possible schedule in use, relevant data would usually be needed if both types of basic schedule are to be recommended in the SPC. For regimens that employ three doses within the first six months of life, the demonstration of satisfactory immunological responses at the most challenging schedules (e.g. 2, 3 and 4 months or the WHO EPI schedule starting at 6 weeks of age) could be extrapolated to less condensed schedules. In contrast, it is not be possible to recommend that a vaccine may be used at these more challenging schedules if the clinical data relate only to less condensed schedules (e.g. 2, 4 and 6 months).

With expectation of further increases in the total number of antigens to be administered in infancy, possible limitations on the ability to co-formulate some of these into a single combination vaccine and a general desire to limit the number of injections per visit, applicants are encouraged to explore the possibility that a novel vaccine for use in infants may not necessarily have to be administered at the schedules employed for vaccines that contain diphtheria, tetanus and pertussis (with any others required by country).

With regard to travellers, different primary vaccination schedules should be explored depending on the mode of use. In addition to standard schedules, accelerated immunisation schedules could be studied for use in those that have to travel at very short notice or present late for immunisations.

In all cases, extrapolation of the actual data obtained in clinical studies to potential use at schedules or to populations that have not been studied requires scientific justification.

2.4.3 Persistence of protection and the need for and timing of booster doses

Ideally, the need and timing of booster doses after the primary series should be determined before initial authorisation but this may not always be possible. On occasions, mathematic modelling might be used to help to predict (at least provisionally) the need for and timing of boosting. However, models cannot adequately take into account such factors as natural boosting that may occur on encountering circulating wild types following adequate priming with a vaccine. Other important considerations include observations that for some pathogens a decline in antibody below the known or presumptive seroprotective level may not necessarily indicate loss of protection if immune memory has been elicited. In contrast, for pathogens that can cause invasive disease very rapidly after colonisation, it may be necessary to maintain a certain level of circulating antibody for immediate protection.

Therefore, recommendations for boosting (or confirmation of provisional recommendations) may have to be based on long-term immunological follow-up (humoral antibody and, where possible cell-mediated immunity) and/or data on vaccine effectiveness that are obtained during the post-authorisation period. Also, more than one booster dose may be needed to provide life-long protection.

Therefore, whatever the data available at the time of initial authorisation, plans should be in place for appropriate post-marketing studies for the determination of the need for booster doses and these should be presented in the application dossier.

The immune responses to booster doses should be based on comparisons of the pre- and post-dose immunological status of recipients. Studies of the antibody kinetic and changes in antibody avidity as indicators of past priming and of maturation of the immune response may be useful components of the evaluation. It may not be necessary to administer the same dose for boosting as was used in the primary series and so exploration of booster doses is encouraged.

3. EFFICACY

3.1 Introduction

This section considers the design of pre-authorisation studies that have the primary aim of evaluating the protective efficacy of a vaccine. It also briefly discusses the estimation of vaccine effectiveness in the post-authorisation period.

This section should be read in conjunction with:

- Sections 2 and 4: These discuss the extent of the data to be provided when efficacy may be predicted or has to be otherwise inferred from information on immune responses to vaccination.
- Section 2.3.3: This discusses the collection of serological data from subsets of vaccinees during studies of protective efficacy in order to establish an immunological correlate of protection.
- Section 4.6: This addresses the data that might form the basis for authorisation when a study of protective efficacy cannot be performed and there are no known criteria on which to predict efficacy from data on immune responses.
- Section 5. This discusses the surveillance of vaccine failures during routine use and the monitoring for the possibility of strain replacement (i.e. emergence of types of an organisms not covered by the vaccine as important causative pathogens). Such information should appear in PSURs but may also be the subject of a more urgent report if a problem becomes apparent.

3.2 General considerations

If a protective efficacy study is performed, the choice of study location(s) should be adequately justified. The epidemiology of the disease(s) of interest may necessitate that the study population is entirely resident outside of the EU. In this case, the extrapolation of the study results to the EU situation (in terms of factors that may include population demographics, mode of use, disease epidemiology, potential for natural boosting and organism types) must also be justified.

Pre-authorisation studies of protective efficacy are not always necessary or feasible, as in the following situations:

- A study of protective efficacy is not necessary if the applicant can justify the use of immunological data to predict protection against infection. For example, when there is a well established immunological correlate for protection against a specific infection (e.g. diphtheria, tetanus) the candidate vaccine should elicit satisfactory responses based on the relevant correlate(s).

- Estimating protective efficacy is not feasible if the potentially preventable infectious disease does not occur (e.g. smallpox) or occurs at too low a rate for a study to be performed in a reasonable period of time (e.g. brucellosis, Q fever). Also, such studies may not be feasible if

the disease tends to occur in unpredictable and short-lived outbreaks that would not allow for an assessment of vaccine efficacy (e.g. some viral haemorrhagic fevers).

- If there is no immunological correlate of protection and it is not feasible to perform a study of protective efficacy, it may sometimes be justifiable to gauge the likely efficacy of a vaccine by comparison of immunological responses with those seen in past studies of protective efficacy with similar vaccines (e.g. acellular pertussis vaccines).

- There will be instances in which an efficacy study is not feasible and there is no established immunological correlate of protection or previous efficacy studies that might provide immunological data for comparison (e.g. anthrax).

The applicant should always provide a sound justification for the lack of data on protective efficacy in an application dossier.

3.3 Endpoints in studies of protective efficacy

3.3.1 Possible clinical endpoints

When efficacy studies are feasible and are deemed to be necessary:

- In most instances, the evaluation of protective efficacy will focus on the ability of the vaccine to prevent clinically apparent infections (e.g. past studies that have looked at the prevention of invasive disease due to *Haemophilus influenzae* type b, invasive pneumococcal infections and rotavirus infections). If an organism is able to cause a range of infections (e.g. from life-threatening meningitis to otitis media), it may be appropriate that the primary analysis should focus only on specified manifestations of infection while secondary analyses might consider all infections. Occasionally, the primary endpoint will be based on clinical relapse of infection (e.g. vaccines intended to prevent herpes zoster).

- It may sometimes be appropriate to base the estimation of efficacy on prevention of infection that may or may not be clinically apparent at the time because it is known that this will prevent an infection-related disease later in life (e.g. this situation might apply to candidate vaccines against hepatitis C infection).

- Less commonly, the primary endpoint may be some other marker that predicts progression to clinically apparent disease (e.g. vaccines against specific types of human papilloma virus may focus on histological changes in the cervix).

- A candidate vaccine may contain antigens derived from one or several types of the same species for which there is a potential for cross-protection against types not included in the vaccine (e.g. as may be postulated for pneumococcal vaccines, rotavirus vaccines and human papilloma virus vaccines). While the primary endpoint will usually be defined as protective efficacy against any vaccine type, it may sometimes be justifiable to base the primary analysis on all infections due to the species (i.e. vaccine type and non-vaccine type) while a secondary analysis focuses on infections due to vaccine types. In any case, studies with candidate vaccines with a potential to confer cross protection should plan for secondary analyses of rates of infection due to non-vaccine types (see also section 4.1.2).

In all the possible scenarios that may arise, the applicant must provide a clear and adequate justification for the primary and secondary endpoints. In turn, the choice of primary endpoint may have a major influence of the selection of the most appropriate study design (see section 3.4).

3.3.2 Case definition and detection

Case definition

Whatever the chosen endpoint(s), well-validated methods should be used for diagnosis (e.g. clinically apparent and/or non-apparent infections) or for other evaluation (e.g. histology) and should be pre-defined in the protocol. However, there may be instances when it is necessary or even desirable that the applicant employs experimental laboratory methods for establishing infection and/or progression of infection because no well-validated methods exist. In such cases, every effort should be made during the clinical development programme to evaluate the sensitivity, specificity and reproducibility of the methods used. See also section 2.3.1.

Ideally, all clinical staff involved in case ascertainment should be kept unaware of the treatment group. If possible, a centralised laboratory should be used or should or at least confirm the findings of local laboratories and laboratory staff should always be blinded as to treatment assignment.

- When clinically apparent disease is the primary endpoint, immunological confirmation of an acute infection would usually be expected whenever relevant tests exist. When such data are not relevant (e.g. in the diagnosis of tuberculosis), the diagnosis may rest on clinical features that may include radiological studies and other investigations and/or laboratory confirmation and characterisation of the organism.

- If clinically non-apparent infections are to be monitored, the diagnosis may be immunological and/or may involve isolation and characterisation of the causative pathogen.

- If other endpoints are proposed, it is critical that the criteria for staging and progression are pre-defined in protocols as appropriate to the nature of the investigation.

Once a case of infection (or appropriate alternative marker of progression) is confirmed in a vaccinated subject, it is necessary to consider whether the case represents a true vaccine failure. For example, depending on knowledge of the kinetic of the immune response, it may be appropriate that true vaccine failures are limited to subjects that have completed the primary immunisation series and have a failure-defining event more than a specified number of days after the final dose. However, the applicant should always provide an analysis of all cases of infection or progression (i.e. breakthrough cases) regardless of time in relation to vaccine doses and it may also be informative to look at numbers of cases that occur after sequential doses in a schedule. All vaccine failures (as defined) and any other breakthrough cases should be investigated in detail to determine whether they might have failed to mount a response due to host-related factors.

Case detection

Whatever the chosen study design (see 3.4), accurate and comprehensive case detection is essential. When the study aims to compare rates of specified endpoints between vaccinated and unvaccinated groups or between groups that receive a candidate vaccine or a licensed vaccine, it is critical that the same methodology for case detection is applied in all treatment groups and throughout the duration of the study.

If the primary endpoint is clinically apparent disease, the possible range of clinical presentations will determine the mode of case ascertainment. For example, this may be hospital-based for cases of life-threatening infections or community based for less severe infections. If community based, case detection may depend on family practitioners and on first suspicion of infection by vaccinated subjects themselves or their parents/guardians. In each case, it is critically important that the individuals who are most likely to initiate detection of a possible case should have clear instructions. These may need to cover issues such as criteria for stimulating contact with designated healthcare professionals, telephone contacts, initial investigations and further investigations once a case is confirmed.

When the endpoint is other than clinically apparent disease, it becomes critical that subjects are monitored at regular intervals to detect clinically non-apparent infections or changes in other selected markers. The frequency of visits, and acceptable windows around the visits, should be laid down in the study protocol and must be carefully justified.

The appropriate period of pro-active case ascertainment during a study requires special attention and will be determined mainly by the characteristics of the disease to be prevented and the claim for protection that is sought at the time of initial authorisation. Anticipating that in most instances such studies will cover periods of perhaps 1-5 years (at most), plans should be in place to determine the duration of protection and need for boosting or for additional booster doses. This follow-up will likely have to be performed in an unblinded fashion. See also section 2.4.3.

3.4 Possible study designs

The following sections discuss some general statistical considerations and the most common study designs, including the selection of appropriate controls. Other study designs may be applicable under specific circumstances and applicants are encouraged to discuss these with EU Competent Authorities. The determination of vaccine effectiveness in the post-authorisation period is discussed in section 3.5.

When selecting the most appropriate study design, it should be borne in mind that protective efficacy may be evaluated in various settings that may influence the perceived overall benefit of vaccination. For example, depending on the infectious disease to be prevented and so the likely mode of use of the vaccine once licensed, it may be appropriate to conduct a study in which large sectors of the population are vaccinated. This has the potential not only to protect individuals but also to confer a degree of herd immunity. In contrast, when the intent is to protect travellers against specific infections much smaller studies may be appropriate that will usually provide results that reflect only the benefit to recipients.

3.4.1 Statistical considerations

Applicants should consult all relevant ICH and CHMP guidance that would be appropriate to the selected study design and objectives. The following constitutes only some of the most important issues that should be addressed.

Whatever the study design and objectives, the protocol should state the hypothesis(es) to be tested and clearly describe the primary and secondary endpoint(s). The study populations of interest (e.g. per protocol, intent to treat and any others to be analysed) should be defined and the primary analyses should be listed in accordance with the main study objectives. While the primary population for analysis will depend on whether the study is intended to demonstrate superiority or non-inferiority, it is expected that sensitivity analyses of efficacy will be provided (i.e. analyses of efficacy in other defined study populations). Exclusions from each defined population must be justified and described in detail. The primary analysis should focus on cases that meet the definition of vaccine failures although the applicant should also provide an analysis based on all confirmed cases of the disease to be prevented.

The sample size calculation will inevitably reflect the study design and planned analysis. The underlying assumptions (e.g. unit of randomisation, Type I error) should be stated in the protocol and there should be sufficient power to address the study objectives. Special attention should be paid to defining the criteria on which judgements of superiority or non-inferiority are to be made.

3.4.2 Randomised controlled studies

The absolute protective efficacy of a vaccine for a specific disease is usually defined as the reduction in the chance of developing the disease after vaccination relative to the chance when unvaccinated as determined in a prospective randomised controlled study. Depending on the disease to be prevented and the acceptability of withholding a potentially efficacious vaccine from some study participants, the control group might be given a placebo or an alternative vaccine that does not protect against the disease under study but provides some other potential benefit to vaccinees. In both these instances, a double blind study design would be possible. The alternative is that the control group receives no treatment but this means that a double blind design is not possible.

If it is not appropriate that a potentially efficacious vaccine might be withheld from some study participants it may be possible to use a randomised controlled study design to estimate the relative protective efficacy of a candidate vaccine by comparing it with a licensed vaccine that protects against the same infection. However, the fact that at least one vaccine is already approved for prevention of the disease may make it difficult to identify a study population that still has a sufficient incidence of disease before the study commences to allow for reliable estimates of efficacy to be made.

If an active comparator is to be used, the choice of vaccine should take into account the strength of the evidence to support its efficacy. If it is well-recognised that the protective efficacy of the licensed comparator(s) is sub-optimal and the candidate vaccine has been developed to improve on available products (e.g. as might be the case for new vaccines against tuberculosis), the study should demonstrate that the candidate vaccine is superior to the licensed product(s).

3.4.3 Secondary attack rate studies

In the context of determining protective efficacy, the commonest alternatives to prospective randomised controlled studies are secondary attack rate studies. These may be appropriate when the infection to be prevented is associated with a relatively high incidence of secondary cases and are based on an assumption of equal chance of vaccinees and non-vaccinees catching the infection from the index case. However, such an assumption requires justification and may need to be investigated prior to starting the study. Units of randomisation to vaccination may include the individual, the household or the cluster under study (e.g. a school population). Possible biases include the need to use an open label or single blinded study design and the fact that such studies may be partly retrospective. In addition, estimates of vaccine efficacy from such studies should be viewed with some caution because of the select nature of the study population compared to the target population.

3.5 Vaccine effectiveness

Vaccine effectiveness reflects direct (vaccine induced) and indirect (population related) protection during routine use. Thus, the assessment of vaccine effectiveness can provide useful information in addition to any pre-authorisation estimates of protective efficacy. Even if it was not feasible to estimate the protective efficacy of a vaccine pre-authorisation it may be possible and highly desirable to assess vaccine effectiveness during the post-authorisation period. See also section 4.6 for conditions under which taking advantage of an opportunity to measure vaccine effectiveness may be particularly important to further knowledge on the most appropriate mode of use of a vaccine.

Vaccine effectiveness may be estimated from observational cohort studies that describe the occurrence of the disease to be prevented in the target population over time. However, there is no randomisation step and there is the potential for considerable biases to be introduced. Alternatively, vaccine effectiveness may be estimated during a phased (e.g. in sequential age or risk groups) introduction of the vaccine into the target population in which the groups might form the units of randomisation.

It may not be possible or appropriate for applicants to conduct studies to estimate vaccine effectiveness since co-ordinated regional or national networks may be necessary to ensure that cases are reliably detected. However, applicants should discuss arrangements for ongoing disease surveillance and the potential for estimating effectiveness with appropriate public health authorities in countries where the product is to be marketed. It may be that reliable estimates of effectiveness can only be obtained in certain countries in which appropriate vaccine campaigns are initiated and where there is already a suitable infrastructure in place to identify cases. Therefore, it would likely be inappropriate to extrapolate any estimates of effectiveness that are obtained to other modes of use (such as introducing the same vaccine to different or only to highly selected sectors of the population).

Also, in conjunction with public health authorities, applicants should try to ensure that emerging data that might throw light on the duration of protection, need for boosting, immune interference and the description or further confirmation of putative immunological correlates of protection are disseminated to all interested parties, including EU Competent Authorities, and that the prescribing information is updated accordingly. As appropriate to the vaccine and its anticipated mode of use, the potential long-term impact of vaccination on the epidemiology of the vaccine preventable infection(s) should also be addressed in the post-authorisation period.

4. SPECIAL CONSIDERATION FOR VACCINE DEVELOPMENT

4.1 Vaccines that contain more than one antigen

4.1.1 Immune interference

There is a potential for each antigen in a vaccine to interfere with immune responses to one or more other antigens in the same product. Immune interference may be due to chemical interactions and/or immunological interactions and may result in enhancement or depression of responses to one or more antigens and/or may alter the nature of the immune response. Responses to antigens that are conjugated to protein carrier molecules may be especially unpredictable when more than one is included in the same vaccine. Also, inclusion of a conjugated antigen in a vaccine may affect responses to certain other antigens that are the same as (e.g. tetanus toxoid) or similar to (e.g. diphtheria toxoid and CRM197) the carrier protein. If notable enhancement or interference is detected, the amount of antigen(s) in the product may need adjustment and/or other formulation changes might be needed and/or a change in dosing regimen might need to be explored. In association with these phenomena, there could be effects on the local and systemic tolerability of vaccination.

An adequate exploration of the effects, if any, of combining the antigens in any one vaccine on the immune responses to each component is usually required. Nevertheless, there may be circumstances in which it might be considered unnecessary to give all or even some antigens in a novel combination separately and together if the ultimate product can be shown to be satisfactorily immunogenic, safe and efficacious. Therefore, consideration of the need for and extent of immune interference studies should be on a case by case basis. Applicants are advised to consult with EU Competent Authorities if the situation is not clear and/or the applicant plans to omit formal immune interference studies.

In most cases, the assessment of immune interference will be based on serological data and note should be taken of the guidance provided in section 2, especially with regard to the definition and evaluation of potentially clinically significant differences. Special difficulties in assessing immune interference occur when there are no immunological correlates of protection for some or all of the antigens of interest. In these circumstances, the assessment of immune interference can only be based on simple comparisons and it is recommended that, whenever possible, the focus should be on parameters most likely to reflect clinical protection, such as functional antibody levels.

The design of studies to evaluate interference will depend on the nature of the antigens that are to be combined. For example, if two antigens have never been formulated together before, the immune response to each antigen when given alone should be compared with administration in a combined product. However, it may not be necessary or feasible to compare the separate and combined administration of every antigen in a product if several of these have already been formulated together in licensed products or if there are very many antigens involved. In such cases, the effects of adding antigen(s) to an established combination product can be evaluated by comparing responses to the novel combination and separate administrations of the additional antigen(s) plus the licensed combination. All such studies should also provide a careful comparison of safety data.

4.1.2 Cross-reacting immune responses

Cross-reacting immune responses may occur when a vaccine contains one or more antigens that may elicit immune responses that cross react with other antigens.

A beneficial cross-reaction might occur when antibody to an antigen from a particular micro-organism (species or type within a species) shows considerable affinity to antigen(s) of one or more other species or types within a species. In some cases, it may be possible to accumulate sufficient evidence from studies of protective efficacy and/or from studies of functional immune responses to support a claim for protection against species or subtypes not included within the vaccine.

In contrast, antibody elicited by a vaccine that shows cross-reactivity to human antigens may trigger a harmful effect. It may not be possible to fully explore the potential for this to happen before initial authorisation. If there are grounds to anticipate such problems, very special consideration is needed for post-marketing safety studies.

4.2 Concomitant administration of vaccines

The potential for immune interference and effects on overall safety are also important considerations for the concomitant but separate administration (by whatever route) of two or more vaccines. While there are general principles that may be applied in the absence of specific data, several examples of unexpected immune interference have come to light in recent years. These have included the effects of acellular pertussis vaccines on responses to conjugated saccharides and variable enhancement or depression of immune responses to the conjugated saccharides when the carrier proteins are the same or different. In assessing the potential for immune interference to occur, it is very important to justify the criteria applied to judge whether concomitant administration exerts potentially clinically significant effects on immune responses to individual antigens (see section 2.3.4). If any studies identify important immune interference or an unacceptable increase in unwanted effects, applicants should explore the minimum interval that might be allowed between administrations to avoid these problems.

At the time of initial authorisation of a novel vaccine, it would be desirable that there should be safety and immunogenicity data on concomitant administration with at least one type of licensed vaccine that would very likely be given at the same time. In many circumstances, satisfactory results would likely suffice to make a general statement about co-administration with particular types of antigens without referring to brand names. However, there may be occasions when product-specific problems could be anticipated or may come to light that might necessitate distinguishing between brands in the prescribing information.

For some vaccines, such as those intended for the primary series in infants, the clinical trials will inevitably involve co-administration with certain products at one or more schedules since protocols must allow for the usual recommended antigens to be given on time. Therefore, it is likely that information on the safety of co-administration and some data on immune responses to all antigens before and after completion of the primary series would be available. A formal assessment of immune

interference might not be necessary if it can be established that the antigens satisfactorily prime infants and elicit acceptable antibody responses for at least short-term protection. However, studies might need to involve omission of the new vaccine from one group may compare concomitant administration with administrations made in a staggered fashion (e.g. together at 2, 4 and 6 months compared to the usual antigens at this schedule and the new vaccine at 3, 5 and 7 months).

The data on immune interference based on one schedule cannot necessarily be extrapolated to other schedules. For example, potentially clinically important interference may be detected at an accelerated schedule but may not be apparent at less concentrated schedules. Therefore, if only the latter is studied, immune interference that could occur might not be identified.

For routine vaccinations administered later in life or administered for travel purposes, studies that evaluate immune interference should usually compare concomitant with separate administrations of products. As for studies in the primary series, it may be acceptable that the data are derived from co-administration with only one brand of a particular type of vaccine that is likely to be co-administered.

4.3 Interchange of vaccines within a schedule.

For most inactivated vaccines it is necessary to give more than one dose of an antigen to obtain adequate priming and to maintain protection against infection. Therefore, for primary series and for booster doses, the question arises as to whether the first and all sequential doses must be administered with the same product or whether other products that contain similar antigens can be used interchangeably.

If active endorsements in the prescribing information for switching are sought, these need to be supported by appropriate data. The design of studies intended to support claims for inter-changeability should be tailored to reflect the exact claim required and should provide safety and immunogenicity data. The final wording of the prescribing information will have to be considered in the light of the potential for extrapolating data on interchangeability obtained with one brand to other similar vaccines.

4.4 Vaccine lots and lot-to-lot consistency studies

Ideally, vaccine from several lots of the exact formulation intended for marketing should be adequately tested during the clinical development programme, especially during the confirmatory studies of immunogenicity and, if feasible, in protective efficacy studies. In addition, the manufacturers should ascertain that the lots used in the clinical trials, especially those in the later stages of development, are adequately representative of the formulation intended for marketing throughout its shelf life. See also sections 2.3.4 and 2.4.1.

The need for a formal lot-to-lot consistency study should be considered on a case by case basis. Such a study might be important when there is an inherent and unavoidable variability in the final formulation of the vaccine in one or more respects. However, for vaccines with a very reproducible method of manufacture such studies may not provide useful information in addition to that generated during the rest of the clinical programme.

If a lot-to-lot consistency study is considered appropriate, it is recommended that the design should be discussed in advance with EU Competent Authorities. Besides determining the number of lots to be compared, one issue is whether the lots tested should be consecutively produced or chosen at random. The pre-defined criteria for concluding comparability between lots will usually be based on one or more immunological parameters although a comparison of safety data is also important in these cases. Very careful consideration needs to be given to which immunological parameters are the most valid and clinically relevant and how large a difference between lots might be potentially clinically significant.

4.5 Bridging studies

Classically, clinical bridging studies generate immunogenicity data to support the extrapolation of data on safety and protective efficacy obtained under specific circumstances of use to other situations (e.g. different formulations, additional schedules and/or populations). In designing such studies, it is important to consider the critical immunological parameters for determining comparability of immune responses (see 2.3.4). When there is an established immunological correlate for protection, the proportions reaching this level should not only be similar between treatment groups but should also be acceptably high in the light of all previous experience with responses to the antigen in question. When there is no known correlate or this is questionable (for example, with respect to predicting long-term efficacy), it may be more relevant to compare proportions reaching a pre-defined cut-off for functional antibody than to compare GMCs.

On occasion, the term may be more loosely applied to simple comparisons between immunogenicity datasets. For example, between data from premature infants compared to full term infants, immunosuppressed compared to healthy individuals or between different formulations of the same vaccine. The same considerations as outlined above apply to the assessment of the findings. Special caution may be needed if comparisons are made between studies rather than within a single study.

4.6 Circumstances in which approval might be based on very limited data

Special consideration is needed for the clinical development of vaccines when protective efficacy studies are not feasible and when there is no established immunological correlate of protection. For example, vaccines intended to prevent rare infections that carry considerable morbidity and mortality including some pathogens that have the potential to cause widespread disruption to mankind in case of an epidemic or deliberate release. Applicants seeking a marketing authorisation for such a vaccine should discuss considerations for the basis on which authorisation might be possible with EU Competent Authorities at the earliest stages of development.

In principle, there are several ways of approaching this scenario. In some cases, it may be possible to obtain some relevant data on protective efficacy from challenge studies in animal models. There may be immunological correlates of protection established for very similar but not identical antigens that might be used *pro tem* as a guide to likely efficacy. If possible, immunological studies should focus on the measurement of functional immune responses. Taking the results of these and any other relevant investigations together, it is possible that a reasonable case for likely efficacy could be put together. A presumptive risk-benefit relationship could be derived that might support authorisation. However, the prescribing information should explain the basis for the opinion.

If authorisation has had to be based on such limited data, it may not be possible to estimate vaccine effectiveness in the post-authorisation period unless a substantial natural epidemic or deliberate release occurs. In any case it is likely that reliable data can only be obtained from national surveillance programmes operated by public health authorities. Therefore, applicants should work with public health authorities to develop plans that would allow for the collection of data on safety and efficacy if the opportunity (e.g. a significant outbreak or major epidemic) should arise.

5. SAFETY

5.1 Introduction

This section provides guidance on the essential data on vaccine safety needed to support a marketing authorisation for a new vaccine. A brief overview of the special considerations for vaccine safety

surveillance is also given. Detailed guidance on post-authorisation vaccine pharmacovigilance will be provided in a separate guideline that is currently under development.

5.2 Safety evaluation in pre-authorisation studies

Pre-authorisation studies are usually primarily designed to provide data on the immunogenicity and/or protective efficacy of a vaccine. However, it may be necessary to conduct pre-authorisation studies that are primarily designed to address specific safety issues that may have been identified during preclinical testing or in the early clinical studies.

5.2.1 Extent of the database

As a minimum, the total data from pre-authorisation studies should be sufficient to reliably determine the nature and frequency of local and systemic adverse events occurring at a frequency >1/1,000. If the marketing authorisation is based solely on immunogenicity studies, it is unlikely that the database would be sufficiently large to identify rare events. However, this may be possible if a large study of protective efficacy is performed.

Any cases of rare and/or unusual adverse events that are observed in pre-authorisation studies trials should be subjected to a thorough causality assessment, taking into account biological plausibility. Depending on the nature of these events and their possible relatedness to vaccination, it may be necessary to expand the safety database in order to better evaluate a putative safety signal before initial authorisation and/or to incorporate a prospective post-authorisation evaluation of such events in the Pharmacovigilance Plan.

Studies might also indicate that the safety profile may be very different in various subsets of the target population or may be very different between doses (e.g. much higher rates of adverse events after boosting compared to the primary series). In these cases, it may be necessary to obtain sufficient data to detect at least uncommon adverse events in various subsets before a marketing authorisation could be granted.

5.2.2 Methodological considerations

In each study performed during a clinical development programme, whatever the primary objective, every effort should be made to record safety information at appropriate protocol pre-specified intervals and for a sufficient period of time after each dose of vaccine in all vaccinees. However, if a large study of protective efficacy is to be performed, it may sometimes be acceptable that all adverse events are actively collected from only a defined subset of vaccinees. The size of this subset requires careful justification. Also, the nature of the subset should be appropriate to support extrapolation to the total target population. In such cases, all serious adverse events must still be collected on the entire study population.

Protocols should clearly define the method for collecting data on adverse events (e.g. diary cards, questionnaires), who will fill out the forms (e.g. investigators, nurses, vaccinees, or parents/guardians), duration of follow-up and intervals for collecting safety data. Since most adverse reactions to vaccines occur within the first few days after each dose, it is common and generally acceptable practise that special attention is paid to collecting information on any adverse event that occurs within approximately 5-7 days (perhaps longer for live vaccines), whereas later events are elicited by telephone contact or when vaccinees attend for the next dose.

Data collection should be sufficiently detailed so that, for example, any differences in adverse events according to the site and/or route of injection (e.g. intramuscular versus subcutaneous) could be

assessed. Documentation of the batch number of the candidate and any co-administered licensed vaccines is essential and it may sometimes be appropriate to examine adverse events according to batch. Case definitions developed by the Brighton Collaboration for specific events should be referred to if available (http://brightoncollaboration.org).

In order to facilitate and standardise the collection of all possibly relevant data in the immediate post-vaccination period, patient diaries may be very useful. These should usually provide a check list of local (e.g. injection site redness, swelling and induration) and systemic events (e.g. fever, abnormal crying or irritability in infants) that have the potential to be due to the vaccine and should determine when these should be recorded. To assist the use of diary cards, provision of graded rulers may help parents/guardians and vaccinees to gauge the size of local redness or swelling. Digital reading thermometers make it easier to measure temperature by the chosen route and there should be clear guidance given on the prophylactic and/or therapeutic use of antipyretics. However, if patient diaries are employed, it is important that vaccinees or their care-givers appreciate that all other adverse events regardless of perception of relatedness to vaccination should be reported. There should be an appropriate mechanism in place to collect this information, including attention to timing so that serious adverse events can be picked up and reported in accordance with regulatory requirements (see ICH E2A).

Clear guidance should be provided to investigators regarding the assessment of all adverse events according to causality, seriousness, expectedness and severity. For each serious adverse event that occurs, information is required on medical history (including any underlying diseases), concomitant medications and/or vaccinations, the course of the event, any interventions required, the outcome and the investigator's and sponsor's assessment of causality. Analysis of the possible vaccine-relatedness of the adverse event should use standardised categories for causality assignment (Causality classification in the European Community, III/3445/91). In addition, adverse events following immunisation should also be categorised according to whether they are:

- due to intrinsic characteristics of the vaccine preparation and/or the individual response
- vaccine precipitated i.e. triggered due to the receipt of the vaccine but probably would have occurred at a later time
- due to administrative and other errors, including GMP errors, dosing errors
- co-incidental i.e. temporally related but not due to immunisation.

Applicants should always give consideration to the need to institute a Data Safety Monitoring Board during the clinical development programme. This may be particularly important if the candidate vaccine is of a very novel type and/or is to be given to a large population in pre-authorisation studies.

5.3 Post Marketing Surveillance

In the post-marketing period a much larger and likely much more diverse population will be exposed to the vaccine compared to clinical studies. The general considerations for pharmacovigilance and for development of a pharmacovigilance plan are the same as for all other types of medicinal products. However, vaccines are almost always administered to healthy persons. This fact has implications for the continued re-assessment of the overall risk-benefit relationship for the vaccine. Please consult the separate guidance under development regarding pharmacovigilance for vaccines.

In addition, there are some specific issues for vaccines that may need to be monitored. Section 3.3.5 discusses the estimation of vaccine effectiveness in the post-authorisation period. Even if it is not possible or necessary to make formal estimates of effectiveness, it is considered very important that countries that have an appropriate infrastructure should conduct surveillance to monitor for any sign of waning protection of a vaccine or type of vaccine within a population. In addition, for vaccine that may protect against only some types of organism within a species, appropriate surveillance should be in place to detect strain replacement phenomena. It is understood that these issues would usually fall to public health authorities rather then to marketing authorisation holders. However, applicants are

encouraged to assess the ability of countries to conduct these exercises and to work with at least some public health bodies to try to ensure that such data can be made available.

6. CONSIDERATIONS FOR THE SPC

This section provides guidance on the format and content of sections 4 (Clinical particulars) and 5 (Pharmacological properties) of the SPCs that raise some issues specific for vaccines. Where appropriate, recommendations are made for standardised text.

4.1 Therapeutic indications

The indication should routinely cover:

- The disease(s) to be prevented (including specific types of an organism if appropriate to the vaccine content)
- The minimum age for use (e.g. infants from the age of 2 months)
- Appropriate age categories (e.g. neonates, infants, children, adolescents, adults)
- The maximum age for use if such a limit would be appropriate based on factors such as the disease epidemiology or antigen content of the vaccine

It may also be necessary to mention:

- Particular populations for which the vaccine is suitable (e.g. naïve, primed, at risk).
- Populations for which the vaccine is not suitable should usually be mentioned elsewhere.

4.2 Posology and method of administration

Posology

If appropriate, this section should clearly describe and separate doses and schedules for primary and booster vaccinations. In general, the recommendations should reflect the minimum age at the time of the first dose, minimum dose interval and minimum interval between the last dose of the primary series and first (and perhaps sequential) booster dose(s) that were evaluated in clinical studies.

For most vaccines intended for use in infancy, and for many intended to boost antigens routinely delivered in infancy, it will be necessary to include a general statement regarding the need to follow official guidance on the exact timing of these doses.

Advice on dose and schedule may need to be given separately for different age groups or other defined populations (e.g. the immunosuppressed).

It may be appropriate to state whether interchangeability of vaccines within a schedule can be recommended.

Method of administration

The route of injection should be specified, preferably with the place of first choice (e.g. deltoid muscle).
Important statements may include:

- Do not inject intravascularly
- Exceptional administration subcutaneously to patients with thrombocytopenia or bleeding disorders. Any data on safety or immune responses under these circumstances should usually appear in 4.4.

4.3 Contra-indications

The contra-indications should usually be limited to absolute contra-indications that should apply at the time of administration.
The following should usually appear as a minimum:

- TRADENAME should not be administered to subjects with known hypersensitivity to any component of the vaccine.
- As with other vaccines, TRADENAME should be postponed in subjects suffering from an acute severe febrile illness.

4.4 Special Warnings and precautions for use

Appropriate common statements might include:

- As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.
- (Tradename) should under no circumstances be administered intravascularly.
- Thiomersal has been used in the manufacturing process of this medicinal product and residues of it are present in the final product. Therefore, sensitisation reactions may occur.
- As with any vaccine, a protective immune response may not be elicited in all vaccinees.

This section may also describe:

- Lack of protection or limits of any cross protection there may be against strains or serotypes not in the vaccine.
- Situations (e.g. administration to persons already in the incubation phase) or populations (e.g. elderly) in which the efficacy of the vaccine has not been investigated or could not be anticipated.
- Factors that might be associated with an impaired immune response.
- For live attenuated vaccines, the potential for transmission of vaccine strains should be described, as well as the possibility of reversion to virulence or of re-assortment with wild-type strains.

4.5 Interaction with other medicinal products and other forms of interaction

The section should clearly differentiate endorsements for concomitant administration that are based on clinical data as opposed to statements based on general principles. In general, satisfactory data obtained on concomitant administration with a representative vaccine of a certain type (e.g. giving a combination vaccine against diphtheria, tetanus, pertussis and other antigens vaccine with one of the MMRs on the market) should serve to support a general statement for co-administration.

Clinically important or potentially clinically important immune interference should be mentioned.

If there are no data regarding co-administration with a type of vaccine that is very likely to have to be co-administered, this should be stated.

Appropriate common statements may include:

- It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited.
- Immunoglobulin is not to be given with TRADENAME or
- If it is necessary to provide immediate protection, TRADENAME may be given at the same time as (normal/x-specific) immunoglobulin. Injections of TRADENAME and immunoglobulin should be made into separate limbs.

4.6 Pregnancy and lactation

For vaccines that will be administered only in the pre-pubertal years, it is sufficient to state:

- TRADENAME is not intended for use in adults. Human data on use in pregnancy or lactation and animal reproduction studies are not available.

For vaccines to be used in individuals of childbearing age, the section should describe the available preclinical and clinical experience.
For inactivated vaccines, it is usual to advise the following:

- As with other inactivated vaccines, harm to the fetus is not anticipated. However, TRADENAME should only be used during pregnancy when there is a clear risk of infection.

For live attenuated vaccines it is usual for use to be contra-indicated in pregnancy. However, if the vaccine is a well known product for which there is reported experience, it may be sufficient to discourage vaccination during pregnancy unless clearly necessary.

Regarding lactation, in the absence of data, it is usual to state for inactivated vaccines:

- The effect on breastfed infants of administration of TRADENAME to their mothers has not been studied.

Recommendations for live attenuated vaccines must be considered on a case by case basis.

4.7 Effects on ability to drive and use machines

For vaccines that will be administered only in the pre-pubertal years, it may be sufficient to state:

- TRADENAME is not intended for use in adults.

The usual considerations apply regarding statements to be made when the vaccine is intended for adults.

4.8 Undesirable effects

Some considerations specific to vaccines may include:

- Details of local and systemic reactions
- Special notes on certain ADRs such as fevers, febrile convulsions
- ADRs and ADR rates separated according to age group, number of doses, previous vaccination history, occurring in studies or reported from post-marketing surveillance
- Special notes on any increased rate of ADR(s) observed on concomitant administration with other vaccines.

4.9 Overdose

Any experience with overdose should be mentioned. It may be appropriate to mention that overdose is unlikely due to the mode of presentation (e.g. single dose pre-filled syringe).

5.1 Pharmacodynamic properties

This section should briefly summarise (tabulation may be appropriate) the most pertinent immunological data (using the most relevant parameters) and any estimates of efficacy or effectiveness considered to be valid (with caveats regarding the population in which these were measured). As necessary, the data should be broken down by primary series and boosting, by age group or by other factors, such as immunosuppression.
The section may include details of the established or putative immunological correlate of protection.