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GUIDELINE ON CLINICAL EVALUATION OF NEW VACCINES

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EXECUTIVE SUMMARY

The *Guideline on clinical evaluation of vaccines (EMA/CHMP/VWP/164653/2005)* covers the design of clinical development programs for new vaccines that are intended to provide pre- and post-exposure prophylaxis against infectious diseases. Some of the guidance provided is also relevant to the further development of licensed vaccines (i.e. generation of clinical data to support changes to the prescribing information in the post-authorisation period).

In the development of any new vaccine adequate data on immunogenicity should be assembled during the clinical development programme. Some of the areas that should usually be covered include characterisation of the immune response, investigation of an appropriate dose and primary schedule, assessment of the persistence of detectable immunity and consideration of the need for and response to booster doses.

An assessment of protective efficacy is not necessary and/or is not feasible for all types of vaccines. The design of pre-authorisation studies that have the primary aim of evaluating the protective efficacy of vaccines will be influenced by the incidence and characteristics of the infectious diseases that are to be prevented. Special attention should be paid to issues surrounding case definition and detection. The analysis of these studies requires careful consideration of the most appropriate efficacy variables and populations to be analysed. Whether or not protective efficacy is assessed in the pre-authorisation period attempts should be made to estimate vaccine effectiveness in the post-authorisation period.

With the increasing complexity of vaccines (e.g. combined vaccines intended to confer protection against many infectious diseases or against many types of a single species) and the frequent need for co-administration of multiple vaccines immune interference has become a very important consideration. The design and interpretation of studies intended to assess immune interference must be tailored to the antigens involved and should take into account any relevant experience about the possible effects of their combination and/or co-administration.

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. In addition, it may be possible to generate only very limited data for new vaccines intended to prevent rare infections that carry considerable morbidity and mortality. The extent of the data that might be acceptable to support a marketing authorisation requires consideration on a case by case basis.

The extent of the safety data that can be provided pre-authorisation will depend on the overall content of the clinical development programme, such as whether or not protective efficacy studies have been performed. There are also some special considerations for the collection of vaccine safety data depending on such factors as route of administration, recording of solicited signs and symptoms in addition to all other adverse events, definitions of some adverse events and the determination of their relationship to vaccination. Detailed guidance on post-authorisation vaccine pharmacovigilance will be provided in a separate guideline.

An Annex to this guideline provides recommendations on the presentation and content of SPCs for vaccines.

1. INTRODUCTION

This guideline was developed to replace the previous Note for Guidance (CPMP/EWP/463/97) in response to the many new developments in the vaccine field in the last decade and in the light of the types of questions that have arisen in requests to CHMP for Scientific Advice. Particular effort has been made to describe the scope of immunogenicity studies that would usually be required. Consideration is also given to the extent of the data that might be acceptable under special circumstances such as for vaccines intended to prevent rarely encountered infections and for use in the event of a deliberate release of micro-organisms.

With regard to the assessment of protective efficacy in the pre-authorisation period recent experience has led to a detailed consideration of when such studies could and should be done and the issues surrounding their design, conduct and interpretation. The importance of well-conducted assessments of vaccine effectiveness after initial authorisation has been underlined in recent years and so a specific section has been included.

The consideration of vaccine safety takes into account the ongoing work of the Brighton Collaboration with regard to definitions of adverse events and the recently introduced requirements for provision of information on pharmacovigilance systems and risk management plans in the application dossier. However, more detailed guidance on the post-authorisation assessment of vaccine safety will be provided separately.

Finally, the particular circumstances of use of the types of vaccines covered in this guideline raise some special considerations for certain sections of the Summary of Product Characteristics. The guidance provided in the Annex to this guideline (EMEA/CHMP/VWP/382702/2006) is intended to improve consistency in the content of the prescribing information for vaccines.

Any proposals for major deviation(s) from this guidance should be explained and discussed in the Clinical Overview.

It is recommended that applicants should obtain scientific advice from EU Competent Authorities whenever a major deviation from this guidance is being considered. Since this guideline cannot provide specific and/or concise guidance to cover every conceivable situation that may arise applicants may find it particularly useful to obtain scientific advice from EU Competent Authorities regarding any unusual scenarios of vaccine development.

This guideline should be read in conjunction with all relevant current and future CHMP and ICH guidelines and WHO regulations pertaining to vaccines for pre- and post-exposure prophylaxis against infectious diseases.

2. SCOPE

The major areas addressed in this guideline are:

1. Characterisation of the immune response and related immunogenicity issues.
2. The design and conduct of studies of protective efficacy and vaccine effectiveness.
3. The evaluation of potentially clinically important immune interference.
4. Circumstances in which very limited data might be acceptable.
5. Pre-authorisation and post-authorisation safety data.

The following issues are not addressed in this guideline:

- Non-clinical studies, except with regard to those that might be relevant to characterisation of the immune response to the antigenic components of vaccines.
- Clinical development of “therapeutic vaccines”, viral-vector based gene therapy products, anti-tumour vaccines and anti-idiotypic vaccines (including monoclonal antibodies used as immunogens).

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

3. LEGAL BASIS

This guideline has to be read in conjunction with Directive 2001/83/EC, as amended and Part II of the Annex I of Directive 2001/83/EC, as amended.

4. MAIN GUIDELINE TEXT

4.1. Pharmacokinetic / Pharmacodynamic studies

Pharmacokinetic studies are usually not required for vaccines. However, such studies might be applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients. The need for pharmacokinetic studies and their design should be considered on a case by case basis and it is recommended that applicants should obtain scientific advice from EU Competent Authorities.

In relation to vaccines, pharmacodynamic studies are essentially comprised of the immunogenicity studies that characterise the immune response to the vaccine. Therefore, this section will focus on considerations for an appropriate range of immunogenicity studies that may be conducted throughout the clinical development programme. The applicant should justify the final range of tests performed, with an explanation of the rationale for each investigation, in the Clinical Overview.

4.1.1. Immunogenicity

- **General methodological considerations**

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 primary immunisation schedule and optimal dose 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 of protection if none is already established. These issues are discussed further below and in section 4.2.

- **Characterisation of the immune response**

Minimum requirements for immunological testing

Biological specimens (e.g. blood for serum and cellular subpopulations, other bodily fluids if relevant) should be collected 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

Protocols should specify and give details of the methodologies to be used to evaluate immune responses to vaccination. These should be consistent across studies, 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

formulation. 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 that have proven protective efficacy. For novel antigens, characterisation of the humoral immune response should usually 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).

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 complex task and applicants that are considering such studies should seek scientific advice from EU Competent Authorities at an early stage.

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 antibody level measured by a non-functional immunoassay (e.g. measured by enzyme-linked immunoassay) could be acceptable if the relationship with functional antibody is well described.

Ideally, confirmation of an immunological correlate of 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 microorganism is performed. 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 4.2).

Established animal challenge models for infection could be used to support a putative immunological correlate of protection in man. Human challenge studies might also provide valuable information. However, such studies are appropriate only for selected diseases for which successful treatment is available and if ethically acceptable. 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 derived from 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.

• **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.

The primary aim of most of these studies 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 of protection with respect to an antigen, a parameter should be selected and justified, e.g. seroconversion rate.

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 (EMA/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.

- **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” (with 95% confidence interval) 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 their management
- ❖ 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 an *intent to treat* population (e.g. a modified ITT population defined 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 for any other populations 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.

- **Essential immunogenicity studies**

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.

The lowest amount of antigen that elicits a protective immune response (if known) should be explored and the results should be taken into consideration when determining an appropriate end of shelf life specification for 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.

Determination of the primary vaccination 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 by administration of a booster dose at least 6-12 months after completion of the primary series. Boosting studies may also include in-vitro detection of antibody production by B-lymphocytes and measurements of antibody avidity.

In the specific case of bacterial saccharides conjugated to protein carrier molecules (i.e. conjugate vaccines) the investigation of the induction of immune memory during the primary series has often been assessed by administering a challenge dose of a small amount of unconjugated saccharide at least 6 months later. However, for certain saccharides there have been reports of depletion of immunological memory and antibody hyporesponsiveness after a dose of unconjugated vaccine in naïve recipients and in persons already primed with conjugate vaccine. Although the clinical consequences of these observations are not clear, administering a booster dose of conjugate vaccine to assess prior induction of immune memory circumvents any concern there might be regarding challenge with unconjugated saccharide.

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 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 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 in populations that have not been studied requires scientific justification.

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 kinetics 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.

4.2. Efficacy and effectiveness

This section considers pre-authorisation studies that have the primary aim of evaluating the protective efficacy of a vaccine and the evaluation of vaccine effectiveness in the post-authorisation period.

4.2.1. Vaccine efficacy

- **General methodological considerations**

Ideally, protective efficacy studies should be performed prior to licensing a new vaccine. However, it is acknowledged that there are situations where such studies are either not necessary or not feasible prior to licensing:

- ❖ 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

an established immunological correlate of 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 it is not feasible to perform an efficacy study and there is no immunological correlate of protection, 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 similar vaccines with proven protective efficacy (e.g. acellular pertussis vaccines).
- ❖ There will be instances (e.g. anthrax) 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.

If a protective efficacy study is not performed the applicant should provide a sound justification for the lack of such data in the Clinical Overview.

When planning a protective efficacy study all relevant and current ICH and CHMP guidance on clinical trial methodology should be consulted.

The protocols used for studies of protective efficacy should include a rationale for the choice of the study population and a detailed description of the methods used for diagnosis of infection (e.g. clinically apparent and/or non-apparent infections). Validated methods should be used for diagnosis (e.g. clinically apparent and/or non-apparent infections) or for other evaluation (e.g. histology). If no well-validated methods for establishing infection and/or progression of infection exist during the period of pre-licensure clinical development then experimental laboratory methods could be used. The sensitivity, specificity and reproducibility of the methods used should be included in the study reports.

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) should be justified in the Clinical Overview.

• **Randomised controlled trials**

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, the adjuvant alone or an alternative vaccine that does not protect against the disease under study but provides some other potential benefit to vaccinees. If there is a concern regarding injection of inactive solutions and there is no approved active vaccine that could be administered to the control group at the same schedule as the test group it may be necessary that the control group receives no treatment. This is less desirable as a double blind design would not then be possible, in which case it would be very important that persons involved in the administration of the vaccine should not be otherwise involved in the conduct of the study (and especially not in assessing efficacy).

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).

- **Secondary attack rate studies**

Secondary attack rate studies are sometimes used when the infection to be prevented is associated with a relatively high incidence of secondary cases. Such studies are based on an assumption of equal chance of vaccinees and non-vaccinees acquiring the infection from the index case. However, such an assumption requires justification and should 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). Evidence for the external validity of the study results should be provided in the study report and discussed in the Clinical Overview.

Other study designs may be appropriate in special circumstances. It is recommended that scientific advice should be sought from EU Competent Authorities on a case by case basis.

- **Populations for analysis**

In protective efficacy studies, the populations of interest should be pre-defined and the primary analysis population should be selected in accordance with the main study objectives. Exclusions from each defined population must be justified and described in detail. It is also expected that analyses for relevant pre-specified subgroups are submitted (if appropriate).

In studies that compare disease rates between vaccinated and control groups that do not receive a product that would confer protection then the intent would be to demonstrate superiority for the vaccinated group. In this instance it may sometimes be appropriate, with adequate justification, that the primary analysis would be based on true vaccine failures i.e. cases of disease in persons who received all the allocated doses of study medication and were caused by the organism type(s) included in the vaccine. However, it is very important that additional analyses are presented. These should include analyses of disease rates due to all possible types of the organism and in all participants who receive at least one dose of study medication.

If the study compares the relative efficacy of a new vaccine with an approved vaccine then the aim would be to show at least non-inferiority in terms of protection. In this instance the primary analysis population would usually consist of those who received all the allocated vaccine doses, were infected with the organism type(s) in the vaccine and had no major protocol violations. However, it is again essential that adequate sensitivity analyses should be provided, including those who received incomplete vaccination regimens regardless of any other protocol violations.

- **Clinical endpoints**

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.

In most instances, the evaluation of protective efficacy will focus on the ability of the vaccine to prevent clinically apparent infections. If an organism is able to cause a range of infections (e.g. from life-threatening invasive infections to otitis media), the primary endpoint in any one study should be carefully selected in accordance with the proposed indication(s).

Alternative primary endpoints may include:

- ❖ Clinical manifestations of latent infection (e.g. vaccines intended to prevent herpes zoster).
- ❖ Laboratory evidence that a candidate vaccine reduces primary infection rates. This situation might apply when the primary infection is not necessarily clinically manifest but it is known that persistence of the organism can occur and can cause an infection-related disease later in life (e.g. candidate vaccines against hepatitis C infection).
- ❖ Other markers that predict progression to clinically apparent disease. For example, in the evaluation of the efficacy of vaccines against specific types of human papilloma virus the focus has been on demonstrating the prevention of certain histological changes in the cervix that are recognised to be pre-cursors of malignant neoplasia.

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.

- **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.

- ❖ When clinically apparent disease is the primary endpoint, laboratory confirmation (immunological and/or microbiological) of an acute infection would usually be expected whenever relevant tests exist.
- ❖ If clinically non-apparent infections are to be monitored, the diagnosis may involve isolation and/or detection of the pathogen or may be immunological.
- ❖ 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 kinetics 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) 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**

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. Plans should be in place to determine the duration of protection and need for boosting or for additional booster doses.

4.2.2. 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. The information gained from assessments of vaccine effectiveness may be particularly important to further knowledge on the most appropriate mode of use of a vaccine (e.g. need for booster doses in at least some segments of the population to maintain adequate protection over time).

Vaccine effectiveness may be estimated from:

- ❖ 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.
- ❖ During 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.
- ❖ On occasion, by means of prospective case control studies.

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 used and where reliable surveillance systems are in place. 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.

4.3. Special considerations for vaccine development

4.3.1. Immune interference

An adequate exploration of the immune response to each antigen when included in a combined vaccine or when co-administered by means of two or more different vaccines is usually required (see sections below). 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 4.1, especially with regard to the definition and evaluation of potentially clinically significant differences and the need to focus on functional immune responses.

In general the greatest concerns regarding the potential for immune interference and possible clinical consequences occur with regard to the primary infant immunisation series. These concerns relate both to the need to co-administer a range of antigens simultaneously (including by means of one or more combination products) and to the relative immaturity of the immune system especially during the first four months of life. Indeed, the extent of the immune interference observed has generally been more marked with schedules that involve administering all doses by the age of four months compared to more relaxed schedules, which may not even detect the effect. Therefore it is recommended that immune interference should be assessed in more concentrated primary series.

- **Vaccines that contain more than one antigen**

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. Nevertheless, there may be circumstances in which it might be unnecessary and also not feasible to give all or even some antigens in a novel combination separately and together. Therefore, consideration of the need for and extent of immune interference studies should be decided 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.

Particular and unpredicted problems with poor immune responses have arisen when some protein-saccharide conjugates have been pre-formulated with certain other antigens and when the inclusion of more than one such conjugate in the same vaccine has been attempted. In contrast, inclusion of a conjugated antigen in a vaccine may enhance 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.

- **Concomitant administration of vaccines**

The potential for immune interference and effects on overall safety are important considerations for the concomitant but separate administration (by whatever route) of multiple vaccines. While there are general principles that may be applied in the absence of specific data, several examples of unexpected

immune interference on co-administration of vaccines have come to light in recent years. 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 of the new vaccine with at least one type of each licensed vaccine that would very likely need to 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 example variable enhancement or depression of immune responses to conjugated saccharides has been observed when the carrier proteins for co-administered products are the same or different so that generalisations cannot be made beyond the specific vaccines studied.

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 and it may not be possible to withhold or significantly delay administration of one or more antigens. However, studies might 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). In older age groups it is more likely that it will be possible to find populations in which co-administration can be compared with separate administrations since it may be less critical to achieve protection against all antigens in a short timeframe. For some types of vaccine, such as those generally given before travel, it would also be important to assess immune interference at the most concentrated schedule that might be needed.

If any co-administration 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.

4.3.2. 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.

4.3.3. Using different vaccines to prime and to boost

If an active endorsement is sought for the use of a vaccine to boost persons primed with another product or *vice versa* the applicant must supply appropriate supportive data. The design of studies should be tailored to reflect the exact claim required and should provide safety and immunogenicity data.

4.3.4. Vaccine lots and lot-to-lot consistency studies

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. 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. 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. It is recommended that applicants should seek scientific advice regarding any lot-to-lot consistency study that might be planned.

4.3.5. 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. changes in the production process, additional schedules and/or populations). In designing such studies, it is important to consider the critical immunological parameters for determining comparability of immune responses. 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 geometric mean antibody titres/concentrations.

4.3.6. 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. It is recommended that applicants should seek scientific advice from EU Competent Authorities regarding the clinical development plan.

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 in the meantime 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 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.

4.4 Clinical Safety and Pharmacovigilance Requirements

- **Pre-authorisation**

Study protocols should provide details of the methods for collection of safety data (i.e. diary cards, questionnaires) including intervals for collection of the data (e.g. after each dose) and the total

duration of follow up. Case definitions developed by the Brighton Collaboration for specific events should be referred to if appropriate (<http://brightoncollaboration.org>).

Safety data should usually be collected after each dose of the vaccine. 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 (longer for live vaccines), whereas recording of later events (e.g. up to 14 days post-dose or up to the time of the next dose in multiple dose schedules) is elicited by telephone contact or when vaccinees actually attend for the next dose. The duration of the follow up period after the last dose has been given should be justified by the applicant.

Analysis of the possible vaccine-relatedness of adverse events should use standardised categories for causality assignment. In addition, adverse events following immunisation should 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.

If the marketing authorisation is based solely on immunogenicity studies, it is unlikely that the database would be sufficiently large to identify rare events. As a minimum, the total data from pre-authorisation studies should usually be sufficient to reliably determine the frequency of uncommon local and systemic adverse events i.e. that occur at a frequency between 1/100 and 1/1000 vaccinated persons. Unless otherwise justified, the recommended minimum sample size would be at least 3000 subjects for new vaccines. If a total safety database is projected that would be insufficient to reliably determine anticipated rare adverse events then scientific advice should be obtained from EU Competent Authorities.

Differences in the safety profile might be observed between certain subpopulations and also with consecutive doses during the immunisation schedule. 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 and/or the applicant should address these matters in adequately powered post marketing studies.

- **Post-authorisation**

By the time that a marketing authorisation is granted:

- A risk specification should be finalised that includes a description of possible safety issues related to the intrinsic character of the vaccine and/or the intrinsic character of the individual response.
- A risk management plan should be agreed with EU Competent Authorities. This should be drawn up in accordance with current EU legislation and pharmacovigilance guidelines. Any specific safety monitoring imposed should be taken into consideration in the risk management plan. Plans should be in place for the monitoring of vaccine effectiveness (see section 4.2).
- Pharmacovigilance systems (as defined in the current EU legislation) and procedures (including batch numbers and concomitant vaccinations in addition to the traceability as described in the current EU guidelines) to achieve adequate monitoring of safety should be in place.

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. Applicants should consult the separate guidance under development regarding pharmacovigilance for vaccines.

REFERENCES (scientific and / or legal)

- ICH topic E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)
- ICH topic E8 General Considerations for Clinical Trials (CPMP/ICH/291/95)
- ICH topic E9 Statistical principles for clinical trials – Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)
- ICH topic E11 Clinical Investigation of Medicinal Products in Paediatric Population
- Guideline on Risk Management Systems for Medicinal Products for Human use (EMA/CHMP 96286/2005)
- Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)
- ICH Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03 - Final approval by CHMP on PHV)
- Points to Consider on Missing Data (CPMP/EWP/1776/99)
- Guideline on the Choice of the Non-Inferiority Margin (EMA/CPMP/EWP/2158/99)
- Points to Consider on Switching between Superiority and Non-Inferiority (CPMP/EWP/482/99)
- Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)