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Guideline on clinical evaluation of vaccines

Draft

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This guideline replaces 'Guideline on the clinical evaluation of new vaccines' (EMEA/CHMP/VWP/164653/05) including its 'Annex on SPC requirements' (EMEA/CHMP/VWP/382702/06) and 'Guideline on adjuvants in vaccines for human use' (EMEA/CHMP/VEG/134716/04)

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Guideline on clinical evaluation of vaccines

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Executive summary

This guideline addresses the clinical evaluation of vaccines intended for the prevention of infectious diseases. It includes considerations for trials intended to document the safety, immunogenicity and efficacy of new candidate vaccines and to support changes in the prescribing information of licensed vaccines. It also considers the need for and use of vaccine effectiveness studies.

Since the adoption of EMEA/CHMP/VWP/164653/2005 many new vaccines have been approved in the EU or have received a positive opinion under Article 58 of Regulation (EC) No 726/2004, including several intended to prevent infectious diseases for which there was previously no vaccine available. Some of these vaccines include antigenic substances from multiple pathogens or from multiple subtypes of a single pathogen. These applications have raised several issues for vaccine clinical development programmes that were not addressed in the previous guideline. Furthermore, there have been requests for scientific advice on vaccine clinical development programmes that have pointed to the need to provide updated or additional guidance on some issues. For example, on considerations for conducting vaccine efficacy trials, identification of immune correlates of protection, vaccines intended to be used in heterologous prime-boost regimens and vaccines to be administered to pregnant women to protect their infants during the first months of life.

In response to recurring issues arising in scientific advice and in application dossiers, this revised guidance includes a discussion of factors to consider when planning and interpreting the results of comparative immunogenicity trials. For example, the importance of considering the severity, mortality and/or risk of permanent sequelae of the infectious disease to be prevented as well as the robustness of the assays to determine the immune response when selecting non-inferiority margins and assessing the clinical impact of failing to meet pre-defined criteria. In trials that compare candidate and licensed vaccines containing antigens from different numbers of subtypes of the same organism consideration is given to interpretation of immune responses to non-shared subtypes.

The guideline also expands on considerations for the design of vaccine efficacy trials, including the selection of appropriate control groups in different circumstances. Moreover, the role of sponsors in the provision of vaccine effectiveness data in the post-licensure period has been reconsidered to reflect the fact that most studies are conducted by public health authorities.

There are some special considerations for the evaluation of vaccine safety in clinical trials, including the parameters to be documented in specific age sub-groups. The guideline addresses general considerations for the size of the pre-licensure safety database, such as the vaccine construct and the use of antigens or adjuvants not previously included in licensed vaccines.

1. Introduction (background)

The Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/2005) covered the clinical development of vaccines intended to provide pre- and post-exposure prophylaxis against infectious diseases. The Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004) included a section on the clinical evaluation of vaccines proposed to contain adjuvants. This revision combines the clinical guidance provided in these two documents. In replacing them, it updates and adds to the guidance provided previously to address issues that have come to light since they came into operation.

2. Scope

This guideline is focussed on the clinical development of vaccines intended for the prevention of infectious diseases, whether administered before infection occurs or for post-exposure prophylaxis. It does not address the clinical development of immuno-therapeutic products.

The guidance is relevant to vaccines intended to prevent infectious diseases due to single pathogens, including those directed at multiple subtypes of single pathogens, and to vaccines consisting of multiple antigenic components intended to prevent a range of infectious diseases. It is relevant to vaccines that contain:

- Organisms that have been inactivated by chemical or physical means;
- Live organisms that are naturally non-virulent in humans or that have been treated or genetically modified to attenuate their virulence;
- Antigenic substances extracted from pathogens or secreted by them, which may be used in their native state, detoxified by chemical or physical treatments or aggregated, polymerised or conjugated to a carrier to increase their immunogenicity;
- Antigenic substances produced by genetic engineering or chemical synthesis;
- Live bacterial or viral vector vaccines expressing foreign antigenic substances;
- Naked nucleic acid, including plasmids engineered to express specific antigens.

The guideline addresses clinical development programmes to support the approval of candidate (i.e. unlicensed) vaccines, adjuvanted or non-adjuvanted, and to support modifications to vaccines in the post-approval period (e.g. changes in, or additions to, the posology, the age range for use or recommendations for concomitant vaccination).

The guidance addresses trials to document vaccine safety, immunogenicity and/or efficacy. It considers situations in which a pre-licensure demonstration of vaccine efficacy would or would not be required, the design of pre-licensure trials to evaluate vaccine efficacy and the assessment of vaccine effectiveness in the post-approval period.

It also considers the evidence that may be provided from nonclinical studies to support vaccine efficacy but it does not consider other types of nonclinical investigations, which are covered in other guidelines relevant to vaccines.

Vaccine pharmacovigilance is not covered because it is addressed in detail in separate CHMP guidance.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- 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 E11 Clinical Investigation of Medicinal Products in Paediatric Population
- ICH E7 Studies in Support of Special Populations: Geriatrics Q&A (EMA/CHMP/ICH/604661/2009)
- 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)
- Guideline on Influenza Vaccines; Non-clinical and Clinical Module. (EMA/CHMP/VWP/457259/2014)
- Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines. (EMA/CHMP/VWP/141697/2009)
- ICH Q2 (R1) Validation of analytical procedures: text and methodology (CPMP/ICH/381/95)
- ICH topic E9 Statistical principles for clinical trials – Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)
- Points to Consider on Missing Data (CPMP/EWP/1776/99)
- Guideline on the Choice of the Non-Inferiority Margin (EMEA/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)
- Points to consider on application of 1. Meta-analyses 2. One pivotal study (CPMP/EWP/2330/99)
- Guidance on format of the risk-management plan in the European Union (EMA/PRAC/613102/2015 Rev.2 accompanying GVP Module V Rev.2)
- Guideline on Risk Management Systems for Medicinal Products for Human use (EMEA/CHMP 96286/2005)
- Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases (EMA/488220/2012 Corr)
- Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (EMA/876333/2011 Rev 4)
- Guideline on good pharmacovigilance practices: Module V – Risk management systems (EMA/838713/2011 Rev 2).

4. Immunogenicity

4.1. Characterisation of the immune response

For each antigenic component in a candidate vaccine, and depending on any available information on immune responses to the same or similar antigenic components in licensed vaccines, characterisation of the immune response in sera, plasma, whole blood, peripheral blood mononuclear cells or other biological matrix may include some of the following investigations:

- Measurement of functional antibody (e.g. neutralising antibody, bactericidal activity or opsonophagocytic activity) and/or binding antibody (e.g. total binding IgG, IgG subclasses);
- Description of the kinetic of the immune response (e.g. time to reach peak antibody levels and the antibody decay curve);
- Induction of immune memory;
- Exploration of immunological factors that could affect the humoral immune response (e.g. pre-vaccination antibody levels resulting from prior vaccination and/or natural exposure);
- Evaluation of cross-reactive antibody (e.g. antibody elicited by an antigen that cross-reacts with antigen[s] of one or more other species or subtypes within a species);
- Evaluation of cross-priming (e.g. the ability of one antigen to induce immune memory to [an]other antigen[s]);
- Assessment of the cell-mediated immunity (CMI) component of the immune response (e.g. by quantifying T-cells specific for vaccine antigen[s] and/or antigens derived from wild-type organisms *in vitro* via direct labelling or based on cytokine release);
- Investigation of the correlation between cytokine or gene expression profiles (e.g. innate immune or plasma cell signatures) and an immune correlate of protection, antibody levels or clinical events, such as immune-mediated adverse effects.

Whenever possible it is preferred that each immune parameter is assayed in a single central laboratory and that the same laboratories are used throughout the clinical development programme. If this is not possible, inter-laboratory variability should be evaluated and any impact on the results and conclusions should be addressed in the application dossier.

Protocols should specify and give details of the performance characteristics of the assays to be used to evaluate immune responses to vaccination. The assays used in pivotal trials should be fully validated. If there is an internationally-accepted reference assay, any modifications to the reference assay methodology that are made by a sponsor should be supported by an assay bridging study. Assays should be calibrated against the relevant International Standard(s) whenever these exist. If changes to assay methodologies occur during the clinical development programme, data should be provided to demonstrate no effect on the results or to support the use of a correction factor.

4.2. Immune correlates of protection

In this guideline an immune correlate of protection (ICP) is defined as a type and amount of immunological response that correlates with vaccine-induced protection against an infectious disease and that is considered predictive of clinical efficacy. Widely accepted and well-supported ICPs exist for a limited range of infectious diseases.

When there is no established ICP for a specific infectious disease, the predictive value of the immune response for protective efficacy (short-term and/or longer-term) should be investigated whenever

vaccine clinical development programmes include efficacy trials. For example, by collecting sera from all or a large subset of subjects in the test and control groups at a time point corresponding to a selected interval after completion of primary vaccination in the test group and comparing immune parameters between those who do and do not develop the infectious disease to be prevented. Alternatively, or in addition, repeated sera collection and determination of vaccine efficacy at timed intervals (e.g. annually) during follow-up may be used to identify an ICP for long-term protection.

If a vaccine efficacy trial is not feasible (see section 5.1) or if the analyses of an efficacy trial fail to identify an ICP, it may be possible to derive an ICP from a prospective vaccine effectiveness study (see section 6). Furthermore, an indication of the immune parameter of greatest importance for protection and sometimes a preliminary ICP may be obtained from one or more of nonclinical efficacy studies, sero-epidemiological studies (i.e. examining natural protection) and human challenge trials.

An ICP may not be applicable beyond the vaccine and the population in which it was identified. For example, an ICP against a specific infectious disease that is based on a functional humoral immune response cannot be applied to vaccines intended to prevent the same disease which confer protection via a different immune mechanism. Additionally, an ICP derived from an efficacy trial in infants may not necessarily be applicable to adults, an ICP established for one subtype of a pathogen may not be applicable to all subtypes and an ICP may not be applicable to all possible routes of administration of the same antigens.

In rare cases, it may not be possible to identify an ICP but clinical trial data may point to a threshold value of a certain immune parameter that could serve for making comparisons between vaccines or population groups (e.g. as applied to serotype-specific IgG elicited by conjugated pneumococcal polysaccharides). Threshold values may be used as a benchmark when interpreting immunological data from further trials with a specific type of vaccine.

4.3. Design of comparative immunogenicity trials

This section considers general principles for comparative immunogenicity trials regardless of the trial objectives.

4.3.1. Primary and secondary endpoints

Primary and secondary endpoints reported from comparative immunogenicity trials may include some of the following:

- Percentages of subjects with an immune response to vaccination that is above the defined ICP (i.e. the seroprotection rate) or above a threshold level;
- Percentages of subjects with a pre-defined increment (e.g. at least a 4-fold rise) in antibody concentration/titre from pre- to post-vaccination (i.e. the seroconversion rate);
- Percentages of subjects defined as seronegative or seropositive pre-vaccination and post-vaccination according to the lower limit of detection of the assay;
- Post-vaccination seroprotection and seroconversion rates separately for those who were seronegative or seropositive at study baseline;
- Geometric mean antibody concentrations (GMCs) or titres (GMTs) and pre-/post-vaccination ratios (GMRs);
- Pre- and post-vaccination numbers or percentages of subjects with sensitised (i.e. antigen-specific) T-cells (including sensitised CD4+ and CD8+ T-cells), presented according to the antigenic substance(s) used for stimulation and the cytokine(s) detected in the assay(s).

Primary vaccination

If there is a relevant ICP or threshold value the usual primary endpoint is the post-vaccination (i.e. after a single dose or after the last dose of a primary series) seroprotection rate or the percentage with an immune response at or above the threshold value. If there is no ICP or threshold value the primary endpoint is usually the seroconversion rate. The post-vaccination seropositivity rate may also be informative as a secondary endpoint.

The post-vaccination GMC or GMT and the pre- to post-vaccination ratio (GMR) are not usually appropriate primary endpoints after primary vaccination but should be included in secondary endpoints. Exceptions in which the GMC or GMT may be the primary endpoint include, but may not be limited to, lot-to-lot consistency trials.

Post-primary vaccination

For vaccines that elicit immune memory during primary vaccination, post-primary doses will result in very high seroprotection, seroconversion and seropositivity rates in all randomised groups. If the primary objective of the trial is to detect any differences there may be between vaccines, it may be appropriate to designate the post-vaccination GMC or GMT or, occasionally, the GMR (pre-boost to post-boost) as the primary endpoint, in which case the secondary endpoints should include the primary endpoint that was selected for assessing the immune response to primary vaccination.

If the vaccine does not elicit immune memory, the primary endpoint should be the same as that selected for assessing the immune response to primary vaccination.

4.3.2. Primary analyses

Comparative immunogenicity trials conducted early in the development of a candidate vaccine (e.g. to identify formulations, doses and regimens for further study) may plan for descriptive analyses. In trials that are designed to support hypothesis testing, CHMP guidance on statistical issues should be followed including, as appropriate, randomisation with stratification factors and the possible need to adjust for multiplicity.

When the primary aim is to demonstrate non-inferiority of the test group(s)vs. the reference group(s) with respect to immune responses to each or selected antigen(s) of interest, selection of the non-inferiority margin should consider the severity of the disease to be prevented, the mortality rate and the risk of serious permanent sequelae. For example, if the vaccine is proposed to prevent an infectious disease with a high mortality rate it is appropriate that the non-inferiority margin is more stringent compared to vaccines intended to prevent infectious diseases that are rarely fatal and do not result in serious permanent sequelae. In addition, selection of the non-inferiority margin could consider the expected precision of the measurement and the performance characteristics of the assay applied to the primary immune parameter.

Comparative immunogenicity trials may aim to demonstrate superiority of the immune response to one or more antigen(s) in a test group compared to a reference group. For example, when the reference group does not receive the antigen(s) in question, when comparing doses or regimens of the same candidate vaccine and when the effect of adding an adjuvant is under evaluation. Alternatively, the same trial may be designed to demonstrate non-inferiority of immune responses to some antigens and superiority for responses to others or may plan to test for non-inferiority and, if the criterion is met, to sequentially test for superiority. For example, when a candidate vaccine contains antigens from more pathogen subtypes compared to a licensed vaccine, the aim may be to demonstrate non-inferiority for shared subtypes and superiority for non-shared subtypes.

4.4. Formulation, dose and schedule

4.4.1. Formulation and dose

For an antigen that has not previously been included in a licensed vaccine the relationship between dose and immune response should be explored in clinical trials, considering that data from in-vivo non-clinical studies are not usually helpful for selecting the human dose. If it is not known what might constitute a protective immune response, the antigen dose above which there is no appreciable increment in the immune response (i.e. a plateau effect is observed) should be explored unless there are dose-limiting safety issues. For candidate vaccines that include vectored antigens the dose-finding trials should evaluate the potential effect of pre-existing as well as vaccine-elicited immune responses to the vector on the immune responses to the antigens derived from the target pathogens.

For candidate vaccines that contain one or more antigens that have not previously been combined in a licensed vaccine, the immune responses may be compared with those observed after separate administrations. This approach may not be necessary or feasible if i) a very large number of antigens are to be combined (e.g. multiple subtypes of a pathogen); ii) the antigen(s) in question will be added to a licensed combination vaccine, in which case the trial may compare the candidate combination vaccine with separate administrations of the licensed combination vaccine and the additional antigen(s); iii) the candidate combined vaccine includes only antigens already included in other licensed vaccines, in which case the candidate could be compared with separate administrations of the licensed vaccines or, if they are already approved for co-administration, the candidate could be compared with concomitant administration of the licensed vaccines. Other scenarios may be foreseen and the need for, and extent of, the trials should be decided on a case by case basis.

Unpredictable effects on immune responses have been observed when some protein-saccharide conjugates have been included in candidate combination vaccines with certain other antigens, including other conjugates. For example, immune responses to antigens that are the same as (e.g. tetanus toxoid) or closely resemble (e.g. diphtheria toxoid and CRM197) the carrier protein in the conjugate may be enhanced. The potential for increases or decreases in immune responses to the conjugated antigens and to the conjugative proteins should be carefully explored.

Inclusion of an adjuvant in a candidate vaccine requires adequate justification, which may be based on a combination of nonclinical and clinical data. An adjuvant may be justified based on enhancement of the immune response to one or more of the antigenic components demonstrated in a trial that directly compares adjuvanted and non-adjuvanted formulations. Alternatively, or in addition, inclusion of an adjuvant may serve to reduce the amount of the antigenic component(s) required to achieve a target immune response. This strategy may be important when there are vaccine supply limitations related to manufacture of the antigenic component(s) and there is anticipation of a need to provide large numbers of doses within a limited time frame (e.g. to address pandemic influenza). Whenever an adjuvant is to be included, safety and immunogenicity data should support the amount that is provided in each dose.

4.4.2. Schedule

Primary vaccination

The immunogenicity data should suffice to identify the minimum number of doses required to elicit immune responses at or above the ICP or threshold value or, if neither is available, to maximize the immune response that can be safely achieved in the target population or sub-populations (e.g. age sub-groups). The appropriate dose interval(s) should be explored considering available data on the kinetic of the immune response to each sequential dose.

In infants, it is often important to identify a schedule that provides protective immune responses as early as possible. Therefore, the effect of maternal antibody on the infant immune response should be evaluated when the first infant dose is given at different ages. If the presence of maternal antibody has a blunting effect on the magnitude of the infant immune response it may be useful to assess whether priming still occurred when determining the earliest age at which the first dose may be given.

It is not necessary to evaluate immune responses to a candidate vaccine at multiple infant immunisation schedules in routine use. For example, if it is concluded that 2 doses are likely required, an evaluation of immune responses at 2 and 4 months would suffice to support use at a schedule that starts and/or ends at a later age since immune responses are generally higher rather than lower as age at time of vaccination increases within infancy. An evaluation of immune responses at 2 and 4 months of age would not support starting before 2 months of age or using a 1-month dose interval.

Different schedules may have to be established for various target populations (e.g. premature infants, the elderly, the immunosuppressed and haemodialysis patients). Specific schedules may also be needed for populations in which a single dose or short schedule is needed for practical reasons (e.g. travellers and pregnant women).

Post-primary vaccination

The ability of a primary series to elicit immune memory may be demonstrated by administration of a post-primary dose of the same vaccine at least 6-12 months after completion of the primary series. If the post-dose GMC or GMT is higher than the post-primary value and/or is higher in a group that previously received a primary series compared to administration of a single dose to a previously unvaccinated age-matched group, it may be inferred that the primary series elicited a T-cell-dependent immune response leading to an anamnestic response to the post-primary (booster) dose.

If it is known that additional doses will be needed to maintain protection, the immune responses to one or more post-primary doses should usually be investigated in the pre-licensure trials. If it is not already known that additional doses are needed to maintain protection against the target pathogens the need for and timing of an additional dose(s) after the primary series should be investigated. It is recognised that the need for additional doses may have to be determined after initial authorisation.

For some vaccines that elicit immune memory in the primary series it may not be necessary to administer the same dose for boosting. Therefore, it may be appropriate to investigate the safety and immunogenicity of lower antigen doses for boosting than were used for priming or to boost with a formulation that does not include an adjuvant.

Generally, it is not recommended to draw conclusions on the need for post-primary doses based only on waning antibody. For some pathogens, a decline in antibody, including levels below a putative ICP, may not necessarily indicate loss of protection if immune memory has been elicited (e.g. hepatitis B vaccines). In contrast, for some pathogens that rapidly invade after colonisation (e.g. *N. meningitidis*) it may be necessary to maintain a certain level of circulating antibody to ensure protection even if primary vaccination elicited immune memory. For these reasons, it is recommended that, whenever feasible, the need for and the timing of further doses should be determined from long term follow-up of subjects enrolled into vaccine efficacy trials and/or from vaccine effectiveness studies or disease surveillance data obtained during the post-authorisation period.

Use of different vaccines within schedules

To support the use of more than one vaccine to deliver the total number of doses required within the primary schedule, it should be demonstrated that similar immune responses are achieved using more than one vaccine compared to a single vaccine to complete the schedule.

To support the use of a vaccine to boost immune responses in subjects who received a primary series using a different vaccine, subjects primed with one vaccine could be randomised to receive a booster dose with the priming vaccine or the proposed alternative vaccine with the aim of demonstrating non-inferiority of immune responses.

To support the use of one vaccine construct to prime and another to boost the test regimen could be compared with a repeated dose of the first vaccine construct with the aim of demonstrating superiority of immune responses and/or broadening of the immune response (e.g. to multiple subtypes of a pathogen).

4.4.3. Route and/or method of administration

For a new candidate vaccine, the choice of route of administration should be investigated as needed during the initial dose, formulation and regimen studies.

To support an alternative route of administration of a licensed vaccine without altering the vaccine formulation (e.g. to allow a vaccine licensed for intramuscular administration to be given subcutaneously, intranasally or using a new device, such as a microneedle patch), with or without changing the antigen dose(s), the possible need for an efficacy trial should be considered (see section 5).

4.5. Concomitant administration

Concomitant administration of vaccines may result in higher or lower immune responses to certain antigenic components compared to separate administration.

At the time of initial authorisation of a vaccine, it is desirable but not required that there should be data on concomitant administration with vaccines that are most likely to be given at the same time. When there are several licensed vaccines that protect against the same disease(s) that may be co-administered, a trial with a single example may suffice to make a general statement about concomitant vaccine use. However, 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 the specific type of conjugate for which data are available should be stated in the Summary of Product Characteristics (SmPC).

For some vaccines, such as those intended for the primary series in infants, it may be necessary to ensure that all subjects in a clinical trial receive all the required antigens before reaching a certain age. To address this need, trials may need to compare concomitant administration with separate administrations made in a staggered fashion (e.g. to compare concomitant administration at 2 and 4 months with administration of routine infant vaccines at 2 and 4 months and the candidate vaccine at 3 and 5 months). In older age groups, it is more likely 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 reductions in immune responses, further trials could explore the minimum dose interval that does not lead to any impact so that advice can be provided in the SmPC.

4.6. Lot-to-lot consistency

A lot-to-lot consistency trial is not routinely required but may be considered useful under certain circumstances that should be considered on a case by case basis. If such a trial is conducted it is

important to consider and justify the number of lots to be compared and the method of lot selection (e.g. consecutively produced or chosen at random). Careful consideration needs to be given to the primary immune response endpoint and the pre-defined acceptance criteria.

It is recommended that several lots of the candidate vaccine with a formulation similar to that of the final product intended for marketing should be tested during the clinical development programme. If this is not possible due to late stage manufacturing changes, the sponsor should justify the relevance of the clinical trial data to the lots intended for marketing based on quality attributes and/or should conduct a clinical comparison between lots.

5. Efficacy

5.1. Requirements for efficacy trials

Vaccine efficacy trials are not required if any of the following apply:

- It is possible to interpret immune responses to all the antigens in a candidate vaccine using well-established ICPs. In this case demonstration of non-inferiority to a licensed vaccine for immune responses to each antigen is not necessary. Nevertheless, it is recommended that trials include randomisation to an appropriate licensed vaccine to allow a descriptive comparison of safety profiles. Determination of immune responses to the comparator may be useful to put the results into context in case the seroprotection rates in the candidate vaccine group are unexpectedly low or high (e.g. due to characteristics of the trial population and/or issues with the assay).
- There is/are no ICP(s) but vaccine efficacy can be inferred by demonstrating non-inferior immune responses between the candidate vaccine and a licensed vaccine for which efficacy and/or effectiveness has been estimated. If the exact vaccine for which efficacy or effectiveness was determined is no longer available, the comparison may be made with a licensed vaccine that was itself approved via an immunobridging strategy and, preferably, has been widely used without any concerns regarding protection.
- Immune responses to all antigens in the candidate vaccine can be interpreted using a combination of the above approaches.

If immunological data cannot be used to select a dose, formulation and schedule that can be predicted to provide satisfactory protection against the infectious disease(s) to be prevented a vaccine efficacy trial should be conducted whenever this is feasible. Considerations for the feasibility of conducting a vaccine efficacy trial include the following:

- The infectious disease to be prevented does not occur (e.g. smallpox) or occurs at too low a rate for a study to be performed in a reasonable timeframe (e.g. anthrax, brucellosis, Q fever).
- The infectious disease to be prevented occurs in unpredictable short-lived outbreaks that, even if large numbers are affected, do not allow enough time to accrue sufficient cases for an assessment of vaccine efficacy (e.g. some viral haemorrhagic fevers).

When a demonstration of vaccine efficacy is considered necessary and it is feasible, a single pivotal vaccine efficacy trial may be acceptable, especially if there is a low incidence of the infectious disease to be prevented so that a very large trial is necessary to accumulate sufficient cases to estimate vaccine efficacy.

For pathogens that have multiple subtypes, it is possible that the cases that occur in an efficacy trial may be due to one or only a few subtypes of the pathogen. Sponsors could consider conducting the

pivotal efficacy trial in regions selected to increase the likelihood that cases are due to a broad range of subtypes, although it would not be expected that the trial is designed to estimate subtype-specific efficacy. Alternatively, sponsors may consider conducting more than one vaccine efficacy trial in different regions where certain subtypes are known to predominate. Depending on the vaccine construct, nonclinical and/or other clinical evidence may also be used to support the likely consistency of efficacy across all subtypes.

For some infectious diseases, there may be good scientific reasons to anticipate that the protective efficacy demonstrated in a pivotal efficacy trial in one population in a specific age range may not be extrapolated to other populations with the same age range. For example, in some regions there may be multiple co-infections in populations and/or there may be considerable boosting of the immune response due to natural exposure that could have positive or negative effects on the estimate of vaccine efficacy. In these cases, it may be necessary to conduct a pivotal trial that enrols representative samples of different populations or to conduct more than one trial in separate populations.

5.2. Efficacy trial designs

The absolute protective efficacy of vaccines is usually determined by comparing the reduction in the incidence of the infectious disease in question after vaccination compared to the incidence when unvaccinated in prospective randomised and double-blind trials.

If there is no licensed vaccine against the disease to be prevented or there is no licensed vaccine that is widely recommended for use in the target population, it may be acceptable that the control group receives a placebo. A true placebo may not be considered acceptable if this would require injections in some age groups. If a placebo control is considered inappropriate, a licensed vaccine without an effect on the disease to be prevented by the candidate vaccine could be administered to the control group.

One alternative is to demonstrate that the protective efficacy of the candidate vaccine is non-inferior to that of a licensed vaccine. This design may be necessary when withholding vaccination from the control group is not possible and there is at least one widely-recommended licensed vaccine. Furthermore, if the candidate vaccine has been developed to improve on one or more licensed vaccines it may be appropriate to demonstrate that the efficacy of the candidate vaccine is superior to that of a licensed vaccine.

Other efficacy trial designs include secondary attack rate trials, which are sometimes used when the infection to be prevented is known or expected to be associated with a relatively high incidence of secondary cases. In these trials, an assumption is made that vaccinees and non-vaccinees have an equal chance of acquiring the infection from the index case. The preferred design would be to randomise the direct contacts, and sometimes secondary contacts, of a case on an individual basis to receive or not receive the candidate vaccine. Alternatively, individuals may be randomised to immediate or delayed vaccination. An additional possible design would be to randomise all the members of each ring to the same arm, i.e. a cluster-randomised approach, which should be accounted for in the analysis.

In a randomised step-wedge trial, the candidate vaccine is administered sequentially to predefined groups such that each group is a unit of randomisation. Groups may be defined by host factors, location or other factors. This design may be particularly appropriate when there are logistical reasons that preclude vaccination of large numbers of subjects with the candidate vaccine in a short interval.

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

5.3. Case definitions

Case definitions to be used for the primary analysis and any alternative case definitions for secondary analyses usually comprise clinical signs and/or symptoms typical of the infectious disease together with laboratory confirmation of the aetiology. On occasion, case definitions for primary or secondary analyses may be based only on clinical features or laboratory investigations.

If an organism causes disease of variable severity or a range of clinical presentations (e.g. life-threatening invasive infections as well as localised infections) the clinical features of the case definition should be selected in accordance with the proposed indication(s). In these instances, separate efficacy trials using different case definitions may be necessary. In addition, for some vaccines it may be important to compare the severity of vaccine breakthrough cases with cases that occur in the control group to determine whether prior vaccination ameliorates or possibly enhances the severity of the disease.

Laboratory confirmation of a case may be based on one or more of immunological tests, pathogen culture, pathogen detection by non-culture-based methods or histological findings. The laboratory methods used to confirm the diagnosis at local study sites and/or at central laboratories should be pre-defined and justified. If there are commercially available tests, the choice of laboratory method(s) should be based on the reported performance characteristics (i.e. the sensitivity and specificity of the assay and whether it is deemed suitable for the trial population). In some cases, there may be interest in selecting an assay that can detect additional pathogens that may co-infect with the target pathogen and possible affect the severity or course of the disease. It may also be necessary to apply additional assays to detect such organisms if this is considered important for interpretation of the trial results.

On occasion, such as when there are no commercially available tests available with satisfactory performance characteristics, it may be appropriate to use experimental laboratory methods for establishing the presence of infection. In such cases, every effort should be made during the clinical development programme to evaluate the sensitivity, specificity and reproducibility of the methods used. If the case definition is based on histological findings, the criteria for staging and progression should be pre-defined in the protocol and it is recommended that there is a quality control system in place and/or secondary readings conducted at an expert central laboratory facility.

5.4. Case ascertainment

It is usual that there is active case ascertainment at least up to the time of conduct of the primary analysis. If there is to be further follow-up after the primary analysis the decision to switch to passive case ascertainment should consider the importance of obtaining reliable estimates of vaccine efficacy in the longer term and information on the characteristics of cases that occur in previously vaccinated and unvaccinated subjects over time.

When the primary endpoint is laboratory-confirmed clinical disease, the protocol should list the clinical signs and/or symptoms that trigger contact between trial subjects and trial site staff or designated healthcare facilities participating in the trial so that appropriate laboratory testing can be conducted to confirm the case. Regular personal or non-personal contact with trial staff may also be used to determine whether there have been any recent clinical signs or symptoms of potential relevance and to determine whether cases may have been missed. If any cases bypass the designated trial healthcare facilities and present elsewhere, attempts may be made to retrieve available data that could be used to establish whether the case definition was met.

If the primary endpoint is not a clinically manifest infection, trial visits should be sufficiently frequent to obtain the laboratory data of importance. Every effort should be made to minimize numbers that are lost to follow-up and to conduct trial visits within protocol-defined windows.

5.5. Duration of follow-up for efficacy

The primary analysis of efficacy is usually conducted when a pre-defined number of total cases of disease have occurred. In some cases, when the background incidence of disease is well-documented, the primary analysis may be conducted when it is predicted that a certain number of cases can be expected. See section 5.6.2.

An evaluation of the duration of protection beyond the time at which the primary analysis is conducted is important when there is no prior information for vaccines against the targeted infectious disease but such information is not expected to be available at the time of approval. Data on longer-term protection may come from extensions of pre-licensure trials and/or from data collected from various sources in the post-approval period.

For example, the long-term efficacy of a vaccine and determination of the need for and timing of additional doses may be assessed by following trial subjects after conducting the primary analysis. Follow-up of subjects within an efficacy trial may also be important to fully document the severity and aetiology of cases that occur in subjects that did and did not receive the candidate vaccine. These data can be used to assess the potential that vaccination reduces or enhances the severity of disease in breakthrough cases. Furthermore, even if vaccination reduces the risk of a clinical disease, documenting the aetiology of any cases that do occur may point to a change in aetiology (e.g. breakthrough cases may be confined to subtypes of a pathogen not included in the vaccine).

The value and feasibility of obtaining this information within the setting of a prolonged randomised controlled trial must be weighed against alternative methods, such as post-approval vaccine effectiveness studies and routine disease surveillance. Additionally, if the primary analysis indicates that a candidate vaccine is very effective, it may not be appropriate to maintain an unprotected control group. Nevertheless, it may be possible to follow up vaccinated subjects to assess whether there is waning efficacy over time by comparing numbers of cases that occur on an annual basis.

5.6. Analyses of efficacy

5.6.1. Primary endpoint

The primary endpoint is usually based on all cases of an infectious disease that meet the protocol-defined case definition but it may be based on laboratory events without immediate clinical signs and symptoms.

If a candidate vaccine contains antigens derived from several but not all known subtypes of a pathogen it may be acceptable that the primary endpoint is based on cases of disease due to any subtype included in the vaccine. This approach requires that causative pathogens can be subtyped and/or otherwise characterised to determine the degree of matching to the vaccine antigens. If nonclinical or prior clinical data indicate that the vaccine may be able to confer cross-protection against subtypes of a pathogen that are not included in the vaccine, the primary endpoint may be cases of disease due to any subtype of the pathogen.

5.6.2. Primary analysis

The primary analysis may be performed when:

- The last subject enrolled reaches a specific time elapsed since vaccination or has previously discontinued. This approach may be used when the background rate of disease is well described so that there is confidence regarding the number of cases likely to be observed in the control group during a pre-defined post-vaccination interval.

- The required number of events (i.e. cases) has been accumulated. This case-driven approach may be most appropriate when the rate of accumulation of cases is less certain.

The primary analysis should be aligned to an agreed target of estimation (estimand) as determined by the trial objective. Examples of issues to consider when defining a target of estimation include the target population about which confirmatory conclusions are to be drawn and adherence to the treatment schedule. Depending on the specific situation there could be others, including events such as death that preclude observation of the variable of interest.

Depending on the infectious disease to be prevented, including factors such as the expected proportion of subjects who are already naturally protected prior to vaccination, different approaches to constructing an estimand and associated primary analysis could be acceptable. In each case the sponsor should fully justify the primary objective of the trial, which will determine the primary analysis population of major interest. For some vaccines and infectious diseases, it may also be acceptable that the primary analysis is confined to those subjects who were seronegative or had no ongoing infection with the target pathogen at trial baseline. Some considerations include the following:

- When the major interest is to estimate the vaccine efficacy that could be expected in routine use, the primary analysis may be conducted in all randomised subjects who receive at least one dose of assigned treatment.
- When the major interest is to obtain a best-case estimate of vaccine efficacy, the primary analysis may be conducted in subjects who received all the allocated doses within pre-defined windows. For some vaccines and infectious diseases, it may also be acceptable that the primary analysis is confined to those subjects who were seronegative or had no ongoing infection with the target pathogen at trial baseline.

The primary analysis of efficacy may be based on all cases meeting the primary case definition that occur from randomisation or may be confined to cases that occur more than a specified number of days after the final vaccine dose. The post-dose interval before counting cases should be determined from information on the kinetic of the immune response. If the latter approach is taken there should be secondary analyses of all cases that occur from the time of randomisation and all cases that occur after different numbers of doses.

5.6.3. Other issues for the interpretation of vaccine efficacy

Vaccine efficacy can only be demonstrated in regions where there is sufficient disease to enable a trial to be conducted within a reasonable time frame. Therefore, use of a vaccine to prevent a disease that occurs rarely within EU countries will be based solely on clinical data generated in regions of high endemicity.

If the pivotal clinical efficacy trial was conducted in endemic regions outside of the EU where there was considerable natural priming before vaccination and/or cross-priming following vaccination against closely related pathogens, the data obtained from subjects who were naïve to the relevant pathogen(s) at trial baseline may be of most relevance to EU residents. In these cases, sponsors should consider whether an assessment of the benefit in EU residents should be supported by a comparison of immune responses to vaccination between seronegative subjects who are resident in an endemic area and age-matched EU residents.

A further issue may arise if a vaccine was shown to be efficacious in a region where the circulating pathogen subtypes were substantially different to those most common in the EU and existing data indicate that cross-protection across all subtypes cannot be assumed. In this case it may be useful to assess the degree of cross-protection that can occur in vitro to support the expected efficacy of the

vaccine in different regions. For example, depending on the pathogen, functional immune responses elicited by the vaccine could be assessed using a range of circulating wild-type strains isolated from EU cases.

5.7. Other approaches for estimating vaccine efficacy

For some infectious diseases, there may be i) no ICP or threshold value that could be applied interpret immune responses, ii) no possibility of comparing immune responses between a candidate vaccine and a licensed vaccine for which there is documented efficacy or effectiveness, and iii) no possibility of conducting a vaccine efficacy trial. In such situations, other approaches to estimating vaccine efficacy could be considered. If a suitable challenge strain can be identified and, if considered necessary for subject safety, an effective treatment is available, it may be possible to obtain an estimate of vaccine efficacy from a human challenge study. Nevertheless, there are recognised limitations of estimates of vaccine efficacy derived from human challenge trials for predicting protection against wild-type pathogens (since attenuated organisms may need to be used) and natural infecting doses (since the minimum dose to elicit measurable signs or symptoms is often used and the typical inoculum in natural infections is often not known).

On occasion, the only option for assessing the efficacy of candidate vaccines may be the use of appropriate animal models of infection, which may include post-vaccination challenge studies and studies of passive immunisation using sera or T-cells from vaccinated or naturally infected animals and/or humans. The choice of model(s) requires careful justification. Extrapolation of vaccine efficacy observed in animals to humans requires an understanding of the immune parameter(s) that aremost important for mediating protection.

Whenever licensure is based on such data, it is important that plans are in place at the time of approval to estimate vaccine efficacy and/or vaccine effectiveness should the opportunity arise.

6. Effectiveness

Estimates of vaccine effectiveness reflect direct (vaccine induced) and indirect (population related) protection during routine use. Vaccine effectiveness may be estimated from studies that describe the occurrence of the disease to be prevented in the vaccinated target population over time. For example, these may be observational cohort studies, case-control or case-cohort studies. Alternatively, effectiveness may be estimated from data collected during phased (e.g. in sequential age or risk groups) introduction of the vaccine into the target population and on occasion, using other study designs or disease registries.

Vaccine effectiveness studies are not always necessary but may be particularly useful in some situations and/or to address certain issues, including but not limited to the following:

- Licensure was based on nonclinical efficacy data and a comparison of immune responses between protected animals and vaccinated humans and/or on a human challenge trial;
- It is not known how long protection will last after the primary series and/or after post-primary dose(s);
- It is proposed to use the data collected to address long-term protection to support identification of an ICP;
- There are unanswered questions regarding the efficacy of a vaccine against a wide range of pathogen subtypes;

- There are scientific reasons to suspect that an estimate of vaccine efficacy documented in a pre-licensure trial may not be widely applicable to other populations (e.g. to subjects who are resident in different endemic or non-endemic regions);
- Different vaccine implementation strategies are in use in different countries or regions that may impact on the estimate of vaccine effectiveness (e.g. when introduction of routine use in infants is accompanied by a catch-up programme in older subjects and the upper age of the catch-up). In these instances, estimates of vaccine effectiveness obtained using different strategies can inform the optimal strategy to achieve rapid and efficient control of the disease;
- There is reason to suspect that widespread use of a vaccine could result in a change in the subtypes of a pathogen causing disease compared to the pre-vaccination era.

Vaccine effectiveness studies require a suitable infrastructure to be in place for case ascertainment and confirmation of cases in accordance with clinical and laboratory criteria and it may not be possible to obtain reliable data in all countries or regions. In addition, for some infectious diseases an estimate of vaccine effectiveness is possible only in case of a naturally occurring epidemic or a deliberate release of a pathogen in the context of bioterrorism. Furthermore, the conduct of a vaccine effectiveness study requires that a policy decision has been made to vaccinate a sufficiently large population to support the analysis.

Whenever it is perceived that valuable information could be gained from conducting a vaccine effectiveness study it is important that plans are in place to enable its initiation whenever a suitable opportunity arises in the post-licensure period.

The role of the licence holder in designing vaccine effectiveness studies, generating protocols, and collecting and analysing the data requires consideration on a case by case basis. In most cases, unless the incidence of the infectious disease is very high in some regions so that a relatively small and short study is possible, a study sponsored by the licence holder is not a practical undertaking. The only feasible way to evaluate vaccine effectiveness is often from studies put in place by public health authorities when initiating large vaccination programmes. Nevertheless, the licence holder has a responsibility to ensure that relevant data from non-sponsored studies are reported to EU Competent Authorities and to update the SmPC if the results have clear implications for the advice given (e.g. on the need for additional doses to maintain protection). Therefore, when an estimate of vaccine effectiveness is perceived to be very useful, licence holders should engage with public health authorities or with organisations that may be involved in control of epidemics to explore the feasibility of conducting vaccine effectiveness studies.

7. Safety

7.1. Assessment of safety in clinical trials

The main considerations for the assessment of safety in vaccine trials are the same as those for other types of medicinal products. All available and relevant CHMP guidance should be followed. Some additional considerations for the assessment of vaccine safety in clinical trials follows.

Since most adverse reactions to vaccines occur within the first few days after each dose, it is common practise that solicited local and systemic symptoms are collected for approximately 5-7 days after each dose and that an appropriate grading system to assess severity is pre-defined in protocols. A longer post-dose period of collection of solicited symptoms may be applicable for replication-competent live vaccines and the duration of shedding of the vaccine organism(s) should be assessed, with consideration of any potential risk to contacts of vaccinees.

Details of all other (i.e. unsolicited) post-dose adverse events should be obtained at trial visitsand/or using remote contact. During very long-term follow-up it may be acceptable that only serious adverse events and adverse events of special interest are captured.

The duration of safety follow-up after the last dose has been given should be justified based on the candidate vaccine construct, the inclusion of a new adjuvant and prior data of relevance to any of the components.

If the target population for a candidate vaccine includes paediatric subjects the need for an age de-escalation programme (e.g. so that safety is first assessed in adolescents before moving to 6-12 years, 2-5 years, 1-2 years and less than one year) should be considered on a case by case basisdepending on the age range of the target population and the relevance of safety data collected in older sub-populations to younger sub-populations.

For example, age de-escalation may be necessary because it is expected that different vaccine formulations will be required for different age sub-groups, in which case the safety and immunogenicity data from one age subgroup are analysed before moving to the next group. Furthermore, if the antigen(s) and/or adjuvant in a vaccine differ from those in licensed vaccines then a more cautious approach may be appropriate.

Age de-escalation may not be necessary if the candidate vaccine contains only antigen(s) ± an adjuvant already included in licensed vaccine(s), in which case the available safety information of relevance could be considered. Moreover, no or negligible benefit can be expected for some vaccines in certain paediatric age subgroups, which may lead to some degree of reluctance to enroll such children into clinical trials. If supported by the nonclinical data and information obtained in adult studies, a modified age-de-escalation approach could be appropriate in certain circumstances. For example, it may be justifiable to proceed from adults to toddlers provided that a cautious approach is taken to choosing the initial doses and fully evaluating all data from small cohorts before enrolling the next cohort.

7.2. Size of the safety database

The size of the pre-licensure safety database must be decided on a case by case basis.

If a candidate vaccine contains components not previously included in licensed vaccines it would be usual to aim for a safety database that is sufficient to estimate the frequency of uncommon adverse events (occurring in between 1/100 and 1/1000 vaccinated persons). Nevertheless, this should not be regarded as a generally applicable target since there may be special concerns that need to be addressed for which a much larger database would be needed.

For example, if there are concerns arising from the nonclinical data, from historical experience with a similar vaccine or from the available clinical safety data it may be considered necessary that the pre-licensure safety database is adequate to provide a relatively precise estimate of the risk of uncommon or even rare adverse events. Furthermore, it may be required that the safety database is of sufficient size to estimate the risk of experiencing a specific adverse event after vaccination.

Also, a smaller safety database may be acceptable if a candidate vaccine combines antigens ± adjuvant that are all included in licensed vaccines or contains additional antigens compared to a licensed vaccine but all are derived from the same pathogen and manufactured in a similar fashion.

In general, the considerations above apply to the total safety database, i.e. regardless of numbers or proportions within age or other population sub-groups. Depending on the vaccine and target population, it would usually be expected that at least some safety data are available from all target groups for the vaccine (e.g. age-sub-groups) and it some cases it may be required that the total safety

767 database comprises a minimum number of subjects within a certain age range or with specific host
768 characteristics.

769 8. Special populations

770 *8.1. Pregnant women*

771 Not all vaccines are suitable for administration to pregnant subjects. This section assumes that
772 candidate vaccines proposed for administration during pregnancy will have been assessed in
773 appropriate nonclinical studies and will be comprised of antigen(s) ± adjuvant not known to pose a risk
774 to the pregnant subject or fetus.

775 Vaccination during pregnancy may have one or more of the following aims: i) to protect the pregnant
776 subject; ii) to protect the fetus from intra-uterine infection; iii) to protect the infantfor as long as
777 protective levels of maternal antibody persist in the post-natal period.

778 If the candidate vaccine is not approved for use in non-pregnant adults, safety and immunogenicity
779 data should be obtained from non-pregnant female subjects of childbearing age before proceeding to
780 trials in pregnant subjects. Safety and immunogenicity trials to support selection of dose regimens
781 should enrol subjects at a stage of pregnancy appropriate to the primary objective, i.e. as early as
782 possible in pregnancy to protect the mother and/or fetus and later in pregnancy to maximize maternal
783 antibody levels in the neonate.

784 If the primary aim of vaccination during pregnancy is to protect the infant in the first months of life the
785 dose-finding trials should include measurement of antibody levels in cord blood samples taken at
786 delivery. The data should be sufficient to provide an estimate of inter-individual variability and to
787 assess the effect of time interval between vaccination and delivery on maternal antibody levels in
788 infants. The persistence of detectable maternal antibody in infants against the target organism should
789 be evaluated as part of the dose-finding process. If the overall strategy involves vaccinating pregnant
790 subjects followed by active vaccination of their infants against the same antigen(s), the antibody decay
791 curve in infants may provide a preliminary indication of the timing of the first infant dose.

792 If an ICP is established for the infectious disease to be prevented, and depending on the primary
793 objective and the safety profile, the maternal vaccination regimen should maximise the proportions of
794 pregnant women or cord blood samples with antibody that exceeds the ICP. If there is no ICP and
795 there is no licensed vaccine of known efficacy to which the candidate vaccine could be compared (i.e.
796 using immunobridging to infer efficacy), a vaccine efficacy trial would usually be necessary.

797 In all trials conducted in pregnant subjects, adequate mechanisms should be in place to document the
798 outcome of the pregnancy. For example, information should be collected on the duration of gestation,
799 the condition of the infant at birth and any congenital conditions.

800 It is important that vaccines proposed for use during pregnancy have very benign safety profiles,
801 including low systemic reactogenicity. If the safety profile in non-pregnant subjects raises any safety
802 concerns it may be necessary to conduct larger studies in this population to quantify the risk before
803 deciding whether to proceed to pregnant subjects.

804 *8.2. Elderly subjects*

805 For most vaccines, elderly subjects have lower responses to vaccination compared to younger subjects,
806 which may reflect immunosenescence and/or the prevalence of specific underlying diseases or
807 medications that have a negative impact on the immune system. On occasion, immune responses may
808 be higher in the elderly if they are more likely than younger adults to have been primed by natural
809 exposure or prior vaccination. Therefore, it is important that adequate dose-finding studies are

conducted for vaccines proposed for use in the elderly and that all age subgroups are investigated (e.g. 65-74 years, 75-84 years and 85 years or more) to determine whether different doses and/or regimens are needed as age increases. If efficacy trials are to be conducted in elderly subjects it is recommended that there is stratification by age sub-groups. Furthermore, the impact of any underlying conditions or medications known or likely to affect immune responses should be investigated during the clinical trials. The safety of vaccines in the elderly should be documented in subsets with certain underlying conditions and levels of frailty to determine whether the safety profile is broadly acceptable.

8.3. Immunodeficient subjects

Due to the wide range of types of immunodeficiency that may result from congenital or acquired conditions or from iatrogenic intervention, only some of which may impact on the immune response to a specific type of vaccine, trials that assess safety, immunogenicity or efficacy in a broad immunodeficient population are not recommended.

Trials intended to support dose recommendations for immunodeficient subjects should plan to enrol well-defined sub-populations of subjects with immune deficiencies that have been selected based on those most likely to affect the immune response to a specific vaccine. Unless there is a well-established ICP that can be applied to the data, the usual aim of such trials will be to identify a posology that achieves comparable immune responses to those observed in immunocompetent subjects.

It is not expected to be feasible to study all immunodeficient sub-populations. The extent to which any one posology may be recommended beyond the exact population in which it was studied must be decided based on what is known about the relative importance of different immunological parameters for protection.