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**NOTE FOR GUIDANCE ON
CLINICAL EVALUATION OF NEW VACCINES**

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1. INTRODUCTION

The present Note for Guidance intends to give guidance in the clinically relevant issues in the evaluation of new vaccines for human use.

Vaccines are a heterogeneous class of anti-infective medicinal products containing antigenic substances capable of inducing specific and active immunity against the infecting agent or the toxin or other important antigenic substances produced by this agent. Vaccines for human use may contain: organisms inactivated by chemical or physical means that maintain adequate immunogenic properties; living organisms that are naturally avirulent or that have been treated to attenuate their virulence whilst retaining adequate immunogenic properties; antigens extracted from the organisms secreted by them or produced by recombinant DNA technology. The antigens may be used in their native state or may be detoxified by chemical or physical means and may be aggregated, polymerised or conjugated to a carrier to increase their immunogenicity (Ph.Eur.1998:0153 definition for vaccines).

Combined vaccines are products intended for protection against a single infectious disease complex caused by different strains or serotypes of organisms; or protection against multiple infectious diseases; or Combinations of 1 and 2 (Note for Guidance on pharmaceutical and biological aspects of combined vaccines).

Although the general clinical aspects of this document apply to non-conventional vaccines such as the new developments in DNA-vaccines, or live genetically engineered organisms as vaccines or vaccine constituents, these products require special attention with regard to vectors, immune response, immunological mechanisms and safety considerations, and these aspects are not covered in this document.

The present document does not intend to replace the specific Note for Guidance for influenza vaccines as adopted in March 1997.

Viral-vector based gene therapy, tumour vaccines and anti-idiotypic vaccines such as monoclonal antibodies used as immunogens are not covered by the present Note for Guidance.

For pre-clinical studies, the Note for Guidance on Pre-clinical Pharmacological and Toxicological Testing of Vaccines as well as the corresponding Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines should be consulted.

1.1 Scope of the note

The present Note for Guidance focuses on the clinical evaluation of new vaccines, including combined vaccines as defined above. Within the context of this document new vaccines are those containing antigens not yet described in the Ph.Eur. monographs or WHO requirements, or using a new conjugate for a known antigen, or any new combination of known and/or new vaccines. In general, any change in the composition of a vaccine should be evaluated as to the need to additional clinical evaluation.

2. ETHICAL CONSIDERATIONS

In the design and conduct of vaccine trials, ethical considerations apply as described in GCP (Good Clinical Practice) guidelines. Special attention should be given to the ethical considerations underlying *testing in* special groups, such as children and in particular use of placebo controls or challenge test. In general, every effort should be given to minimising the non-validated use of drugs and the assurance of minimal risk.

See also Note for Guidance on clinical investigation of medicinal products in children.

3. ASSESSMENT OF EFFICACY

3.1 General remarks

Before embarking on the clinical testing of a new vaccine the required preclinical safety and efficacy properties of the vaccine in appropriate animal challenge models (whenever possible) must have been explored and sufficiently established.

Careful consideration should be given in the clinical testing programme to obtain sufficiently consistent data with regard to the appropriate route of administration, dose schedules and age categories of exposed subjects in relation to efficacy of the vaccine in targeted groups. The immunogenicity (humoral and/or cell-mediated immune response) and efficacy of the new product should be appropriately studied. Any use of immunological correlates of protection, e.g. specific antibody titres correlating with protection, must be adequately substantiated in the protocol.

Unless an immunological correlate for protection is fully validated, the primary endpoint in vaccine trials is protection against clinical disease.

Any extrapolation from the clinical efficacy data from a licensed vaccine to a new antigenically similar-vaccine must be scientifically justified. The same holds for the use of known adjuvants and on a case by case basis, for preservatives in these new preparations.

Each new product must be supported by product specific data. The formulation intended for marketing should be adequately tested.

Clinical study vaccine-lots should be well documented in the studies. These lots should be adequately representative of the formulation intended for marketing.

Regional differences within the European Union (EU) and outside the EU area, caused by variability in infection epidemiology, vaccination strategy, demographic characteristics should be explored before initiation of a trial and should be discussed in the protocol.

Potential differences between the antigenic variants of the circulating infective strains of organisms and those of the vaccine should be appropriately addressed. It is the responsibility of the applicant to demonstrate that clinical trial data on efficacy are applicable for the intended target populations.

A single clinical study may not be able to demonstrate efficacy for different populations and areas. Whenever applicable, bridging studies may be considered to allow extrapolation of data from one target population to another.

Extrapolation of these data to other populations or dose regimens requires full scientific justification. Additional trials need to be considered in order to obtain conclusive results. Pharmacodynamic data obtained in clinical trials may assist in extrapolation to other populations or in the adjustment of dose regimens.

Attention should be paid to the fact that populations studied in the vaccination schedules are detailed in the SmPC (Summary of Product Characteristics) text.

These notes are intended to provide guidance for the evaluation of vaccines for the prevention of infectious diseases. They should be read in conjunction with the Directive 75/318/EEC and relevant EC and ICH guidelines.

3.2 Clinical studies

A well-organised dossier on a rational clinical development of a new vaccine based on staged clinical trials from phase I through phase III (to IV) should be provided. It is important to realise that there are not always clear differences between these phases, in particular for phases

II and III. Phase IV studies are usually postmarketing surveillance studies and may have similar design to those conducted earlier.

See the flowchart in the Annex.

3.2.1 Pharmacological studies (phase I-II)

Pharmacokinetic studies are generally not required for injectable vaccines. The kinetic properties of vaccines do not provide information useful for establishing adequate dosing recommendations. However, they should be considered when other routes of administration are claimed, e.g. oral vaccines. The same holds when the vaccine contains novel adjuvants or excipients. For live antigens, the multiplication and distribution of the agent should be investigated.

Pharmacodynamic studies should be performed. Information should be provided on characteristics of the immune response according to the known or presumed activities of the vaccine. Such information may include the level, class, sub-class and function of specific antibody produced, the lag-time for the appearance and duration of adequate antibody titres, the induction of cell-mediated immunity, formation of neutralising antibodies, cross-reactive antibodies, or interactions which might affect the immune system (such as pre-existing antibodies, concomitant administration of vaccines). If an appropriate challenge test exists and is ethically justified, this may be used to illustrate protection against a challenge of the target pathogenic micro-organism.

Studies evaluating immunological interference between vaccine components of a new combined vaccine as well as interaction with respect to adverse effects of the combined vaccine as contrasted with the separate administration of new vaccine component(s) and the established combined vaccines must be provided. Such studies will be performed in the early clinical development of the new vaccine.

Also studies must be provided to evaluate immunological interference between a new vaccine and other vaccines which are expected to be administered simultaneously in the same time period to the target population. Immunological interference between these vaccines as well as safety may need evaluation at simultaneous administration in comparison to separate administration at different time-points.

Pharmacodynamic studies should also evaluate the dose response relationship and provide the basis for dosing recommendation with respect to quantity of antigen per dose and number and timing of initial vaccinations and the possible need for booster vaccination.

When the essential mechanism of protection of a vaccine is cell-mediated this may be difficult to evaluate in pharmacodynamic studies although experimental models exist to explore the pharmacodynamics of the cellular response. In this case dose-finding studies should include appropriate measurement of protective activity in order to elucidate the protection level of the vaccine.

3.2.1.1 Immunogenicity

Immunogenicity data are usually generated in phase I-III of a clinical testing programme. Every effort should be placed in determining the exact nature of the immune response and to find correlations with vaccine efficacy for novel vaccines. In case a serological surrogate could not be shown within the frame of an efficacy trial alternative strategies such as antibodies in pre-disease (subclinical) or acute disease samples should be explored.

When the induction of humoral (specific antibody) immune response to a vaccine is hypothesised to correlate with vaccine efficacy, appropriate consideration should be given to confirm that a clear qualitative and quantitative relationship is determined in the clinical trial. Seroconversion criteria, titre and type of antibody response (type of Ig) and percentage

responders should be adequately defined, described and illustrated.

Presentation of immunological data emanating from the efficacy trial should be extensive, including GMT, median, SD and range of antibodies in both pre-and post-vaccination sera. The serological data should be presented either by high-quality reverse cumulative graphs and/or by dividing the pre- and post-vaccination titers or antibody concentration to arbitrary (or if available protective) levels, e.g. 0.01, 0.1 and 1 IU/ml for diphtheria and tetanus antibodies. The same extensive presentation should be used to determine the similarity of immune response in all subsequent immunogenicity trials in order to allow the assessment of validity of efficacy data to other populations or other vaccine combinations and to support the efficacy of booster-vaccination. Appropriately validated standardised serological methodology should be used.

The protocols should predefine when and how, in cases of vaccine failure, the immunological evaluation of the patient and typing of the infecting micro-organism is performed (e.g. after unblinding or as part of a pre-planned interim analysis).

3.2.2 Pivotal efficacy studies (phase II-III)

Randomised controlled studies are considered the pivotal studies to establish vaccine efficacy. To establish the vaccine efficacy for population based vaccination strategies, community based prospective studies are the method of choice. Pre-exposure studies are preferred for establishing vaccine efficacy in outbreak investigations in populations.

The reasons for performing uncontrolled studies of new vaccines, rather than randomised comparative trials, at any stage of development should be justified. In principle, uncontrolled, open studies may be used only to generate additional information with regard to serological responsiveness (immunogenicity) and the tolerance (reactogenicity) of the vaccine.

For vaccines with a new conjugate, containing a known antigen for which the protective antibody level is established, immunogenicity studies may be more suitable in establishing efficacy. In each case, the absence of studies using clinical endpoints should be justified.

3.2.2.1 Experimental studies (phase III)

The choice and feasibility of randomised controlled confirmatory efficacy trials will depend upon the indication sought, vaccination strategy and type of prophylaxis, e.g. pre-exposure protection or community protection.

For new vaccines with a new antigen or strain with no adequate comparator vaccine, efficacy assessment is always dependent upon the use of an appropriate control. For monovaccines, the control may be one of the following comparators: a true placebo control or a non-true placebo control containing an antigenically different monovaccine. In combined vaccines, administered together in one preparation, the test antigen or strain should be omitted from the control arm of the study.

For vaccines containing a known antigen with a new conjugate, a change in adjuvant, excipient or preservatives, or a new method of administration, the choice for an antigenically similar active comparator may be considered. A clinical trial intended to establish the relative efficacy (i.e. a 2-arm study versus an antigenically similar active control) may be appropriate if the absolute efficacy of the active control vaccine is established, otherwise a 3-arm study (i.e. including a placebo control arm for internal validation) is required. Also factors such as vaccine quality, antigenic variation and vaccination grade of the population will influence the protective efficacy of a vaccine. In these cases an active comparative study may not give an appropriate estimate of vaccine efficacy unless internally validated. When, in these cases, an internal control is not included, this should be justified, e.g. due to severity of disease.

The choice of endpoints, such as disease incidence or immunological surrogate marker values

for protection or both endpoints, depend on whether an established qualitative and quantitative surrogate for protection exists or has yet to be established. When immunological surrogates for protection are not established, studies should be performed in areas where an appropriate impact of active immunisation may be expected and can be captured with a controlled trial setting. For instance, for infant vaccinations studies should be performed in an area of preferably moderate-high endemicity or prevalence where no other means of prophylactic coverage will be used e.g. pertussis, meningococcal-, pneumococcal- and H. Influenzae disease.

For pre-exposure use of certain vaccines, studies should be performed in groups or populations at specific risk in areas with preferably low endemicity e.g. hepatitis A, or low natural long-term protection.

Well-designed randomised controlled studies provide most reliable and accurate information on the vaccine efficacy since relative risks can be calculated. Furthermore, study results are generalisable. Early information on long term protection and insight into the need of booster vaccination may be obtained. However, generally it is not feasible to perform confirmatory trials on booster vaccination prior to licensing. Therefore, commitments must be made at licensing to perform post-licensing sero-epidemiological surveillance studies to establish long term protection, the need for booster vaccination and the serotypic correlation between vaccine strains and wild strains.

When randomised controlled community based studies are not feasible due to the low incidence of the target infectious disease (e.g. a community based prospective study on clinical endpoints for pertussis is unrealistic in an area with a high vaccination coverage against pertussis) or will take decades to establish sufficient data for vaccine efficacy calculations (hepatitis B in neonates), supportive evidence of efficacy can be derived from the secondary attack rate or case control study or observational study. However, for case control or retrospective observational studies in low incidence diseases, extensive prior use of the vaccine is required. This condition is unlikely to be met in development of a new vaccine.

When efficacy in the trial population has been established, data may be extrapolated to other areas, populations or immunisation schedules, on the basis of bridging studies.

3.2.2.2 Secondary attack rate studies

Secondary attack rate studies in households or clusters may be useful in infections with a relatively high secondary attack rate and in outbreaks. In these instances the advantage of this study design is the assumption of uniform exposure between vaccinees (household contact) and the index case. For example, studies in measles have shown that the secondary attack rate in non-vaccinees is generally consistent from family to family, implying that within a household there is generally a uniform exposure. Secondary attack rate studies in clusters are used in urban or semi-urban settings. The set-up is logistically easier than intra-household studies, but comparability of exposure of vaccinees and non-vaccinees is less definite, however, may be improved through randomisation. In the experimental secondary contact studies units of randomisation may include the individual, the household or the cluster under study (like schools). The clusters should be defined operationally in the protocol.

In secondary attack rate studies in households vaccinees and non-vaccinees from several families may be added to determine the overall attack rate in the vaccinated and unvaccinated population, provided that the risk of infection exists for both groups .

However, these studies are subject to bias in many ways, e.g. study design (open label or single blinded, at least partly retrospective) and conduct. All measures taken to minimise bias should be described adequately in the protocol.

Furthermore, these studies do not provide conclusive information on vaccine efficacy because of the population selection, e.g. selection of clusters that do not represent the target population. Although the calculation of odds ratios is possible, this does not provide information on the actual risk of developing an infection with or without active immunisation. Such studies give qualitative and semi-quantitative insight into the relationship between the exposure and the outcome.

3.2.3 Other studies (phase III-IV)

3.2.3.1 Case control studies

Case control studies may be considered useful when prospective controlled trials are not feasible (see section 3.2.2.1.).

Relevant information regarding vaccine efficacy may be obtained from case control studies, especially in those cases where a serological correlate for a specific antibody titre appears to be present. These studies should be performed in well-defined and relevant patient samples. The advantage of these studies is the relatively small-scale set-up and short follow-up period. The value of these studies should be carefully balanced against the need for confirmatory prospective randomised studies.

Such studies can be considered as “supportive” data for the substantiation of clinical efficacy. Such studies can also be part of post-licensing surveillance.

3.2.3.2 Observational cohort studies

Observational cohort studies may be considered in those situations where a randomised controlled trial is not considered ethically justified. The observational study focuses on events, exposures and diseases occurring in the target population during the course of routine living conditions. Using this study design information may be obtained on the vaccine effectiveness, since both direct (vaccine induced) and indirect (population related) protection are evaluated. To further substantiate the vaccine effectiveness data, nested household surveys may be considered, in which a select data collection (e.g. addresses to obtain information on the vaccination status and disease incidence) may be used to minimise bias. The disadvantage of this design is the absence of randomisation. However, the randomisation from the phase III trials may be used to provide background information on long-term protection and/or the need for booster vaccination.

The extent of information gained should be judged from case to case.

4. METHODOLOGICAL CONSIDERATIONS

4.1 Validity of methods for diagnosis

Since in vaccine efficacy studies (phase II-III) the efficacy of a vaccine is determined by the number of breakthrough infections, the validity of diagnosis of infection is one of the most vital aspects in the evaluation of a new vaccine and the methods used should be justified by the applicant. Diagnoses should be described in the protocol, considering both case definitions and case ascertainment.

1 Case definition

Highly specific, validated, equally sensitive methods for case ascertainment and consistent definition of cases should be developed before and applied during the study. This should be a reliable and valid definition. Laboratory confirmation of cases is necessary to validate a clinical case definition.

2 Case detection

It is important to ensure that all efforts to detect cases among vaccinated and unvaccinated populations are equal. If in outbreak investigations the attack rates are high the number of cases in the sample may be sufficient to accurately estimate vaccine efficacy. If the attack rate is low, other surveillance data should be used to gain additional cases and increase precision of the estimate. In secondary attack rate studies all cases in the target age group found in the surveyed household or cluster during the predetermined time period should be included as well as the case, which led to studying the cluster. In case control studies, case ascertainment is the same as described for outbreak investigations, although all cases need not to be detected.

Thus, attention must be paid to the methods used to verify the aetiology of infections, ensuring high specificity of the diagnosis. However, highly specific methods of diagnosis may not always be available or may be highly invasive. In those cases where diagnosis based on strictly defined clinical criteria is used, validation and justification of these criteria must be provided.

4.2 Vaccine efficacy

Vaccine efficacy may be evaluated and assessed either on the basis of clinical (protection) endpoints and/or validated serological surrogate endpoints whenever appropriate. Efficacy of vaccination is usually defined as the reduction in the chance or odds of developing clinical disease after vaccination relative to the chance or odds when unvaccinated. Determination of efficacy by the clinical endpoint without serological confirmation may be acceptable, if clinically justified as stated in the protocol. When it is not feasible to obtain clinical endpoints, appropriate serological data (immunogenicity of the vaccine and natural infection), as determined by an adequately validated method, may be used to support evidence of efficacy. These instances may include situations where it takes a long time to get answers on clinical disease (slow acting viruses/bacteria): in case of multivalent combinations (e.g. the 23 component pneumococcal polysaccharide vaccine) or in low incidence infections.

In all other cases, whenever possible, the endpoints including serological markers should be presented separately.

The formula by which vaccine efficacy is calculated should be clearly defined and validated. These formulae are dependent upon the study design, which, determine the use of relative risks or odds ratios.

Vaccination "failures" should be addressed in detail, if possible with serological and/or microbiological confirmation. When applicable, information on the antigenic match between vaccine strains and circulating strains should be provided, in order to get insight into the possibility of strain selection.

It is the responsibility of the applicant to demonstrate that the use of a certain serological surrogate is valid for short term and long term protection.

There are several surrogate serological tests known to be useful in predicting vaccine efficacy e.g.: diphtheria (toxin neutralising antibody level ≥ 0.01 IU/ml), tetanus (toxin neutralising antibody ≥ 0.01 IU/ml), hepatitis A (neutralising antibody ≥ 10 mIU/ml), hepatitis B (antibody

to HB surface antigen ≥ 10 mIU/ml), rabies (neutralising antibody ≥ 0.5 IU/ml). See further citations in the relevant WHO and Ph.Eur. requirements.

4.3 Sample size

The criteria for determining an adequate sample size of a trial will typically be based upon methodological and statistical considerations; clinical and epidemiological and basic scientific judgement; and may vary from product to product and from one setting to another.

The protocol should include sample size calculations for each primary endpoint (immunogenicity, safety and efficacy whenever applicable). However, immunogenicity evaluations typically comprise a sub-sample randomly selected, if possible, from the initially enrolled population. When immunogenicity is the sole primary endpoint to evaluate efficacy, the sample of subjects for the vaccine in whom established serological markers will be measured should be randomly selected from the target population. In all instances due consideration should be given to aspects such as the appropriate choice of active comparator, placebo control and expected protection rates.

4.3.1 Study design and sample size

Population based prospective controlled studies include community investigations e.g. testing of acellular pertussis vaccine and pre-exposure prophylactic studies, e.g. for hepatitis A. Since community investigations are intended for population based strategies and when vaccine efficacy has to be determined on clinical grounds solely, e.g. pertussis, these studies usually require a large sample size, at least 1000 vaccinees per arm. Furthermore, determination of vaccine efficacy on clinical endpoints in community investigations is only possible in a susceptible population (see below).

The prospective controlled studies in outbreak investigations can be considered confirmatory trials of secondary attack rate studies in clusters. These studies imply “intermediate sized” confirmatory trials. The area under investigation should be specified as well as the period during which the population is followed up (for example hepatitis A). Although sample size is generally smaller than in community investigations, because of the anticipated higher attack rate, each arm usually includes at least several hundreds (to thousands) vaccinees.

When the sole primary endpoint to evaluate efficacy is based on validated serological surrogates the study design generally allows for small-scale set-up (see section 4.4).

In secondary attack rate studies in households or clusters the basic assumption is uniform exposure (i.e. equal level of susceptibility) of vaccinees and non-vaccinees to the index case. Comparability of exposure of vaccinees and non-vaccinees should be taken into account in sample size calculations. To minimise this potential bias of previous exposure the age group studied is generally limited to 9-35 months and efficacy assessment should be limited to a predefined, relatively short term follow up period post vaccination (e.g. 6 months). Long-term follow up may bias vaccine efficacy outcome because of a decrease in infection risk in the vaccinated population compared to the unvaccinated population. In experimental settings, such studies allow a relatively small-scale study set-up.

In case control studies emphasis should be placed upon response measures to avoid bias e.g. matching of cases and controls with respect to age, sex and residence etc. Every effort should be made to get as many cases as possible. The study design generally allows for small-scale set-up. But the numbers chosen should be justified.

4.3.2 Epidemiological and basic scientific judgement and sample size

The feasibility of determination of vaccine efficacy by clinical endpoints as measured by numbers of vaccinees needed is also dependent upon other factors. These include the mode of

spread of the disease in the community, population immunity and infectious capacity of the micro-organism. This is also called the reproductive rate. This can be defined as the average number of persons directly infected by an infectious case during the entire infectious period, when the infectious person enters a totally susceptible population. The opportunity of the infection to spread in the community decreases, either through vaccination, natural infection, or other methods of prevention. This has to be taken into account when determining the proportion of the target population needed and thus the feasibility of using clinical endpoints.

4.4 Statistical criteria

In prospective, randomised controlled studies as well as in observational cohort relative risks may be determined; in secondary attack rate and case control studies odds ratios will be determined. In both instances confidence intervals should be included.

Tests of significance for differences in efficacy between test and control treatments are not an appropriate analysis in non-inferiority trials. In non-inferiority trials the purpose is to show that the efficacy of the test treatment is not inferior to that of the reference treatment by more than a minimum clinically relevant difference δ , which has to be discussed in the protocol. The statistical method of choice for the presentation of the results is as confidence intervals for relative efficacy. Typically the sample size should be such that, if the treatments are equivalent or the test vaccine is superior, there is a high probability (>80%) that the lower limit of a 95% confidence interval for the difference in clinical or serological protection rate (test minus reference) will not fall below the predefined $-\delta$. The precise choice of value is influenced by the prior plausibility of the hypothesis under test and the desired impact of results. For more details on non-inferiority testing see the EU Biostatistical Methodology and Clinical Trials Guideline. In individual trials, δ can often be set to about 10 percentage points, but will need to be smaller for very high protection rates. Ultimately it should be based on clinical judgement and available evidence from previous clinical trials, and should be judged on a case by case basis. It should exclude by a large margin the possibility that the test vaccine is ineffective and should represent a clinical insignificant shortfall in efficacy.

When efficacy assessment in equivalence trials is based upon immunological surrogate parameters the relationship between the surrogate endpoint and the clinical endpoint must be taken into consideration, since this does not necessarily have to be a linear relationship.

Sample size will also depend upon whether an immunological surrogate is known for protective efficacy.

The statistical methodology to be used for each endpoint should be described in the study protocol.

4.5 Duration of follow-up and assessment of outcome

The duration of follow-up, number of visits and interval between visits should be clearly described in the protocol. These aspects are dependent upon the chosen endpoints for the claimed indicated vaccination (disease incidence, immunological marker value and safety parameters) with the used vaccination strategy and novelty of the vaccine, but the follow up should be at least 6 months following the last immunisation. For population based immunisations intended to be given in a vaccination programme follow-up should be at least 1 year following the last immunisation. In addition, post marketing surveillance to ensure long term efficacy assessment will be required.

In pre-exposure vaccinations (such as hepatitis A) the most important follow up periods are during or shortly after the assumed exposure.

Every effort should be made to obtain fully documented follow-up information on as many

patients as possible during and/or after vaccination.

During the follow-up period preliminary information should be gathered with respect to the need for booster vaccination. This information should include both serological evaluation as well as clinical evaluations. In addition, efforts should be made to gain further information on the cell-mediated immunity especially with respect to memory function.

In many instances the question regarding the need for and/or the determination of the interval to booster vaccination has to be also part of a planned post marketing surveillance programme.

For vaccines whereby the immunity is driven by humoral response at least preliminary estimations of the duration of protection should be provided before registration.

5. SPECIAL CONSIDERATIONS FOR COMBINED VACCINES

In all instances the efficacy of each component and the safety of the combination must be established, whether the combination consists of previously licensed or unlicensed vaccines. In principle, such studies should be randomised and controlled, whenever feasible. For both safety and immunogenicity the studies should include 3-arm comparisons of simultaneous administered vaccines at different sites (different limbs) with the combination and separate administration (different times). When the control group (different times) is not included, this should be sufficiently justified.

5.1 Combined vaccines protecting against multiple infectious diseases

When a new vaccine is developed combining two or more different vaccines to prevent multiple diseases, the risk of a clinically relevant adverse interference between the vaccines must be ruled out. This may be based upon serological evaluation, when adequate serological criteria for response (which may include the quality of antibody response) are available and sufficiently validated. Information about each assay used to evaluate immunogenicity should be adequately documented. Consistent use of the most appropriate assays is necessary. Studies of the immunogenicity of all vaccine components in the combination in comparison with that induced by the separate but simultaneously administered individual vaccines should be performed. If a new vaccine consists of established composition and with evidence of no interference among antigens, it should be shown that the addition of one or more new antigens has no effect on the immunogenicity of the antigens in the combination, as well as on the immunogenicity of the newly added antigens. Such studies should be sufficiently powered to rule out clinically meaningful differences (defined and described in the protocol) in the immunological response parameters. The sample size calculation should take into account the similar considerations as those formulated for monovaccines (see section 4.3.). The clinical consequences of any potential differences observed should be evaluated.

When antibody concentrations following the administration of the combined vaccine are lower than those observed following separate administration or simultaneous administration of the individual vaccines at different sites, the applicant should justify that these findings are not clinically relevant. Any change in the dose or dosage scheme for individual components due to such interference should be substantiated.

Also when the cellular immune response is pivotal the monitoring of serological response, whenever possible, can help exploring potential adverse interference.

When a clear surrogate correlate for protection does not exist prospective controlled clinical studies should be performed whenever feasible as described in section 3.2.2.1. When such studies are not feasible (see sections 3.2.2.2 and 3.2.3) alternative approaches may be considered e.g. a secondary attack rate study. Furthermore, if a combined vaccine consists of

components for which well-controlled clinical vaccine efficacy studies are available from adequately detailed publications in the literature these studies may be used in support of the combination product. The generated immunogenicity data in a representative sample of the target population may be used to bridge the existing efficacy data where possible. The latter immunogenicity studies may also be required to demonstrate equivalence in immune response of different vaccination schedules, which could have been used in the latter, published studies and sought vaccination schedule.

When vaccines containing different strains or serotypes of a micro-organism and different vaccines protecting against multiple infectious diseases are developed the recommendations for both types should be considered (see also below).

5.2 Combined vaccines containing different strains or serotypes of a micro-organism

When a combined vaccine consists of multiple strains or serotypes the primary endpoint may be the aggregate of disease cases with all strains or serotypes included in the combined vaccine. The study should be sufficiently powered to make meaningful separate analyses of the prevalent serotypes, that are defined as of major significance to public health in the target area. When useful serological correlates are available these may be used to evaluate the clinical efficacy of the combined serotype vaccine. When limited numbers of strains or serotypes are included in the combination, the limited coverage provided by the vaccine should be justified. When limited numbers of strains or serotypes are studied, the feasibility of extrapolation should be substantiated.

5.3 Vaccines administered simultaneously with combined vaccines

Vaccines developed as monovaccine, however, intended for simultaneous administration with other vaccines (such as H. Influenzae B vaccine with Diphtheria-Tetanus-Pertussis) should be investigated and presented in such a manner that the clinical relevance of the interference can be assessed. However, the studies may be set-up as 2-arm studies, excluding the combined administration. Ideally, the immunogenicity obtained with such simultaneous administration should be evaluated early in clinical development for all components to detect any possible immunological interference. Typically the studies will evaluate safety and interference of the new combination vaccine with one type of simultaneously administered vaccine per indication in a statistically valid manner.

6. ASSESSMENT OF SAFETY OF VACCINES

The safety assessment of a new vaccine containing a new antigen includes information from controlled studies and relevant data from uncontrolled studies.

In the pharmacodynamic studies safety data should be collected in a controlled fashion after single and repeated doses, both with regard to local (e.g. injection site induration) reactions and systemic reactions (e.g. fever, cardiovascular effects, and neurological effects). Specific safety issues emerging from the pre-clinical testing should be monitored and assessed.

For combined vaccines comparative studies with the combined vaccine versus the separate components should be performed. The size of the study groups should be appropriately determined and the difference in rates for common adverse reactions to be ruled out should be specified in the protocol. If blinding of the study is not feasible, the methods to minimise bias should be described. Any influence of differences in injection sites and in the route of administration, e.g. intramuscular versus subcutaneous should be addressed.

All adverse events and reactions (as defined by ICH topic E2A-Clinical Safety Data

Managements: Definitions and Standards for Expedited Reporting) which occurred during clinical trials are collected and recorded.

Reactogenicity will be reported in CRFs (Case Report Forms) using pre-listed terms defined in the protocols, other adverse reactions will be described in free text.

Less frequent and rare adverse reactions will require large sample sizes.

Adverse reactions should be presented in local and systemic reactions, classified according to causality, seriousness, expectedness and severity.

Serious adverse reactions are rare, and are generally not observed in the clinical trial programme. Nonetheless, a large number of subjects exposed to the vaccine are desirable to assess whether such a reaction will occur with a very low probability (if at all) in the target population. If serious adverse reactions possibly related to the vaccine or vaccination do occur in the clinical trial programme the safety profile of the product should be questioned.

An appropriate analysis of the relation of the observed adverse events to the vaccine using standard categories for causality assignment (Causality classification in the European Community, III/3445/91) is warranted when possible. However, considering the fact that vaccines are expected to produce a response, analysis should additionally use the following categories:

- (1) vaccine induced adverse reactions following immunisation: those due to intrinsic characteristics of the vaccine preparation and the individual response
- (2) vaccine precipitated: those triggered due to the receipt of the vaccine but probably would have occurred a later time
- (3) programmatic errors, including GMP errors, administration errors
- (4) coincidental; only temporally related, not due to immunisation.

Targeted monitoring and special studies may be required for certain types of adverse reactions, which can be anticipated for new vaccines on the basis of their relationship to approved vaccines.

Whenever feasible, besides an overall safety comparison, an additional very thorough comparison should be made during the assessment with the appropriate control vaccines e.g. acellular pertussis vaccines vs. whole cell pertussis vaccines.

For rare adverse reactions an active postmarketing surveillance programme will be required.

7. GLOSSARY

Terminology used within the context of the present Note for Guidance:

Booster vaccination	Vaccination given at a certain time interval (at least 6 months) after primary vaccination in order to induce long term protection.
Bridging study	Study designed to extrapolate clinical data of (a) clinical trial(s) population to a target population and immunisation schedule.
Case control study	An observational study in which the exposure to a particular risk factor (the vaccine in the case of vaccine studies) is determined retrospectively, and this exposure is compared between individuals who experience an event (the disease, in vaccine studies), the cases, and individuals who do not, the controls.
Case definition	A case is defined by 3 components. The symptoms from the infection experienced by the patient, sufficient to seek medical care or advice; the diagnosis suspected by the physician; confirmation by the laboratory. All 3 components should be addressed in the formulation of the case definition.
Community investigations	Population based trials in predefined large segments of the population to investigate the impact of a treatment on a preventable infectious disease.
Cohort studies	Retrospective or prospective studies, in which the development of disease or infection or any other relevant event is observed in a defined group of subjects observed over time.
Control	Any comparator suitable for validation of the trial. The comparator may be either an active treatment or a placebo control.
Experimental study	Experimental studies are studies in which the conditions are under direct control of the investigator. Such studies may include randomisation of subjects to treatment or control groups and blinding of subject and investigator to the placement status.
Immunogenicity	Capacity of a vaccine to induce humoral (specific antibodies) and/or cell-mediated immunity.
Internal control	An additional control arm, usually a placebo, which may be required when the efficacy of the active comparator is not adequately established or is known to give inconsistent results.
Observational studies	Observational studies focus on events, exposures and diseases occurring in the population during the course of routine living conditions, not subject to experimental interventions.
Placebo control	A comparator in a vaccine trial that does not include the antigen under study. In monovaccine studies this may imply a true placebo (e.g. saline solution, vehicle of the vaccine), or an antigenically different vaccine. In combined vaccines, this may imply a control arm in which the test vaccine is lacking.
Pre-exposure trial	Prospective trial in a population expected to be exposed to the pathogen under study within a predefined, relatively short, period.

Primary vaccination	First vaccination or series of vaccinations given within a predefined period with an interval of less than 6 months between doses, to induce clinical protection.
Randomisation	To assure that subject populations are similar in test and control groups, a single sample population is randomly divided into groups that receive the test or control treatments. Randomisation avoids systematic differences between groups with respect to variables that could affect outcome. In vaccine trials the unit for randomisation may be either an individual or a larger group of persons (e.g. household, school), provided the confounders are well known and corrected for.
Reactogenicity	Events that are considered to have occurred in causal relationship to the vaccination. These reactions may be either local or systemic.
Reproductive rate	The average number of secondary cases of an infection arising from one single primary case. The measure is inherent to the potential (infectiousness, susceptibility, measures of protection) of a micro-organism to spread from person to person in a population.
Secondary attack rate study	An outbreak investigation in a defined susceptible population. The population to be studied is either a cluster (in an urban or semi-urban setting) or a household (or family). Outbreak investigations may be observational or experimental. In the experimental design the unit of randomisation may be either the individual, a household or family or a cluster.
Seroconversion	Predefined increase in antibody concentration, either considered to correlate with the transition from seronegative to seropositive or considered to be a clinically significant increase of pre-existing antibody levels, providing information on the immunogenicity of a vaccine.
Serological surrogate	Predefined antibody concentration correlating with clinical protection.
Seroprotective titre	Antibody titre assumed to predict clinical protection
Vaccine (protective) efficacy	The capacity of a vaccine to induce clinical protection in the studied population. Vaccine efficacy measures direct protection (i.e. protection induced by vaccination in the vaccination population sample). Vaccine efficacy is calculated through incidence rates in cohort studies or odds ratio's in case control and secondary attack rate studies, according to the following formula:

$$VE = \left(\frac{I_{uv} - I_v}{I_u} \right) \times 100\% = 1 - \frac{I_v}{I_u} = (1 - RR) \times 100\%$$

I_u = incidence in unvaccinated population, I_v = incidence in vaccinated population, RR = relative risk (in case control or

secondary contact studies to be replaced by odds ratio's (OR)).

Vaccine effectiveness

The protection rate due to vaccination in a certain population. Vaccine effectiveness measures direct and indirect protection (i.e. protection to non-vaccinated persons by the vaccinated population). Vaccine effectiveness is also determined by vaccination coverage, correlation of vaccine strains with circulating strains and selection of strains not included in the vaccine following introduction of the vaccine in that population.

Vaccine failure

The onset of infection, biologically confirmed, in a subject who is supposed to be protected, following completion of age-appropriate immunisation recommended by the manufacturer.

8. ANNEX - FLOW CHART

Nature of Antigen	Surrogate available	Efficacy Feasible/ ethically justified?	Efficacy evaluation	Surveillance***
New Antigen No Active Comparator	PCRT NO ¼ —¼ ¼ ¼ ¼ ¼ ® YES ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ® Immunogenicity ¼ ¼ ¼ ¼ ¼ ¼ ® OCS (SART / CC)			
	NO ¼ ¼ ¼ ¼ ¼ ¼ ® NO ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ® Immunogenicity ¼ ¼ ¼ ¼ ¼ ¼ ® OCS CC and/or SART			
New Antigen/Strain/ Serotype Known Active Comparator	YES¼ —¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ® Immunogenicity ¼ ¼ ¼ ¼ ¼ ¼ ® OCS**			
	NO ¼ —¼ ¼ ¼ ¼ ® YES ¼ ¼ ¼ ¼ ¼ ¼ ® (P)CRT-Immunogenicity ¼ ¼ ¼ ® (OCS)* (SART/CC)			
	NO ¼ ¼ ¼ ¼ ¼ ¼ ® NO ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ® Immunogenicity ¼ ¼ ¼ ¼ ¼ ¼ ® OCS CC and/or SART			
Known Antigen New Conjugate/Adjuvant	YES¼ —¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ® Immunogenicity ¼ ¼ ¼ ¼ ¼ ¼ ® OCS**			
	NO ¼ —¼ ¼ ¼ ¼ ® YES ¼ ¼ ¼ ¼ ¼ ¼ ® (P)CRT-Immunogenicity ¼ ¼ ¼ ® (OCS)* (SART/CC)			
	NO ¼ ¼ ¼ ¼ ¼ ¼ ® NO ¼ ¼ ¼ ¼ ¼ ¼ ¼ ¼ ® Immunogenicity ¼ ¼ ¼ ¼ ¼ ¼ ® OCS CC and/or SART			
			PHARMACODYNAMIC EVALUATION	

(P)CRT: (placebo) controlled randomised trial

SART: secondary attack rate trial

CC: case control study

OCS observational cohort study

*: supportive trials

**: necessity of surveillance trials depends upon the extent of the modifications of the vaccine

***: the need for a surveillance should be judged on a case by case basis