studies are often required to obtain definitive evaluations. If the answer to the scientific question under study will be final, e.g. the determination of the optimal dose to be used in a large phase III efficacy trial, then the phase II trial should be rigorously designed, adequately powered and appropriately analysed to provide conclusive information.

For a live attenuated vaccine, continued active monitoring of specific parameters into the second and third week, or more, post-vaccination is recommended. The duration of follow-up may be determined by a number of factors that may have been identified in the phase I studies including the degree of shedding, transmission and potential reversion characteristics.

The immune responses to vaccine antigen(s) should be carefully evaluated and are a critical part of phase II clinical studies. Such studies are intended to further characterize immune responses elicited by a particular immunogen thought to be relevant to protection, such as level, class, subclass and function of the specific antibodies produced, as well as appearance and duration of adequate antibody titres. Other relevant information such as presence of neutralizing antibodies or cross-reactive antibodies, formation of immune complexes, cell mediated immunity and any interaction that might affect the immune system (e.g. preexisting antibodies, concomitant administration of another vaccine or drugs) should be recorded.

The percentage of responders should be defined and described based on predefined criteria for assessing the immune response (e.g. antibodies and/or cell-mediated immunity). For vaccines for which the immunological correlates of protection are not known, the immunological profile should be studied in detail. Subjects who fulfil immunogenicity criteria (often seroconversion) are regarded as responders (having seroconverted) and the result of an immunogenicity study includes the proportion of responders. For the validation of an immune response, sera should be collected from all participants at regular, predefined intervals throughout the study period. For certain vaccines (e.g. nasally administered vaccines) the investigators should consider whether samples from other body fluids should also be collected. Immunological data from phase II trials should be documented, including geometic mean titre, median, standard deviation, and the range of antibodies in pre and post-vaccination sera (*63*). In the case of vaccines for which the end-point is the induction of antibodies, the immunological data should be presented by dividing the pre- and post-vaccination titres, or antibody concentrations according to arbitrary (or, if known, protective) antibody levels (e.g. 0.01, 0.1

and 1 IU/ml for diphtheria and tetanus antibodies). Presenting reverse cumulative distribution curves may provide additional insight (*64*, *65*). When available, standardized assay methodologies should be used, and details may be found in WHO recommendations, European Pharmacopoeia monographs or US Food and Drug Administration documents. Each assay should be fully documented and consistent use of a validated assay is essential.

B.7 Phase III studies

The phase III studies are large-scale clinical trials designed to provide data on vaccine efficacy and safety. These studies are usually performed in large populations to evaluate efficacy and safety of formulation(s) of the immunologically active component(s). In large-scale efficacy studies of this type, that may enroll many thousands of subjects, serological data are usually collected from at least a subset of the immunized population at pre-defined intervals. It is also important to collect serological data from all persons classified as vaccine failures.

When vaccines containing the same antigens are already in common use and/or the incidence of disease is very low, it may not be feasible to perform a formal study of protective efficacy. In such instances, the phase III trials, although involving larger numbers of persons than previous phases, will be confined to the evaluation of immune responses and comparison with any recognized correlates of protection. However, sometimes there are no established and unequivocal immunological correlates of protection. In such cases, it is important that some attempt should be made to estimate the effectiveness of the vaccine after its licensure and widespread introduction. Phase III trials involve a larger number of subjects than were included in the earlier phases of development and, thus, provide expanded safety assessments.

The duration of follow-up should be determined taking into account the type of vaccine and other relevant factors (e.g. disease incidence, characteristics of immune response to vaccine, and anticipated and safety profile of the vaccine.)

Whether or not a prophylactic vaccine is ultimately accepted as a general public health measure depends upon the availability of clear and definitive evidence that the vaccine is safe and actually able to prevent the infectious disease in question or to significantly reduce the adverse consequences of the disease.

B.7.1 ***Considerations for formal trials of protective efficacy***

Vaccine efficacy is the percentage reduction in the incidence rate of a specific disease in vaccinated individuals as compared to that in unvaccinated individuals. Vaccine efficacy measures direct protection (i.e. protection induced by vaccination in the vaccinated population sample).

B.7.1.1 Trial design

Two general approaches can be applied to efficacy studies; they can be either experimental studies or observational studies. The gold standard for assessing the prevention of disease or infection in a phase III trial is the prospective randomized double-blind controlled trial of protective efficacy. This design will control for other variables that might affect disease risk and avoids potential bias in the assessment of end-points. Thus this design maximizes the chance that a difference in disease incidence between two equivalent groups is due to a true effect of the vaccine being evaluated. However, in certain circumstances other approaches may be necessary. Great care should be taken when designing a vaccine trial to maximize efficiency and to eliminate bias. Observational studies of efficacy or effectiveness are usually part of phase IV post licensure studies.

B.7.1.2 Randomized double-blind controlled trials

The most effective efficacy trials are double-blind, randomized and controlled. This design controls for other variables that might affect disease risk by prospectively randomizing groups being studied. Double-blinding is necessary to avoid bias in the assessment of endpoints. The choice and feasibility of blinded, randomized-controlled trials depends on the vaccination strategy and on the demographic and epidemiological characteristics of the study population. The following approaches may be used:

— prospective cohort studies for population-based vaccination strategies; and
— pre-exposure cohort studies in-groups at risk of the target infection (e.g. vaccination for travellers).

A double-blinded evaluation of disease outcomes minimizes potential ascertainment bias and, therefore maximizes the chance that a difference in disease incidence observed between two equivalent groups is due to a true effect of the vaccine being evaluated.

Randomization is necessary to avoid bias in the assignment of the participants to one of the study groups and it permits statistically valid comparisons to be made between different arms of a study. It allows

the detection of small differences between vaccines and comparators; this is particularly important when an active control is used. Non-randomized study designs such as the use of historical controls or case–control studies allow only larger differences to be detected. If possible, these non-randomized approaches should be avoided in phase III trials.

The unit of randomization is usually the individual included in the trial and this is ideally the unit of statistical analysis. In some situations, however, it may be necessary to randomize on the basis of clusters or groups, e.g. school, geographical or political region (*66*). It is important to specify the randomization procedures and to adhere to them. Failure to do so may lead to biased results. Every effort should be made to use randomized well-controlled designs for phase III trials. However, such studies can be technically difficult and the decision to undertake them should be made on a case-by-case basis.

B.7.1.3 Other approaches for obtaining efficacy data

Several alternative types of study may be considered, depending upon the incidence and epidemiology of the disease of interest, the characteristics of the population and the expected efficacy of the vaccine or prophylactic agent. However, the use of designs other than double-blind randomized-well controlled trials to provide efficacy data is allowed only when fully justified. The possible alternative approaches include:

— secondary attack rate study, or household contact study (which can be randomized);
— uncontrolled, open studies (used only to collect additional information on serological responsiveness and tolerance);
— observational cohort studies; and
— case–control studies.

Secondary attack rate study

A secondary attack rate study is a specific type of pre-exposure cohort trial that usually requires smaller sample sizes than other randomized controlled trials. This may be the method of choice in studies of infections with a relatively high secondary attack rate in closed communities and/or susceptible populations (*53*, *67*). The unit to which the intervention is applied may be the individual, family (household) or community (environment) and the unit of randomization will correspond with this. Randomization of groups or clusters rather than of individuals may be preferred in the following situations:

— when a vaccination programme is to be conducted in a geographical area or community
— when it is logistically easier to administer the vaccine to groups than to individuals; and
— when the purpose of the vaccination is to reduce transmission of the infection, where the unit is the "transmission zone" (the area in which humans, vectors and intermediate hosts interact and share a common pool of pathogens).

Groups of subjects (or clusters), the population and the geographical area under investigation should all be defined in the protocol. Data regarding the presence of infecting pathogens and their attack rates are essential. The follow-up period for subjects after contact with the index case may be short; as a minimum it should cover the assumed incubation period and infectious period of the index cases and secondary contacts. The inclusion period for new cases and controls and their contacts should be set at a maximum of 6 months following the detection of the first case. Inclusion over a longer period may introduce bias in favour of vaccine efficacy, because the exposure to the infecting pathogen and thus the risk of infection will be reduced in the vaccinated groups or clusters compared with that in unvaccinated groups or clusters (*54*).

Observational cohort studies

Supportive evidence may be obtained from observational cohort studies if randomized-controlled trials or secondary attack rate trials are not ethically justified, or are not feasible due to low incidence of the disease or there is a requirement for long-term follow-up for the calculation of efficacy. Such studies provide an estimate of the value of a vaccine for operational purposes.

Observational cohort studies in a clinical programme for marketing approval may be considered in those unusual situations in which a double-blind randomized controlled trial is not ethically justified or where the clinical end-point requires long-term follow-up (e.g. hepatitis B vaccination in neonates (see B.9.3.1)), or where the number of individuals is too large to follow up (*69*). However, the absence of randomization is a major limitation (*70*). Where the results of these observational cohort studies are the principal or only evidence of efficacy, careful assessment of the quality of the study and the strength of its results is needed. Seeking the advice of experts in the conduct and evaluation of such studies is recommended. In all cases,

the use of supportive studies should be justified and their relevance to the investigation in question considered.

Case–control studies

Case–control studies may be useful when prospective controlled trials are not feasible due to low incidence of disease (see also case–control studies, section B.9.3.2).

B.7.2 *General considerations for efficacy trials*

B.7.2.1 Size of trial

A vaccine efficacy trial may be based on clinical end-points, incidence of the infection (as in the case of HIV) or, if they exist, on immunological correlates of protection. Efficacy trials based on clinical end-points often require large samples; possibly thousands of subjects in each arm. Large numbers of subjects are needed for the precise estimation of vaccine efficacy if the incidence rate of the disease in the study population is expected to be low. For diseases with a higher incidence (e.g. influenza), smaller sample sizes will often suffice. When an immunological end-point that correlates with clinical protection is used as the primary efficacy end-point, the number of subjects required per arm to provide a statistically adequate evaluation may be considerably smaller e.g. several hundreds per group (see Correlates of protection B.7.2.3). In the case of large trials (e.g. 10000–50000 subjects) it may take many months to recruit the subjects who might then need to be followed up for a further 2 or 3 years. Large field trials of this type may simulate conditions in clinical public health practice and evaluate large numbers of subjects in a heterogeneous population. However, trials of this size and duration may be logistically difficult. In all cases, the applicant should provide adequate justification of the size and duration of the trial.

B.7.2.2 Choice of control

The choice of control depends on a number of factors as described below and should always be justified. A "placebo" control in vaccine trials usually denotes the use of a comparator arm that does not include the antigen(s) under investigation. If the antigen of interest is incorporated into a combination vaccine, the control arm may utilize a licensed vaccine that contains all the same antigens except that relevant to the efficacy evaluation. A control arm may also be a vaccine (usually already marketed) indicated for a different infectious disease(s). Finally, an active control is a comparator vaccine indicated for the same infectious disease(s).

Placebo control

Demonstrating the protective efficacy of a new vaccine always requires an appropriate control. For monovalent vaccines, an inert placebo or a vaccine that protects against another disease, but gives no protection against the target disease may serve as the control. Combination vaccines involving a new component for a new infectious disease indication require omission of the new component of the vaccine in the control arm of the study. If the new component is an already-licensed vaccine, or one for which efficacy and safety have already been demonstrated, a placebo-controlled study may not be necessary. The new component may be studied in an interference trial, comparing the simultaneous, but separate, administration (at two different sites of administration) of the new component with the combined administration of the combination vaccine with the new component.

Active control

Vaccines containing a new antigen, or an established antigen with a different formulation (e.g. liquid versus lyophilized; changed adjuvant, excipient or preservative; changed dose of antigen) or that involve a new method of administration (e.g. aerosol as opposed to intramuscular administration of an influenza vaccine) may be investigated in a comparative study using an antigenically similar active control vaccine on which adequate information is available (e.g. stability data).

A placebo control arm for internal validation should be considered when there are factors that may influence the stability and validity of the efficacy measure of the active control, such as vaccine quality; antigenic variation; vaccination coverage and other protective measures, or demographic; epidemiological; socioeconomic and other characteristics of the population.

B.7.2.3 Correlates of protection

In clinical trials where prevention of disease is used as an end-point, considerable effort should be made to establish immunological correlates of protection, in addition. Such correlates are also useful, and may be necessary, for situations in which the conduct of clinical trials using prevention of disease as an end-point cannot be practically or ethically justified. Nevertheless, it is important to recognize that correlates of protection may be difficult or impossible to define.

The following section describes a simple definition of correlates of protection. Immune correlates of protection may be population-

based or individual-based (*71*). Validated and standardized laboratory methods for serological assays are essential.

A commonly used measure of population-based correlates of protection requires the identification of a level of antibody that is achieved by most of the subjects in a protected group (i.e. vaccinated) and is not achieved by the majority of a susceptible group (i.e. unvaccinated). The level of protection correlated with the antibody level of vaccinnees is the vaccine efficacy measured in the phase III trial. For a population-based correlate it is only necessary to measure immunogenicity in a representative and statistically adequate sample of the vaccinated and unvaccinated phase III cohort.

The individual-based correlate of protection involves the measurement of pre-immunization and at least one post-immunization antibody level(s) in all study subjects and relating this to whether they subsequently develop the disease. The objective is to identify a threshold level in a vaccinee that predicts protection. For an individual-based correlate, it is necessary to measure post-immunization antibody levels in the entire phase III cohort. An alternative approach for those subjects who have a defined exposure may based on the measurement of early post-exposure antibody levels before boosting.

Immune responses should always be evaluated as part of a phase III clinical protection study with the aim of identifying immunological correlates of protection. For such an evaluation to be clinically meaningful, validated standardized assays are essential. Methods for the validation and standardization of immunological (antibodies and cell-mediated) correlates of protection should be developed and are vital for ensuring comparability of data between one trial and another. To correlate humoral immune responses to a vaccine with protective efficacy, the qualitative and quantitative relationships should be determined. The recommendations concerning the evaluation of immune responses described in phase II (B.6) should also be applied in clinical protection trials.

B.7.3 *Duration of protection and need for booster vaccinations*

Randomized controlled trials may provide an early indication of likely long-term protection and the need for booster vaccination(s). In addition to the course of antibody response and its relation to clinical outcome, longer-term follow-up of antigenically new vaccines should include critical characteristics of the vaccine that serve as prognostic factors for sustained protection. Therefore, in addition to studying the quality and dynamics of the antibody response, informa-

tion should be obtained on the relative importance of antibody titre, the extent of seroconversion and the induction of immunological memory.

When efficacy trials are completed, controlled follow-up of the entire study population (or a subset), which may extend into the post-licensure period, provides the best opportunity to define with confidence the serological correlate(s) of protection, and the need for, and the timing of booster vaccination(s). If efficacy studies were not possible, subsets of recipients may be followed over time for measurement of serological parameters. However, if there is no established correlate of protection, and if induction of memory is thought to be an important component of immunity, these studies may be inconclusive. For the determination of long-term protection and the potential need for booster vaccination, postmarketing serosurveillance studies may be necessary as it may not be possible or appropriate to prolong a trial beyond the point at which efficacy is established.

B.7.4 ***Safety evaluations in phase III trials***

Safety evaluation during clinical development and prior to marketing authorization describes and quantifies the safety profile of a vaccine over a period of time, in a manner that is consistent with the intended use. The safety evaluation should include all subjects enrolled in all trials who receive at least one dose of vaccine, and safety surveillance should begin from the start of enrolment. Data on comparisons with antigenically similar active controls (vaccines used to prevent the same infectious disease) should be provided, if available. Safety issues identified during preclinical testing should be specifically addressed in the phase I, II and III clinical trials. Special considerations should be given to the safety concerns raised in animal studies and to environmental concerns related to vaccines based on genetically modified organisms (*72*).

Frequent adverse events must be thoroughly investigated and special features of the product explored (e.g. clinically relevant interference with other vaccines or drugs and factors leading to differences in effect, such as age or epidemiological characteristics). Obtaining such evidence is often the most difficult task of clinical research and requires large-scale randomized trials that employ clinical, epidemiological, biostatistical and laboratory methods. It is important to have a prospective definition and an order of prioritization for adverse outcomes. The difficulty of conducting such trials is usually determined by the incidence of infection and disease and the ability to establish a specific clinical or laboratory diagnosis for the disease in

question. This, together with the expected vaccine efficacy, is what determines sample size.

Randomized studies must have sufficient power to provide reliable rates of common (>1/100 and <1/10) adverse events, and to detect less common, but not necessarily very rare (<1/10000) adverse events (*30*).

For the earlier phases of the study, a specific monitoring plan with a timetable and methods should be specified in the protocol for all subjects (see methodological considerations). When adequate safety data are available from phase I and II trials, it may be acceptable in the phase III study to actively monitor only a subset of subjects (e.g. several hundred per group) to quantify common and non-serious local and systemic events in the trial participants. For the rest of the phase III participants, active monitoring could focus on the identification of significant and/or unexpected serious events (e.g. hospitalization and death).

B.7.5 ***Serious adverse events***

A serious adverse event is an event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent disability or incapacity, or is otherwise life-threatening in connection with the clinical trial. All reported serious adverse events should be described in detail and the following information recorded:

— patient's study number or identification number;
— study identification;
— type of adverse event;
— how long after the vaccination the adverse event occurred;
— patient characteristics, including any underlying diseases, concomitant vaccinations or drugs;
— actions taken, e.g. therapy administered; and
— course of the adverse event including duration, outcome and investigator's assessment of causality.

The possibility of biological plausibility and/or a causal relationship with the vaccination should be considered and investigated in every case, although attributing causality is often difficult for events that occur anyway in the study population background (such as sudden infant death syndrome). Active monitoring of serious adverse events reported after completion of immunization is of major importance, because serious adverse events should be evaluated following a specific pattern.

Prior to licensure, both the applicant and the regulatory authority need to consider whether any reports of adverse drug reactions raise sufficient concern to warrant a suspension (perhaps only temporary) of product development. Additional clinical safety studies may be needed to confirm the relationship between the vaccine and the adverse event, and to establish precise incidence.

The duration of monitoring of study subjects following a serious adverse event depends upon the specific characteristics. Standard case report forms should be drawn up and used to record information on adverse events. Such forms should be used from phase I onwards.

Some serious adverse events following vaccination may be too uncommon to be observed in clinical trial programmes undertaken for marketing approval. Therefore, to obtain a more precise insight into the risk–benefit balance of the vaccine, a postmarketing surveillance programme should be implemented. In addition, specific postmarketing studies are often performed.

B.8 Bridging studies

Bridging studies within the context of this document are studies intended to support the extrapolation of efficacy, safety and immunogenicity data from one formulation, population, formulation and dose regimen to another. The need for performing bridging studies should be considered carefully and justified in the protocol. The end-points for clinical bridging studies are usually the relevant immune responses and clinical safety parameters.

Various methods may be used, depending on the purpose of the study. These are considered below.

B.8.1 *Design and extent of a clinical bridging study*

The clinical bridging studies (to support comparability with respect to the manufacturing process, change in product composition, or a new dose, route or schedule for immunization) should ordinarily be randomized controlled trials. As a minimum these studies should have adequate power to establish comparability of the relevant immune responses (see non-inferiority, section B.3.3.2) and to detect common adverse events. Additional comparative safety data may be needed to support extensive changes, such as a change in antigen composition in a new combination vaccine.

Clinical bridging studies to support extrapolation of efficacy data for a vaccine from one population to another are not randomized. However, for the outcomes to be valid it is important to minimize relevant

confounding variables. The composition and manufacturing process of the vaccine administered to study subjects should be as similar as possible (e.g. using the same lot for all subjects if available). The nature and extent of a bridging study are determined by the likelihood that vaccine efficacy may vary according to ethnic factors, manufacturing changes or changes in dosing schedule. Such studies are not required when it is sufficiently clear from pharmaceutical and preclinical experience that a change in the manufacturing process will not alter clinical efficacy or safety (e.g. specifications for quality control and lot release are not changed and therefore physicochemical characterization may be sufficient).

A controlled immunogenicity study may suffice (provided the serological correlate for clinical protection is validated) if regions are ethnically dissimilar, provided extrinsic factors are similar. An immunogenicity study will also help to select the appropriate schedule (i.e. the most protective) taking into account the incidence of the disease to be prevented (*73*). Controlled bridging trials using clinical endpoints are necessary when there has been a change of manufacturing process or manufacturing site resulting in a new product, the preclinical efficacy and safety data relating to the already-licensed product are no longer applicable; and a serological correlate for protection is not established.

Such studies would also be required in the target region when:

— the vaccine may be influenced by ethnic differences in the target population, and extrinsic factors are dissimilar;
— there is uncertainty regarding the appropriate dose regimen because local immunization schedules and/or antigenic doses differ from those used in trials conducted elsewhere;
— there is insufficient confidence in accepting the results of randomized controlled trials carried out elsewhere; or
— the vaccine is antigenically new in the region of the target population.

To minimize confounding factors related to the assays, the sera from different groups should be tested at the same time using the same assays, personnel and laboratory conditions. For studies that are not randomized or are not blinded with regard to subject enrolment (e.g. population bridging studies), special efforts should be made to avoid bias in sample testing. This may be achieved by appropriate coding of samples which will avoid any identification that distinguishes a separate group and sequential testing by group.

B.8.2 ***Situations in which bridging studies may be required***

B.8.2.1 Bridging studies for change in manufacturing process

Changes made to the product composition (e.g. adjuvants or preservatives) or manufacture (process, site or scale) after the efficacy trial and prior to approval, or after licensing, may have a significant impact on safety and/or efficacy. Any proposed change in the production of a vaccine must be shown by the manufacturer to result in a product equivalent to that used in preclinical (or earlier clinical) testing. Such changes should be evaluated on a case-by-case basis to determine the supporting data required to demonstrate comparability of the "new" product with the previous version. An additional clinical study comparing the new version to the previous versions may or may not be required.

B.8.2.2 Bridging studies for new dosing schedules

Comparability with the original vaccine is also a concern when changes have been made in the immunization schedule, dose and/or route of administration (e.g. change from subcutaneous to intramuscular administration). In most cases, these changes should be supported by a clinical bridging study. The vaccine should be studied in the most conservative situation (the most restrictive), i.e. where the least response is expected. The most restrictive schedule should be applied in the initial clinical trials (youngest age at first dose, and smallest interval between doses), to make extrapolation to other schedules possible. This approach will allow the extrapolation to less conservative vaccination schedules without additional trials. For example, it is easier to extrapolate from a 2, 3, 4 schedule to a 3, 4, 5 schedule than the other way around.

B.8.2.3 Bridging studies for a new population

There are many situations in vaccine development where a new population has important differences from the trial population in which efficacy was established. The ability to extrapolate the data is particularly important when it is not feasible to repeat an efficacy trial with clinical end-points.

Population bridging studies address the concern that the safety and/or efficacy profiles of a vaccine in a particular target population may differ from those observed in the population studied in the original efficacy trial. The question of efficacy may be addressed by showing that the relevant vaccine-elicited immune response in the new population is similar to that in the population studied in the original efficacy trial. Thus, retaining sera and other relevant samples from the original efficacy trial for such comparisons is important, and this

requirement should be taken into account in the planning of efficacy trials.

Clinical bridging studies are justified only when ethnic or other factors specific to the target population exist, and when the studies do not unnecessarily duplicate clinical studies or delay the supply of important vaccines to populations requiring them. Ethnic factors may be genetic, physiological (intrinsic), or epidemiological, cultural and environmental (extrinsic). Cultural characteristics include the nature of the health care infrastructure and available resources (*21*).

B.8.2.4 Bridging studies for safety

A bridging study for safety may be necessary when there are special safety concerns in the target population.

- Bridging efficacy studies may provide safety data when the power of the study is sufficient to assess the rates of common adverse events. A limited safety study might precede the clinical bridging study to ensure that serious adverse events do not occur at a high rate.
- A special safety study is required if an efficacy bridging study is not needed, or when the efficacy study does not provide adequate safety information, including when:
  - — there is an index case (the individual in whom the event was first reported) or cases of a serious adverse event in foreign clinical data (generated outside the target region);
  - — there are differences in reporting of adverse events elsewhere;
  - — insufficient data on safety in the target population are available from an efficacy bridging study;
  - — the safety profile cannot be extrapolated from foreign data to the target population; or
  - — immunization schedules and/or antigenic doses differ from those used in foreign trials.

B.9 Post-licensure studies and surveillance

Following licensure, when a vaccine is in use, monitoring of its efficacy, safety and quality is referred to as postmarketing surveillance or postmarketing studies (phase IV studies). The purpose of these studies is to monitor the performance of a vaccine in the large target population under conditions of routine use, to detect adverse reactions and to monitor efficacy and effectiveness. In order to obtain more accurate estimates of adverse events and of effectiveness than those from phase III studies, active surveillance and phase IV studies using carefully designed surveys are used. Resource constraints

usually limit such surveys to a subgroup of the population, although for rare diseases it may be necessary to survey the entire population to obtain statistically valid data. Postmarketing studies are planned in study protocols. Although occasionally the designs may be as used in prelicensure trials, in most cases phase IV studies are set up as observational cohort or case–control studies. Whereas phase I, II and III studies make every attempt to standardize subjects, immunizations, evaluations and laboratory studies, it is usually impossible in phase IV studies.

Postmarketing surveillance and studies may be conducted to investigate:

— the optimal use of a vaccine (e.g. age at vaccination, simultaneous administration of other vaccines, changes in the vaccine strains and interchangeability of vaccines);
— efficacy in certain risk groups (e.g. the elderly, immunocompromised patients and patients with certain diseases); and
— maintenance of long-term efficacy and monitoring of long-term safety.

To ensure adequate postmarketing surveillance marketing authorization holders should be committed to presenting a postmarketing surveillance programme at licensure and all national regulatory authorities should endeavour to put in place a system for pharmacovigilance for vaccines. The outcomes of surveillance (assessments of effectiveness, adverse events and quality) should be reported to the national authorities and/or the marketing authorization holder, and they should be published.

Postmarketing surveillance programmes should be appropriate to the disease epidemiology, infrastructure and resources in the target area. Essential standards of efficacy, safety and quality should always be defined before initiating a postmarketing surveillance programme and the programme should include assessment of:

— the impact of the target disease (morbidity and mortality);
— potential of the disease to cause an epidemic;
— whether the disease is a specific target of a national, regional or international control programme; and
— whether the information to be collected will lead to significant public health action.

Ideally, a postmarketing programme should be based on criteria set for a particular vaccine as a part of marketing approval. The essential standards for these should always be defined. To ensure that an

intervention is conducted to an acceptable standard, to identify areas where special attention is required and to ascertain (in cases of vaccine or programme failure) the possible reasons for this failure, each step should be carefully monitored and described in protocols. Important applications of postmarketing surveillance are in the early stages of use of a novel vaccine, or when circumstances change (e.g. the emergence of new antigenic variants of a pathogen) and doubts are raised about the continuing efficacy of the current formulation.

B.9.1 *Safety evaluation*

Postmarketing surveillance may be the only means of detecting long-term or acute events that occur too infrequently to have been revealed by clinical trials. Under specific circumstances active postmarketing surveillance or phase IV studies should be considered to determine the incidence and significance of infrequent and rare emerging serious events following immunization with the vaccine under investigation. With respect to safety, the intent of a phase IV study is to detect the rarer or unexpected events that may not have been seen in the smaller phase II or phase III studies because of their limited statistical power. Rare events are often idiosyncratic; a causal relationship is difficult to establish and this usually cannot be done prior to licensure.

Surveillance for the collection of safety data may be conducted by active or passive processes, and may be directed at an entire population or at a subgroup. In practice, a mixture of these processes is often used. Voluntary reporting of adverse events (passive surveillance) is the most often used. It is effective in detecting severe or lethal events and unusual clinical responses. The true rate of incidence of adverse events, particularly of those that do not have distinctive manifestations, is likely to be considerably underestimated.

Targeted studies of a specific adverse event are usually case–control studies or retrospective studies on exposure cohorts linked to historical controls (*74*). In retrospective exposure cohorts the event of interest can be studied in a controlled setting using sampled historical data identified prospectively. Postmarketing surveillance for safety evaluation should include information from all possible sources. Databases linked to large patient cohorts are a valuable source of information for investigating serious adverse events (*75*). Collecting data on safety using a structured, planned postmarketing surveillance study may be set as a condition for marketing approval.

B.9.2 *Evaluation of vaccine effectiveness*

Following the evaluation of efficacy in a randomized controlled phase III clinical trial, the effectiveness of a new vaccine in routine practice should be determined (*76*). Studies of effectiveness measure direct and indirect protection (e.g. protection of unvaccinated persons by the vaccinated population (herd immunity)). Vaccine effectiveness is affected by a number of factors, including:

— vaccination coverage of the population;
— immune status of the population;
— correlation of strains used in vaccine production with circulating strains; and
— The incidence of disease due to strains not included in the vaccine following introduction of the vaccine in that population.

If conducted consistently over a prolonged period, postmarketing surveillance allows the longitudinal assessment of efficacy under a range of conditions, and it may disclose variations in vaccine quality. The duration of follow-up of subjects in the postmarketing programme should be described in a protocol. Implementation of an immunization programme in a certain population may necessitate the development of a structured plan for postmarketing serosurveillance to identify changes in disease epidemiology in the target population over time. This may include evaluation of:

— the impact of the programme, through analysis of reported vaccine failures, and (if applicable) assessment of why disease is still occurring;
— whether new immunization strategies are necessary; and
— possible harm caused by replacement disease following the intervention (e.g. other serotypes replacing the serotypes in the vaccine).

A protocol for serosurveillance should be presented at the time of marketing authorization, or implementation of a vaccination programme. A structured plan for executing the programme should be presented, including information on participating institute(s) and intervals of reporting (usually every 6 months, for 5 years).

B.9.3 *Study design*

B.9.3.1 Observational cohort studies

The evaluation of the benefit of a community-based immunization programme requires large-scale surveillance. An observational cohort study, directed at the events, exposures and diseases occurring among vaccinated and unvaccinated members of the target

population under normal conditions may provide an estimate of vaccine effectiveness.

In non-randomized studies, nested household surveys in a random sample of the study population may minimize bias. In some cases randomization from phase III trials may be continued concurrently.

Observational cohort studies may require community-wide sampling. The chosen sample size will depend upon the characteristics of the intervention applied (i.e. whether risk-group intervention, community intervention or traveller immunization).

B.9.3.2 Case–control studies

Case–control studies should be considered in investigating diseases of low incidence or when studying adverse events in response to vaccines when they can be particularly useful (*77*). In order to generate adequate information on vaccine efficacy, population samples should be well defined and representative, and a serological correlate for protection, if available, should be used (see B.7.2.3). The advantages of case–control studies are that they can be small-scale and the follow-up period is short. The main limitations are the potential for (a) selection bias, and (b) information bias. Selection bias is due to lack of randomization and the selection of the control group, especially when the study is not population based. Every effort should be made to include as many cases as possible. All aspects of study design and conduct should be detailed in the study protocol and justified.

B.9.3.3 Stepped wedge design

The stepped wedge design should be considered when previous studies have indicated that the intervention is likely to be beneficial (*51*) and the public health need to introduce the intervention precludes withholding it from a population. The intervention is introduced in phases, group by group, until the entire target population is covered. The groups form the unit of randomization.

B.9.3.4 Outbreak interventions

At the start of an outbreak (or epidemic), the susceptibility of all individuals in the target population to the infecting pathogen is assumed to be equal. The methodological approach chosen to study the effectiveness of the intervention should be appropriate to the size and nature of the outbreak.

- Pre-exposure cohort studies or secondary attack-rate studies are preferred in infections with a high attack rate.
- Case–control studies are useful in studies of diseases with a low incidence or in small isolated outbreaks.

- Community-based cohort studies are unsuitable for short-term evaluation; however, they may be useful for the post hoc evaluation of the performance of a vaccination programme or for long-term follow-up of specific clinical outcomes or safety issues.

In areas where the immunization rate is high, outbreak investigations underestimate vaccine efficacy. The degree of underestimation is related to the extent of the epidemic that triggered the investigation, vaccination coverage in the community and the extent of clustering of vaccination failures in the population.

B.9.4 *Monitoring of postmarketing surveillance*

A postmarketing oversight policy should be established by a national regulatory authority to enable control of product release, periodic inspections, reporting mechanisms, recall of batches, or, if necessary, for revoking marketing approvals, approval of manufacturing changes, and evaluation and approval of new indications and/or dose regimens. General guidelines for continued oversight of vaccines after licensure as described in WHO Technical Report Series 858, should be followed (*1*). Guidance on the operation of epidemiological surveillance and monitoring of adverse events are provided by WHO and other bodies (*37*, *78–80*). Standards for assessment of causality are described in these and other regulatory documents. Targeted monitoring and special studies may be required for certain adverse events (*75*). Monitoring vaccines for use in the Expanded Programme of Immunization should include not only efficacy and safety, but also compatibility with existing vaccines (antigens) used in this programme (*81*). Ideally, this should be considered prior to marketing approval. In addition, the immunization programme and vaccine supply should be considered.

B.10 Special considerations for combination vaccines

A combination vaccine consists of two or more vaccine immunogens in a physically mixed preparation intended to prevent several diseases or to prevent one disease caused by different serotypes (or serogroups) of the same organism (*13*, *14*, *79*). The mixing may occur as a manufacturing step or it may be performed by a health care professional on site before administration according to the package insert instructions. Vaccines mixed ad hoc without regulatory approval are not considered to be combination vaccines.

The main goal of a clinical trial of a combination vaccine is to evaluate the efficacy of each component vaccine, and the safety of the combination, regardless of whether or not the combination consists of

previously marketed or investigational individual component vaccines. The immunogenicity and safety of a new combination should be compared with the effects of simultaneous, but separate, administration of the individual vaccines.

B.10.1 ***Efficacy studies***

Once the serological correlates of protection have been validated for each of the antigenic components, consideration should be given to evaluating the efficacy of a new combination vaccine consisting of components already licensed and/or components with proven efficacy using immunogenicity rather than clinical protection end-points. Failing this, prospective controlled clinical studies or alternative approaches such as postmarketing surveillance are required.

Studies of combination vaccines are usually designed and analysed (for efficacy or immunogenicity) as non-inferiority trials, the aim being to demonstrate that the combination is comparable with the individual components. Each of the individual components is expected to add materially to the prophylactic effect of the vaccine (*61*, *79*).

Clinical studies of combination vaccines should:

— have sufficient power to rule out pre-existing differences in response parameters between the study groups;
— use appropriate sample sizes, as for monovalent vaccines (see methodological considerations); and
— consider the clinical consequences of any potential difference observed.

Clinical bridging studies may be needed to facilitate extrapolation of data to a different population or to support a different immunization schedule.

Immunogenicity trials of new combination vaccines to prevent several diseases (multidisease combination vaccines) should be designed to rule out predefined differences in immune responses between the new product and the individual components administered separately. When antibody concentrations following administration of the combined vaccine are less than those observed following separate administration of the individual components or simultaneous administration of the individual of the individual vaccines at different sites, it should be demonstrated that these findings are not clinically relevant. Any change in dose or schedule for individual components should be justified.