くとも、ワクチンの生物学的作用に感受性がある動物種、例えばワクチン抗原に対して免疫反応を生じる動物種を用いて安全性プロフィールを検討する。

一般的に、臨床試験を開始するためには、毒性試験は1種類の妥当な動物種で実施されるが、ヒト以外の霊長類による試験は必ずしも必要とは限らない。動物は通常雌雄両性が用いられる。一方を省略する場合には、その妥当性を示さなければならない。

2.1.3 被験物質（6、7）

ワクチンの非臨床安全性試験で用いる被験物質には剤形及び組成が臨床試験用の製剤と同等であることを考慮する。（6、7）

2.1.4 投与経路

投与経路は臨床試験で使用する経路に一致させる。実際的な理由から、臨床試験と同一経路での投与ができない場合は、別の投与経路も容認される場合があるが、その妥当性を示す必要がある。

2.2 基本的な非臨床安全性評価：個別留意事項

2.2.1 単回投与毒性試験

ヒトの臨床用量に対して適切な安全域を考慮した用量で、（8，9）通常 1 種の動物を用いて実施する。なお、反復投与毒性試験の初回投与後の評価~~、あるいは安全性薬理試験及び免疫原性試験の一部~~として実施することが可能な場合もある。

2.2.2 反復投与毒性試験

通常1種の動物を用いて実施する。投与期間及び投与頻度は臨床の投与計画を考慮して間歇投与とし、動物の抗体反応など誘導される免疫反応を考慮し、臨床の投与回数以上の投与を行う。~~一群の動物数はげっ歯類では雌雄各 10 匹以上、非げっ歯類では雌雄各 3 匹以上を使用する。試験評価のために陰性対照群を設定する。必要に応じて、比較対照群（抗原を含まない製剤など）の追加も考慮する。~~（34）~~適切な安全域を確保できる 1 用量を選択するが、~~（6、7）~~実施した用量で毒性所見が認められた場合は、低用量での検討を考慮する。~~（15、19）高用量の設定は、ヒトの臨床での 1 回投与量と同じ用量（/body）を目安とするが、使用する動物種によっては、投与用量を適宜設定する必要がある。すなわち、げっ歯類において、ヒトと同じ用量（/body）の投与が物理的に困難な場合は、体重換算による mg/kg（または mL/kg）を基準にして、ヒトの用量を超える投与用量を選択することが可能である。また、非げっ歯類において、ヒトの臨床での1回投与量と同じ用量（/body）では適切な安全域が確保できないと考えられる場合は、ヒトの臨床での 1 回投与量の数倍の投与用量を選択することが可能である（20）。実施した用量で毒性所見が認められた場合は、低用量での検討を考慮する。（15、19）~~毒性変化の回復性あるいは遅延毒性を検討する。~~(19) 一般状態観察では投与局所の状態及び過敏反応などにも留意する。~~また、~~病理検査では必要に応じて免疫器官や投与部位近傍のリンパ節への影響にも留意する。また、毒性変化が認められた場合には、その回復性を検討する。なお、遅発性の副作用が懸念される場合には、必要に応じて追加群を設ける。(19)

2.2.3　生殖発生毒性試験

受胎能及び着床までの初期胚発生に関する評価は、反復投与毒性試験における病理組織学的検査で生殖器官への影響が懸念される場合に必要である。(22) 胚・胎児発生に関する評価は、妊婦あるいは妊娠可能な女性に接種されるワクチンについて、安全性を担保するための科学的に妥当な根拠がない場合に必要である。出生前及び出生後の発生並びに母体の機能に関する評価は、妊婦への接種を意図したワクチンについて、安全性を担保するための科学的に妥当な根拠がない場合に必要である。通常1種の動物を用いて試験を実施し、投与間隔及び投与頻度は臨床の投与計画を考慮して決定する。

2.2.4　遺伝毒性試験

通常ワクチンについては遺伝毒性試験を必要としない。~~しかし、新規アジュバント及び新規添加物については、遺伝毒性評価が必要である。~~ (25)

2.2.5　がん原性試験

通常ワクチンでは投与回数が限定されているためがん原性試験を必要としない。~~また、ワクチンに含まれる新規アジュバント及び新規添加物質についても、ワクチンと同様に通常がん原性試験を必要としない。~~ (27)

2.2.6　局所刺激性試験

本試験は単独の試験として、あるいは単回/反復投与毒性試験の一部として実施する (28)。~~臨床試験で使用する製剤と同一組成の被験物質で評価するのが望ましい。~~ (6)

2.2.7　安全性薬理試験

他の非臨床試験あるいは臨床試験より、ワクチンが免疫系以外の生理機能（中枢神経系、呼吸器系、心血管系）に悪影響を及ぼす可能性が懸念される場合には実施する (30、31)。

2.2.8　トキシコキネティクス

通常、全身暴露量の評価は必要ない。

2.3　特別な留意事項

2.3.1　アジュバント

新規アジュバントについては、それ自体の毒性評価が必要である。試験項目は臨床での使用方法、使用頻度等を考慮して設定する。特に、反復投与による局所反応及び過敏反応などに留意する。新規アジュバントと抗原の組み合わせにより毒性反応に差を生じる可能性がある。このため、抗原の新規性の有無に係わらず、新規アジュバントと抗原の両方を含んだ製剤での毒性評価も必要である。また、既存のアジュバントと既存の抗原を組み合わせることによる新たな毒性が懸念される場合にも、局所反応などの毒性評価が必要である。

2.3.2　添加剤（アジュバントを除く）

新規添加剤については、それ自体の毒性評価が必要である。試験項目は臨床での使用方法、使用頻度等を考慮して設定する。新規添加剤を含む製剤を用いた毒性評価の必要性に

ついては添加剤毎に判断する。

WHO Technical Report, Series No. 924, 2004

Annex 1
Guidelines on clinical evaluation of vaccines: regulatory expectations

This document provides guidance for national regulatory authorities and vaccine manufacturers on the clinical evaluation of vaccines by outlining the international regulatory expectations applicable to the different stages of vaccine development and for marketing approval. For this reason, the guidance in this document could also be useful for clinical researchers and investigators.

The text is presented in the form of guidelines rather than recommendations because vaccines are a heterogeneous class of agents, and the preclinical and clinical testing programmes will need to be adapted for each individual product. Guidelines allow greater flexibility than recommendations with respect to specific issues related to particular vaccines.

A separate WHO document intended to provide more detailed guidance on preclinical and laboratory evaluation of vaccines is in preparation. This was subsequently established by the 54th meeting, November 2003, of the WHO Expert Committee or Biological Standardization and is to be published in the WHO Technical Report Series. The section of this document that discusses preclinical and laboratory evaluation consequently provides general guidance, but does not define international regulatory expectations in this area.

Introduction

This document provides guidance to national regulatory authorities (NRAs), manufacturers, clinical researchers and investigators on the clinical evaluation of vaccines by outlining the data that should be obtained during the different stages of vaccine development to support an application for marketing approval. This document has been prepared in response to requests from NRAs for assistance in the evaluation of clinical trials, both during the clinical development of a new vaccine and during the regulatory review of dossiers submitted in support of applications for marketing authorization. The NRAs

should have a mandate to review protocols, and when this is necessary to protect the safety of subjects, to require revision of the protocol and/or termination of the trial. This document is intended to provide basic guidance to NRAs on how to achieve these objectives. Because it is common practice for the clinical development programmes and the individual clinical trials to take place in different countries, each NRA should, as far as possible, collaborate with the other regulatory authorities involved to benefit from shared experiences and to align regulatory considerations (*1*).

The World Health Organization (WHO) has made available the following guidelines and requirements that are relevant to the evaluation of vaccines: good clinical practice for trials on pharmaceutical products (*2*), good manufacturing practice for pharmaceutical preparations (*3*, *4*), good manufacturing practice for biological products (*5*), regulation and licensing of biological products in countries with newly developing regulatory authorities (*1*) and guidelines for national authorities on quality assurance for biological products (*6*). Guidelines and recommendations for the production and control of specific vaccines have been reviewed in detail in a series of WHO technical reports (*7*), which should be consulted where applicable but will not be discussed further here. However, there is no existing WHO document that gives guidance on the planning, performance and assessment of clinical studies on vaccines with a regulatory perspective. Specific WHO guidelines that complement this document are available for malaria (*8*) and dengue (*9*) or are in preparation in the case of certain candidate vaccines, such as for human immunodeficiency virus (HIV). Basic standards of care, including details about the cold chain required for transport and storage of vaccines, proper injection techniques for delivery of vaccines and safety of injections have already been described in the WHO manual *Immunization in practice* (*10*).

Guidance on various aspects of clinical trials of vaccines is also available from several other bodies such as the International Conference on Harmonization (ICH), the European Agency for the Evaluation of Medicinal Products (EMEA), the United States Food and Drug Administration (FDA) and the United Kingdom Medical Research Council (MRC). These WHO guidelines are not intended to conflict with, but rather to complement, these other documents (*11–16*, *18–39*).

Regulation of vaccines

Regulatory issues related to a particular candidate vaccine should be considered early in the development process, since compliance with regulatory requirements is the basis for eventual approval. It is strongly recommended that dialogue with the appropriate national regulatory authority be established early on. The national regulatory authority should review the plans for development of the candidate vaccine and clarify requirements for carrying out clinical trials, as well as for marketing approval.

The regulation of vaccines can be divided into three stages: developmental, licensure and postlicensure (*40*). The developmental stage consists of two parts, preclinical research and development, and clinical research and development.

Preclinical testing

Preclinical research and development are carried out in the laboratory using in vitro techniques or, when necessary, in vivo techniques in animals. The data from preclinical and laboratory research include details of the development and production of a vaccine together with reports of control testing, which should be adequate to justify subsequent clinical studies in humans.

Phases of clinical development (I–III)

Clinical trials in humans are classified into three phases: phase I, phase II and phase III and in certain countries formal regulatory approval is required to undertake any of these studies. This approval takes different forms in different countries (e.g. Investigational New Drug Application (IND) in the United States and Clinical Trial Certificate or Clinical Trial Exemption (CTX) in the United Kingdom). This is in addition to ethical clearance which is required for clinical trials in all countries. All studies of human subjects require proper ethical review, in accordance with the Declaration of Helsinki (see http://www.wma.net/e/).

The phase I clinical studies carry out initial testing of a vaccine in small numbers (e.g. 20) of healthy adults, to test the properties of a vaccine, its tolerability, and, if appropriate, clinical laboratory and pharmacological parameters. Phase I studies are primarily concerned with safety. Phase II studies involve larger numbers of subjects and are intended to provide preliminary information about a vaccine's ability to produce its desired effect (usually immunogenicity) in the target population and its general safety. To fully assess the protective

efficacy and safety of a vaccine, extensive phase III trials are required. The phase III clinical trial is the pivotal study on which the decision on whether to grant the licence is based and sufficient data have to be obtained to demonstrate that a new product is safe and effective for the purpose intended.

By the beginning of the phase III stage of development, a vaccine should have been fully characterized and the final manufacturing process, specifications and batch release testing procedures should have been established. An application for market authorization may be submitted to an NRA on the basis of the data from phase III testing and if approved, the vaccine then becomes commercially available in that particular country. If a product contains or consists of genetically modified organisms an environmental risk assessment should also be undertaken and approved by the appropriate agency.

The structure of the clinical development programme must be tailored to the type of vaccine and the antigenic content. For example, the clinical evaluation of a vaccine that contains only novel antigen(s) may of necessity be very different from that of a vaccine that contains one or more previously evaluated antigens. Such factors also influence whether clinical protection trials will be required, whether or not they are feasible, or whether an approval may reasonably be based on immunogenicity data. In all instances, it is the obligation of the applicant to justify the content and structure of the clinical development programme. Pre-submission meetings with regulatory authorities may assist in ensuring that the content of the final data package is likely to be acceptable.

Issues to be considered after the initial licensure

In addition to phase I, II and III studies that may be performed before or after the first licensure of a new vaccine, which are described under other relevant trials as outlined above, the postmarketing period is critical for the collection of data on the safety and effectiveness of a vaccine in large numbers of recipients; these data may come from both active and passive modes of surveillance. Following licensing, there is continued surveillance of vaccinees for adverse events, especially for those rare events that can be detected only in very large numbers of subjects.

Any change in production methods or scale-up following licensing will necessitate further product characterizations to demonstrate equivalence, although the extent of re-characterization required depends on the nature of the changes implemented. Further characterizations should be documented and the NRA should be notified of all

changes. Regulatory authorities should clearly define and implement in their regulations which changes require only a notification and which changes require a formal approval before they can be introduced. This will be decided on a case-by-case basis and, in all instances, regulatory approval for a change must be obtained before the vaccine is used.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

Adverse event
Any untoward medical occurrence in a clinical trial subject to whom a vaccine has been administered; it does not necessarily have a causal relationship with the vaccine/vaccination.

Adverse reaction
A response to a vaccine that is noxious and unintended and that occurs at doses tested in humans for prophylaxis, or during subsequent clinical use, following licensure. The term adverse reaction is usually reserved for a true causal association with a drug or a vaccine.

Attack rate
The proportion of the population exposed to an infectious agent who become (clinically) ill.

Audit
A systematic examination, carried out independently by persons not directly involved in the clinical trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g. whether data reported or recorded in the case report forms are consonant with those found in hospital files and other original records.

Blinding
A procedure in which one ore more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware of the treatment assigned to them, and double blinding usually refers to the subject(s), investigator(s) and, in some cases, data analyst(s) being unaware of the treatment assignment.

Booster vaccination
Vaccination given at a certain time interval (at least 6 months) after primary vaccination in order to induce long-term protection.

Bridging studies
Studies intended to support the extrapolation of efficacy, safety and immunogenicity data from one formulation, population or dose regimen to another.

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 the effect of this exposure is compared between individuals (the cases) who experience an event (the disease, in vaccine studies) and individuals who do not (the controls).

Case definition
A set of diagnostic criteria that must be fulfilled to confirm a case of a particular disease. Case definitions can be based on clinical criteria, laboratory criteria or combinations of the two.

Case report form
A document used to record data on a subject participating in a clinical trial during the course of the trial, as defined by the protocol. The data should be collected by procedures that guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

Cluster
Aggregation of relatively uncommon events or diseases in space and/or time in amounts that are believed or perceived to be greater than could be expected by chance.

Cohort study
A retrospective or prospective study in which the development of a disease or infection, or any other relevant event, is observed over time in a defined group of subjects.

Colonization
The asymptomatic, often transient, presence of a microbe as a part of the normal microflora of a host (e.g. pneumococci on the mucosae of the upper respiratory tract).

Community investigation
A population-based trial in large predefined segments of the population to investigate the impact of a treatment on a preventable infectious disease.

Comparator product
A pharmaceutical or other product (which may be a placebo) used as a reference in a clinical trial.

Contact
An individual who has had contact with an infected person (case) in a way that is considered as having caused significant exposure and therefore a risk of infection.

Control
Any comparator suitable for validation of the trial. The comparator may be either an active treatment or a placebo control.

Equivalence trial
A trial having the primary objective of showing that the response to two or more treatments differs by an amount that is clinically unimportant. Showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences usually demonstrates this.

Experimental study
A study in which the conditions are under the direct control of the investigator. Such studies may include random allocation of subjects to treatment or control groups and blinding of subject and investigator to the placement status (i.e. whether in the treatment or control group).

Exposure
Having contact with an infectious agent in a way that experience has shown may cause disease.

Foreign clinical data
Clinical data generated outside the target region (i.e. in a foreign region).

Geometric mean titre
Calculation of the average titre for a group of subjects by multiplying all values and taking the *n*th root of this number, where *n* is the number of subjects.

Good clinical practice
A standard for clinical studies that encompasses the design, conduct, monitoring, terminations, audit, analyses, reporting and documentation of the studies, ensures that they are scientifically and ethically sound, and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.

Good manufacturing practice
That part of the pharmaceutical quality assurance process which ensures that products are consistently produced and to meet to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, good manufacturing practice refers to the current good manufacturing practice guidelines published by WHO.

Immunogenicity
The capacity of a vaccine to induce antibody-mediated and/or cell-mediated immunity and/or immunological memory.

Incidence
The number of persons who fall ill with a certain disease during a defined time period.

Informed consent
A subject's voluntary confirmation of his or her willingness to participate in a particular trial, and the documentation thereof. This consent should be sought after giving the subject appropriate information about the trial, including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki.

Inspection
An officially conducted examination (i.e. review of the conduct of the clinical trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of the trial and/or the site of the sponsor in order to verify adherence to good clinical practice as set out in these guidelines.

Internal control
An additional control arm in a vaccine trial, 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.

Investigator
A person responsible for the clinical trial and for the rights, health and welfare of the subjects in the trial. The investigator should have qualifications and competence in accordance with the local laws and regulations as evidenced by an up-to-date curriculum vitae and other relevant credentials. Decisions relating to medical or dental care, and their provision must always be the responsibility of a clinically competent person legally allowed to practice medicine or dentistry.

Minimal risk
A level of risk similar to the risk encountered during an individual's usual daily activities. Minimal risk would apply to activities such as physical examination, venipuncture or urine sample collection.

Non-inferiority trial
A trial with the primary objective of showing that the response to the product under investigation is not clinically inferior to the control vaccine (active or placebo).

Observational studies
Observational studies focus on events, exposures and diseases occurring in the population during their everyday life, not subject to experimental interventions.

Outbreak
The occurrence of two or more linked cases of a communicable disease.

Placebo control
A comparator in a vaccine trial that does not include the antigen under study. In studies of monovalent vaccines this may be an inert placebo (e.g. saline solution or the vehicle of the vaccine), or an antigenically different vaccine. In combined vaccines, this may be a control arm in which the component of the vaccine being studied is lacking.

Post-marketing surveillance
A system for monitoring adverse events following licensure. Postmarketing surveillance can be passive or active and its objectives include, but are not limited to, the following:

— the identification of rare adverse reactions not detected during pre-licensure studies; and
— the identification of risk factors or pre-existing conditions that may promote reactions.

Potency
The quantitative measure of the specific ability or capacity of the product to achieve a defined biological effect.

Pre-exposure trial
A prospective trial in a population expected to be exposed to the pathogen under study within a predefined, relatively short, period.

Prevalence
The number of persons who have a particular disease at a specific time.

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.

Protocol
A document that states the background, rationale and objectives of the clinical trial and describes its designs, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be signed and dated by the investigator, the institution involved and the sponsor. It can also serve as a contract.

Randomization
In its simplest form, randomization is a process by which n individuals are assigned to a test (n_T) or control (n_C) treatment so that all possible groups of size $n = n_T + n_C$ have equal probability of occurring. Thus randomization avoids systematic bias in the assignment of treatment. It also promotes balance with respect to known and unknown prognostic factors that could affect the outcome of interest. While it does not guarantee that treatment groups will be exactly equal with respect to these factors, it does guarantee that any imbalance that occurs arose purely by chance. The process of randomization guarantees the validity of statistical analyses of treatment effect, and (with adequate sample size) allows the detection, or ruling out, of small or moderate treatment differences.

Reactogenicity
Reactions, either local or systemic, that are considered to have a causal relationship to the vaccination.

Reproductive rate
The average number of secondary cases of an infection arising from a single primary case. The measure is inherent to the potential (infectiousness, susceptibility, measures of protection) of a microorganism 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 either observational or experimental. The unit of randomization may be the individual, a household or a cluster.

Sensitivity (statistical)
The probability that a test will detect a disease/condition when it is used on an individual who truly has the disease/condition. It is estimated in a study as the proportion of individuals with positive test results out of all individuals classified by a gold standard as having the disease/condition.

Serious adverse event
An event occurring in connection with the clinical trial that results in death, admission to hospital, prolongation of a hospital stay, persistent disability or incapacity, or is otherwise life-threatening.

Seroconversion
Predefined increase in antibody concentration, considered to correlate with the transition from seronegative to seropositive, providing information on the immunogenicity of a vaccine. If there are pre-existing antibodies, seroconversion is defined by a transition from a predefined low level to a significantly higher defined level such as a fourfold increase in geometric mean antibody concentration.

Serological surrogate
Predefined antibody concentration correlating with clinical protection.

Serosurveillance
The surveillance of an infectious disease by measuring disease-specific antibodies in a population or subpopulation.

Specificity (statistical)
The probability of a negative test result when a test is used on an individual who truly does not have the disease/condition. It is esti-

mated in a study as the proportion of individuals with negative test results out of all individuals classified by a gold standard as not having the disease/condition.

Sponsor
An individual, a company, an institution or an organization that takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator has then also assumed the role of the sponsor.

Standard deviation
The measure of the variability of a sample of observations around the mean.

Superiority trial
A trial with the primary objective of showing that the response to the product under investigation is superior to the control vaccine (active or placebo).

Surveillance
The systematic collection, collation and analysis of data and the dissemination of information to those who need to know in order that appropriate action may be taken.

Survey
An investigation in which information is systematically collected. It is usually carried out in a sample of a predefined population group for a defined time period. A survey is not a continuous investigation and may be repeated after a period of time. If repeated regularly, surveys can form the basis of a surveillance system.

Vaccine (protective) efficacy
The reduction in the chance or odds of developing clinical disease after vaccination relative to the chance or odds when unvaccinated. Vaccine efficacy measures direct protection (i.e. protection induced by vaccination in the vaccinated population sample). Vaccine efficacy is calculated according to the following formula:

$$\mathrm{VE} = \left(\frac{Iu - Iv}{Iu}\right) \times 100\% = \left(1 - \frac{Iv}{Iu}\right) \times 100\% = (1 - \mathrm{RR}) \times 100\%$$

where Iu = incidence in unvaccinated population; Iv = incidence in vaccinated population; RR = relative risk

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

Vaccine failure
The onset of infection or disease, biologically confirmed, in a subject who is supposed to be protected, following completion of age-appropriate immunization as recommended by the manufacturer.

Validation
The action of proving in accordance with the principles of good clinical practice, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually leads to the expected results.

Vector
A carrier, most often an animal or arthropod that transfers a pathogen from an infected person(s) or animal to a susceptible individual.

Scope of the document

Vaccines are a heterogeneous class of prophylactic medicinal products containing antigenic substances capable of inducing specific, active and protective host immunity against an infective agent or toxin, or against other important antigenic substances produced by infective agents. Vaccines for human use contain one of the following: microorganisms inactivated by chemical and/or physical means that retain adequate immunogenic properties; living microorganisms that are avirulent to humans or have been selected for their attenuation whilst retaining immunogenic properties; or antigens extracted from organisms, secreted by them, or produced by recombinant DNA technology. The antigens may be in their native state, detoxified by chemical or physical means and/or aggregated, polymerized or conjugated to a carrier to increase immunogenicity.

This document also covers novel products such as DNA vaccines and live genetically engineered microorganisms used themselves as vaccines or used as carriers for other antigens. However, therapeutic

vaccines (e.g. viral-vector-based gene therapy, tumour vaccines and anti-idiotypic vaccines such as monoclonal antibodies used as immunogens) are *not* considered here.

Part A. Preclinical and laboratory evaluation of vaccines

A.1 General remarks

The preclinical evaluation of a vaccine is a prerequisite for the initiation of clinical trials. Laboratory evaluation should however be continued throughout both the preclinical and clinical phases of vaccine development. This section on preclinical and laboratory testing discusses the general principles for the nonclinical evaluation of vaccines which should be taken into consideration both before and during clinical trials. (A document which deals with the nonclinical and laboratory evaluation of vaccines in more detail has also been prepared by WHO. Established by the 54th meeting, November 2003, of the WHO Expert Committee on Biological Standardization and to be published in the WHO Technical Report Series.)

The primary goal of preclinical testing of a new vaccine product, or a new combination vaccine comprised of previously licensed antigen(s), or vaccines presented in new formulations or new delivery systems, should be to demonstrate that the vaccine is suitable for testing in humans.

Preclinical and laboratory studies are aimed at defining the characteristics (physical, chemical and biological) of a product, including the indicators of safety and immunogenicity in an appropriate animal model. When preclinical testing is performed in animals, there should always be a clear rationale for doing so, and the study should be performed in compliance with Good laboratory practice guidelines (*11*) and with national guidelines on animal experimentation. In addition to establishing the characteristics of the candidate vaccine, preclinical and laboratory studies may also identify possible risks to the vaccinees, and can be used to plan protocols for subsequent clinical studies in human subjects in which safety and efficacy of the candidate vaccine are evaluated.

Close collaboration between the preclinical and the clinical investigators is particularly important in assessing the first results of the administration of vaccines in humans. The clinician, in consultation with the appropriate advisers, has, however, the responsibility of ensuring that the preclinical experiments are adequate in scope and for requesting a full account of all relevant data.

A.2 Production, characterization and quality assurance of candidate vaccines

The basic principles for the production and control of vaccines are set out in the relevant publications in WHO Technical Report Series which cover general requirements (*41–46*). Specific guidelines and recommendations for particular vaccines are also available (*7*) and should be consulted as appropriate. The WHO guidelines and recommendations are often adopted by national regulatory authorities as definitive national requirements. Other useful guidance may be obtained from the documents produced by other bodies (*47*). The characterization, standardization and control of the components, safety and potency of vaccine preparations are key issues during development. The amount of data collected to support clinical studies should increase throughout phases I and II, and product characterization should be completed by the beginning of the phase III stage of development. In-process testing should be performed to ensure adequate control over the manufacturing process and manufacturing consistency. Analytical criteria should be established during product development and used subsequently to evaluate new batches and to establish batch-to-batch consistency. The tests adopted for routine batch release should be a selection of those tests used for the initial characterization of the vaccine. A batch release protocol providing an outline of production and a summary of the test results and establishment specifications should be available for each batch.

Candidate vaccines for clinical trials should be prepared according to good manufacturing practices. The general manufacturing recommendations contained in good manufacturing practices for pharmaceutical and biological products (*3–5*) should be applied by all establishments involved in producing candidate vaccine for clinical studies. Standard operating procedures covering all aspects of production, quality control, storage and distribution should be documented.

Any proposed change in the formulation of a vaccine should be considered carefully both by the manufacturers and NRAs. Some changes in formulation may have a serious effect on the quality, safety and efficacy of vaccines and will subsequently require clinical trials.

Sufficient stability data should be generated to support clinical trials. Accelerated stability data could be used to support preliminary data generated at the normal storage temperature. Further data on stability to support the expiry date of the product for licence should be based on long-term, real-time, stability studies under the real conditions of use. All relevant documentation should be made available to the regulatory authorities.

In accordance with good clinical practice, sufficient samples of each batch of candidate vaccine, together with a record of analyses and characteristics, must be kept for future reference by the manufacturer and ideally a national control laboratory (NCL) for possible subsequent re-testing and investigation. The product should be stored under safe and stable conditions for at least the duration of its anticipated or approved shelf-life and preferably longer.

A.3 Toxicity and safety testing

Toxicity studies in animals may be considered for the assessment of the potential toxic effects of a vaccine in target organs, including the haematopoietic and immune systems as well as to assess systemic toxicity. Such studies may help to identify potential toxicity problems requiring further clinical monitoring. Detailed guidance on toxicological and pharmacological testing may be found in the EMEA *Note for guidance on preclinical pharmacological and toxicological testing of vaccines* (*12*). However, it should be recognized that a suitable animal model may not be available for undertaking toxicological evaluation of candidate vaccines, and such models are not necessarily predictive of human responses the interpretation of the results may be difficult. Furthermore, a classical repeated dose toxicity test as applied to medicines may or may not be applicable for vaccines. Applicability of repeated dose toxicity tests depends on the vaccine dose regimen and the composition of the vaccine. Usually there is no chronic exposure of the subject to a vaccine through repeated administration.

The design and value of repeated-dose toxicity tests should therefore be considered on a case-by-case basis, as should the selection of the animal species used for these investigations. If a vaccine is intended to be clinically tested in women of childbearing age, the need for reproductive toxicity studies and studies of embryo/fetal and perinatal toxicity should be considered on a case-by-case basis. Reproductive toxicity studies, where appropriate, will need to be undertaken before licensing.

Toxicity tests should include:

— an evaluation of the initial safe dose and of subsequent dose escalation schemes relevant to the clinical dose;
— an evaluation of single and repeated doses as appropriate;
— a determination of a set of relevant safety parameters for clinical monitoring;
— a demonstration of potential reversibility of virulence of attenuated vaccine strains;