



The European Agency for the Evaluation of Medicinal
Products
Human Medicines Evaluation Unit

London, 17 December 1997
CPMP/SWP/465/95

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**NOTE FOR GUIDANCE ON
PRECLINICAL PHARMACOLOGICAL AND TOXICOLOGICAL
TESTING OF VACCINES**

| | |
|--|----------------------------------|
| DISCUSSION IN THE SAFETY WORKING PARTY (in co-operation with the Biotechnology Working Party) | November 1995 - February 1997 |
| TRANSMISSION TO THE CPMP | February 1997 |
| TRANSMISSION TO INTERESTED PARTIES | February 1997 |
| DEADLINE FOR COMMENTS | August 1997 |
| DISCUSSION IN THE SAFETY WORKING PARTY (in co-operation with the Biotechnology Working Party) | November 1997 |
| FINAL APPROVAL BY THE CPMP | December 1997 |
| DATE FOR COMING INTO OPERATION | June 1998 |

PRECLINICAL PHARMACOLOGICAL AND TOXICOLOGICAL TESTING OF VACCINES

INTRODUCTION

Vaccines for human use are preparations that contain antigenic substances capable of inducing a specific and active immunity against the infecting agent or the toxin or the antigen produced by it.

Vaccines for human use may contain:

- organisms which have been inactivated by chemical or physical means and 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 organisms, secreted by them, or produced by recombinant DNA technology.

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.

As vaccines represent a heterogeneous class of agents, preclinical pharmacological and toxicological testing of vaccines may be adapted for the product in question as pointed out in Directive 75/318, as amended. The final programme should be described and justified in the pharmacological-toxicological expert report.

SCOPE OF THE NOTE FOR GUIDANCE

This Note for Guidance is intended to cover all vaccines as defined above. It focuses on the preclinical evaluation of new vaccine products including combined vaccines. Within the context of this Note for Guidance, new vaccines are those containing antigens not yet described in the European Pharmacopoeia monographs or in WHO requirements, or using a new conjugate for a known antigen, or any new combination of known and/or new antigens. This Note for Guidance does not describe test procedures for the yearly update of influenza vaccines.

New routes of administration and / or modes of delivery may necessitate studies focusing on specific safety concerns.

When a major change in the manufacture of a vaccine is being made, the need for preclinical testing should be reconsidered.

The present Note for Guidance applies also to development of new vaccine products containing live organisms. It is presented to replace the chapter (3.4) of the former EU guideline 1988 "Preclinical safety testing of medicinal products derived from biotechnology".

Monoclonal antibodies may also be used as immunogens, i.e. anti-idiotypic vaccines and should be considered to fall within the scope of CPMP/ICH/302/95: ICH S6 "Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals". Similarly, recombinant DNA protein vaccines are addressed in the same Note for Guidance.

DNA-vaccines, gene therapy or genetically altered somatic cell therapy are not addressed in this Note for Guidance.

GENERAL REMARKS

It is recognised that suitable animal models are not always available and responses in such models are not always predictive of human responses. Therefore, selection of animal species should be made on a case by case basis.

Potential safety concerns associated with vaccines include general systemic toxicity, (paradoxical) enhancement of the intended disease, induction of local toxicity, pyrogenicity, adverse immunologic effects such as autoimmunity or sensitisation, and in some cases teratogenic/reproductive effects.

Historically, serious neurological events have been associated with the use of some vaccines. The availability of animal models to address these issues should be considered in the development of a new vaccine.

For new vaccine products (see above), preclinical safety tests should always be part of the testing programme, even though it is recognized that full testing may not be necessary to the extent requested for conventional medicinal products. However, in the case of combined vaccines containing known antigens, preclinical toxicity testing may not always be necessary. Immunogenicity testing is still recommended (see § F.1.).

The route of administration should be as close as possible to the proposed clinical route. If this is for practical reasons not possible, another route of administration may be acceptable but this should be justified. Studies to address specific safety concerns (e.g. neurovirulence, testing for complete detoxification of toxins) will often need other routes of administration. It should be considered if methods described in relevant pharmacopoeial monographs are applicable.

Attention should be paid to additives including adjuvants, preservatives, and excipients (see § R).

PRECLINICAL TESTING

When preparing the preclinical documentation (PART III) for “vaccines” as defined above, the following issues have to be taken into account:

A.1 Single dose toxicity

Single dose toxicity data from at least one animal species should be performed with a dose providing an adequate safety margin in relation to the human dose. However, if toxic findings are seen in this study, the dose response relationship should be further characterised. These data may be part of animal immunogenicity studies (see § F.1. Primary Pharmacodynamics) or of safety pharmacology studies (see § F.2. Safety Pharmacology), provided that histopathology of important organs is included.

For the routine production testing of abnormal toxicity or of a pyrogenicity test, see § Q of this Note for Guidance.

A.2 Repeated dose toxicity

A study on repeated dose toxicity in one animal species is normally requested for vaccines that will require multiple doses in the clinical setting. Even in cases where only single doses will be administered in clinical use, a repeated dose toxicity study may nevertheless be appropriate. The selection of an appropriate animal species should be carefully evaluated on a case by case basis.

The route and dosing regimen should reflect the intended clinical use. Its design should take into account potential differences in response time between animals and humans (e.g. repeated doses at monthly intervals in humans may not give the same response as repeated doses at monthly intervals in animals).

Valuable information can be obtained by expanding multiple-dose immunogenicity studies to include measurements normally conducted in preclinical toxicity studies (i.e. body weight, food consumption, clinical pathology, gross necropsy and histopathology). The value of the protocol would normally be enhanced by concurrent measurement of the antibody response to all important components of the vaccine (immunogenicity studies).

Incorporation of safety pharmacology endpoints in the design of these studies should be considered (see also § F.2.).

The applicant should consider the following points on a case by case basis:

- Where appropriate, specific consideration should be given to immunological aspects of toxicity, such as production of complexes with host immunoglobulins (e.g. antibody-dependent enhancement of disease) or release of immunofunctional molecules, (e.g. cytokines) affecting functions of the immune system.
- Hypersensitivity reactions, induced by the antigen itself, by antigens (toxins) modified in new ways (new detoxification procedure, by antigen-carrier complex or presence of minute amounts of impurities) or by additives (adjuvants/excipients/preservatives) may be increased (especially for vaccines proposed to be injected more than once).
- In some rare cases, antigenic substances can induce antibodies that can cross-react with human tissue resulting in possible adverse effects and the availability of an animal model to address these issues should be considered.

B. Examination of reproductive function.

Data on reproductive function (fertility) are usually not necessary. Histopathology in toxicity studies may provide sufficient information concerning the integrity of reproductive organs.

C. Embryo/foetal and perinatal toxicity

In most cases, vaccination of humans occurs during childhood. Therefore, embryo/foetal and perinatal toxicity studies are usually not necessary. Only if a vaccine is intended for use in women of child bearing age or during pregnancy may such studies become necessary.

Some existing vaccines, although safe for use in women who are not pregnant, may cause foetal infection resulting in malformations or abortions in women who are pregnant. Documentation on clinical and/or epidemiological data on exposure to the infectious agent or related vaccines during pregnancy should be provided, and may be sufficient to evaluate the risk. In other cases, the availability of appropriate animal models should be considered.

D./E. Mutagenic and Carcinogenic potential

Genotoxicity and carcinogenicity studies are normally not needed.

F. Pharmacodynamics

F.1 Primary pharmacodynamics (Immunogenicity and protection)

Primary pharmacodynamic studies with respect to the ‘antigen-protective response’ should be carried out in a relevant species. The endpoint in these kind of studies should preferably be the protection against a challenge from the pathogenic organism where there is an animal model reflecting the infections in humans. Therefore, quantification of the immunological response only, is in most cases not a sufficient indication of protection.

Studies that evaluate immune function should involve the evaluation of expected immunogenicity (level of antibody production, class and subclass of the antibody produced, cell-mediated immunity, and duration of immune response). In addition, the formation of neutralising antibodies, immune complex formation, interactions with immune cells to cause dysfunction, and release of other molecules that affect the immune system should also be investigated. It is preferable to study new combined vaccines in comparison with the individual antigens in animals to determine if any augmentation or diminution of response occurs.

Interactions between a particular vaccine and other vaccines may result in reciprocal antagonism. This is seen in certain cases following co-administration of two or more vaccines e.g. between cholera and yellow fever vaccines, and between measles vaccine and meningococcal A&C vaccine.

F.2 Secondary Pharmacodynamics (Safety pharmacology).

The potential for undesirable pharmacological activities e.g. on the circulatory and respiratory systems should be considered for new vaccines (as defined in the Scope) and investigated in appropriate animal models. Where necessary, particular monitoring of these activities might be incorporated in the design of toxicity and/or clinical studies. Effects on CNS parameters as well as on those organs associated with wild type organism pathology may also be included.

Repeated dose studies bearing in mind the proposed administration schedules (see § A.2) may reveal significant effects better than a single administration.

G. Pharmacokinetics

Pharmacokinetic studies (e.g. determining serum concentrations of antigens) are normally not needed. The need for specific studies should be considered on a case by case basis and may include considerations such as local deposition studies which would assess the retention at the site of injection and its further distribution; histopathological studies of the draining lymph nodes (near the injection site) which might illustrate depot characteristics of the vaccine; and viral shedding of live vaccines. Distribution studies should be considered in case of new formulations, novel adjuvants or when alternative routes of administration are intended to be used (e.g. oral or intranasal).

H. Local tolerance

As vaccines will in most cases be administered intramuscularly, subcutaneously or intracutaneously, local tolerance should be evaluated. Ideally, the formulation intended for

clinical use should be tested. In some cases, the potential local effects of the product can be evaluated in single or repeated dose toxicity studies thus obviating the need for separate local tolerance studies.

Q. Other aspects

1. Abnormal toxicity testing is part of the quality control and does not belong to the pharmacological-toxicological development programme of a vaccine. For several vaccines, abnormal toxicity testing of the finished product is no longer requested in the European Pharmacopoeia.
2. Vaccines (either single or combined) may contain substances causing pyrogenic effects, e.g. lipopolysaccharides, endotoxins and other cellular components like glycoproteins, teichoic acid. Therefore, generally pyrogenicity or endotoxin tests should be performed for each product on a batch-to-batch basis to detect these potential contaminations or to confirm that levels are acceptable.

R. Additives (Adjuvants/Excipients/Preservatives)

In formulated vaccines, different additives such as preservatives (substances used in parental medicinal products), excipients (inactive components including stabilisers) and/or adjuvants (substances aimed at increasing the immunogenic response) can be added to the immunogenic entity. If use of a preservative is appropriate, the safety of the preservative has to be documented and discussed. When a new preservative is to be used, documentation should be provided to support the safety and it should be treated as a new pharmaceutical excipient. Safety of new additives can be appraised by using 'mock' vaccines (i.e. total vaccine formulation without antigen and having followed established production processes). For a new adjuvant, it is particularly recommended to evaluate immuno-toxicological effects (e.g. such as hypersensitivity).

If a given additive has not caused important systemic or local reactions in an existing vaccine, this does not exclude the possibility that the same additive may cause serious side effects when used with other antigens. Additives should always comply with the guidance for such substances (See EEC 75/318, part III, p.5).

Vaccines may be adsorbed to different compounds as described in the European Pharmacopoeia. Although local reactions occur with vaccines containing adsorbents, the safety of vaccines containing adsorbents has in general been demonstrated with extensive preclinical and clinical use. Several adjuvants that are not currently components of licensed vaccines have recently been investigated in preclinical studies with the goal of developing more effective immune stimulants. In this case, appropriate preclinical studies should be developed on a case by case basis. The following points should be considered:

- Potential safety concerns for investigational adjuvants should include injection site reactions, fever, other systemic effects including immune mediated events (e.g. anaphylaxis), teratogenicity and genotoxicity.
- In addition, preclinical studies to evaluate the safety profile of the additive/combined vaccine should be performed. It is recommended that the intended additive/antigen combination and the intended clinical route of administration be used where possible and to compare with adjuvant alone or a vaccine formulation without adjuvant.

- If there are limited or no toxicology data for the additive being considered for inclusion in a new combined vaccine, it is advisable to perform toxicity studies on the additive alone.
- It is recommended that these preclinical studies are also designed to evaluate the adjuvant effects on the immune response when a relevant animal model is available.

