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

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CONCEPT PAPER ON THE DEVELOPMENT OF A COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) NOTE FOR GUIDANCE ON REQUIREMENTS FOR THE EVALUATION OF NEW ADJUVANTS IN VACCINES

1. Introduction

Adjuvants (immune potentiators, immunomodulators) have been used for decades to augment the immune response to vaccine antigens. Despite proposals to introduce numerous new adjuvants and despite the fact that there are a number of adjuvants in phase 1, 2 or 3 human trials, essentially only aluminium and calcium salts have been used in human vaccines. Recently, antigens incorporated into IRIV's (immunostimulating reconstituted influenza virosomes) have been licensed in most EU countries. In contrast, for veterinary vaccines there are several additional adjuvants licensed, notably water in oil emulsions, oil in water emulsions and adjuvants based on saponin products.

Interest in vaccine adjuvants has been growing rapidly for several reasons. New vaccine candidates have emerged over the past years, namely those obtained by means of rDNA technology against infectious agents, cancer, fertility, and allergic and autoimmune diseases. Many if not all of these vaccines require adjuvants, because a limitation is generally their low immunogenicity. They require adjuvants both to improve their physical antigen presentation and, in most cases, as immune potentiators to convert these antigens into protective vaccines. Vaccine manufacturers, public health authorities, e.g. WHO, and consumers established ambitious goals for enhancing present vaccines and for developing new ones. New technologies in the fields of analytical biochemistry, macromolecular purification, recombinant technology, and a better understanding of immunological mechanisms and disease pathogenesis have helped to improve the technical basis for adjuvant development and application.

2. Problem Statement

Adjuvant activity is a result of multiple factors and the immune response obtained with one antigen cannot as a rule be extrapolated to another antigen. Individual antigens vary in their physical and biological properties and antigens may have different needs for help from an adjuvant. Adjuvants must be chosen based on what type of immune response is desired and adjuvants must be formulated with the antigen in such a way that both are optimally distributed and presented to the relevant lymphatic tissues. The vaccine administration route is also an important factor influencing the efficacy and safety of an adjuvant.

For the reasons above and because the adjuvant is not the active ingredient, it is an individual vaccine/adjuvant combination which will be licensed.

There are three major areas in which adjuvants may exert their activities: (i) Physical presentation of the antigen, defined by the physical appearance of the antigen in the vaccine; (ii) Antigen/adjuvant uptake and distribution (targeting); (iii) Immune potentiation/modulation which includes activities that regulate both quantitative and qualitative aspects of the ensuing immune response.

Many adjuvants have been developed in the past but were never accepted for routine vaccination because of safety concerns, e.g. their immediate toxicity and the possibility of delayed side effects.

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The current attitude regarding risk-benefits of vaccination puts considerable emphasis on safety over efficacy when a vaccine is given to a healthy population. However, in high-risk groups, including patients with cancer and AIDS, and for therapeutic vaccines, an additional level of toxicity may be acceptable if the benefit of the vaccine is substantial.

Regulatory guidance dedicated to the pharmaceutical and pre-clinical safety assessment of adjuvants is so far insufficient.

3. Discussion

Vaccines of the future will be subject to three potentially conflicting requirements: they must give maximum efficacy, require the minimum number of doses and be delivered safely. The achievement of these goals is dependent upon continuing developments in adjuvant studies. Appropriate regulatory and scientific guidance for such studies should be developed addressing specific pharmaceutical, biological and safety aspects for adjuvants. In particular the guidance should address:

- Pharmaceutical/biological aspects such as
    - Demonstration of the compatibility of the adjuvant(s) with the antigenic components present in a given vaccine
    - Proof of an efficient adsorption of all antigenic components present in a vaccine, where relevant
    - Where relevant, degree of adsorption throughout the shelf life
    - Effect of the adjuvant on the ability to assay components
    - Comparative vaccine adjuvant trials
    - Biochemical purity
    - Pyrogenicity
- Pre-clinical safety aspects such as
    - Local acute and chronic inflammation
    - Induction of hypersensitivity
    - Anaphylaxis
    - Systemic toxicity to tissues or organs
    - Immune suppression
    - Carcinogenisis, genotoxicity
    - Adsorption by tissues and elimination from the organism

New classes of modern vaccine adjuvants are emerging, e.g. liposomes, immunostimulating complexes (ISCOMs), monophosphoryl lipid A, non-ionic block copolymers, protein cochleate formulations, microfluidized emulsions, synthetic adjuvants and cytokines This guidance document should be drafted in such a way as to remain easily adapted to evolving scientific knowledge.

Live vector based systems or polynucleotide vaccines are not considered as adjuvants per se unless they have been designed specifically to be so, either by the inclusion of specific CpG sequence motifs or by expression of an immuno-modulatory molecule. In addition, the proposed guidance should take into account thedelivery system only if it is an integral part of the functioning of the adjuvant or anticipated to have adjuvanting properties.

4. Recommendation

The successful use of new vaccine technologies will require a continued research effort to find adjuvant substances which do not have adverse biological properties. EU recommendations dedicated to the pharmaceutical and pre-clinical safety assessment of adjuvants are so far insufficient (CPMP/SWP/465/95 and CPMP/BWP/477/98).

It is proposed that a Note for Guidance document will be prepared for CPMP giving appropriate EU guidance on pharmaceutical/biological and pre-clinical aspects of novel adjuvants for vaccines.

5. Timetable

For external consultation and comments by end July 2002.

6. References

1. Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines (CPMP/BWP/477/98).

2. Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95).

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